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Sleep and Neuropsychiatric Disorders

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To our families
who continue to support us selflessly and
unreservedly in this and
all our personal and professional endeavours

Preface

Neurological and psychiatric disorders are manifestations of pathology in the brain, an organ that also regulates the sleep-wake cycle in addition to many other physiological functions. Since the substrate is common, sleep disturbances and sleep disorders are frequently present among patients having neurological and psychiatric disorders. For the same reason, many psychiatric disorders manifest as somatic symptoms as well as sleep disturbances. A number of papers are available in the literature documenting these associations. Similarly, many books have been written that cover the whole spectrum of sleep disorders and specific sleep disorders in depth. However, sleep-related symptoms with neuropsychiatric conditions typically have received limited coverage in sleep medicine textbooks. Accordingly, this volume, *Sleep in Neuropsychiatric Disorders*, is a humble attempt by the editors to fill this void.

Readers may find some overlap among chapters which was allowed by the editors as many readers prefer to purchase selected chapters instead of an entire book. However, diligent efforts have been made to keep this overlap contextual only. It does not substitute the concepts presented in detail in the chapter which is dedicated to the topic.

Recently, in addition to pulmonologists, a number of neurologists and psychiatrists have become interested in both physiological and clinical aspects of sleep. However, sleep medicine is still a small part of neurology and psychiatry education leaving the trainees in these specialties with a limited appreciation of sleep disorders. This often culminates in incomplete care to patients as sleep disorders are common in these populations. This book will help the psychiatrists and neurologists to update their knowledge and guide patient care.

This book is divided into five parts. Part I contains basic information and discusses the physiology of sleep, biological rhythms, neurobiology of dreams, and methods and measures that help the clinician to assess patient's condition. Ample space has been provided to history taking, questionnaires used to diagnose or assess the severity of sleep disorders, and laboratory-based detection of sleep disorders. In addition, one chapter is dedicated to factors that enhance the occurrence of sleep disorders in patients with neurological and psychiatric illness. This part also includes a chapter addressing the impact of sleep disorders on the economical milieu of patients and their quality of life.

Many a time, nocturnal or diurnal symptoms of these disorders are mistaken for other psychiatric or sleep disorders, leaving the underlying pathology untreated. This is addressed in Part II, which focuses on behavioural and emotional presentations of various classes of sleep disorders: insomnia, hypersomnia, sleep-related breathing disorders, sleep-related movement disorders, parasomnias, and circadian rhythm sleep disorders. These chapters are written by highly respected authors and represent their experience as well as available scientific literature.

Part III investigates associations between psychiatric and sleep disorders, which may be manifested in various ways—often in a bidirectional manner. Literature pertaining to both aspects—sleep and mental health—are included in this part. In addition, changes observed in sleep macroarchitecture and microarchitecture are addressed wherever scientific data is available. Both Parts II and III shall be helpful to psychiatrists for recognizing and managing sleep disorders commonly seen in a psychiatric practice.

The association between neurological and sleep disorders is addressed in Part IV. Neurological disorders may be causative in promoting sleep disturbances due to altered functioning of neuronal pathways. In addition, some neurological disorders may alter muscular strength, particularly those important for respiratory functions. These concerns, which can lead to incidental sleep disturbances, are covered in depth in this section.

A number of pharmacological agents are used in the management of psychiatric and neurological disorders. These medications act on various neurotransmitter pathways that overlap with those regulating sleep and waking. Hence, psychiatrists and neurologists must know about the sleep-related effects of these compounds. These pharmacological features are covered in Part V in detail.

The editors and authors would appreciate feedback on the contents of this volume with particular regard to any omissions or inaccuracies, which will be rectified in later editions. We also welcome your ideas, comments, and constructive criticisms, which are always appreciated.

Rishikesh, Uttarakhand, India — Ravi Gupta
Baltimore, MD, USA — David N. Neubauer
Toronto, ON, Canada — S. R. Pandi-Perumal

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Producing a volume such as this is a team effort. We were fortunate to experience a warm, professional, and highly enthusiastic support from the wonderfully talented people at Springer Nature made this project a pleasurable one.

Finally, we express our gratitude to our families for their patience and support. Their constant encouragement, understanding, and patience while the book was being developed are immeasurably appreciated.

Contents

About the Editors

Ravi Gupta, MD, PhD, is a certified sleep physician (World Sleep Federation) and Additional Professor in the Department of Psychiatry and Division of Sleep Medicine, All India Institute of Medical Sciences, Rishikesh, India. He has contributed two books *Psychiatry for Beginners and Clinical Atlas of Polysomnography* to the scientific literature. He has more than 150 published articles in various peer-reviewed journals and a number of chapters in national and international book volumes to his credit. He has been serving various professional societies (Psychiatry as well as Sleep Medicine) in various capacities for past 15 years. He is presently the Editor in Chief of Sleep and Vigilance, an official journal of the Indian Society for Sleep Research.

David N. Neubauer, MD, is Associate Professor of Psychiatry and Behavioral Sciences at the Johns Hopkins University School of Medicine and Associate Director of the Johns Hopkins Sleep Disorders Center. He is a Fellow of the American Academy of Sleep Medicine and Life Fellow of the American Psychiatric Association, and he is a member of the Sleep Research Society. He is the author of *Understanding Sleeplessness: Perspective on Insomnia* published by the Johns Hopkins University Press. He also has written numerous journal articles and book chapters on sleep-related topics. He coauthored the 2017 American Academy of Sleep Medicine Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults. Dr. Neubauer was appointed by the American Psychiatric Association as liaison to the National Sleep Foundation Sleep Time Recommendations project. Currently he serves on the National Sleep Foundation Board of Directors. Whenever possible he champions the importance of good sleep as a key component in the pursuit of wellness.

S. R. Pandi-Perumal, MSc is the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. Pandi is popular among the sleep community. He is a world-acclaimed sleep researcher and has authored over 200 publications and has edited over 25 high-profile academic volumes dealing with various sleep-related topics. Drawn to the benefits and significance of the sleep cycle, his personal and professional careers have been involved in advocating/achieving a good night's slumber.

Part I

Basic Sciences

Physiology of Normal Sleep

1

Jaime M. Monti, Ahmed S. BaHammam, and S. R. Pandi-Perumal

Abstract

Several neurotransmitter systems and circulating factors regulate rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wakefulness (W). The nuclei involved in the occurrence of W are located in the brainstem, hypothalamus, and the basal forebrain (BFB). These corresponding to the brainstem include the dorsal raphe nucleus (serotonergic neurons); locus coeruleus (noradrenergic neurons); ventral tegmental area, substantia nigra compacta, and ventral periaqueductal gray matter (dopaminergic neurons); and laterodorsal and pedunculopontine tegmental nuclei (cholinergic neurons). The structures found in the hypothalamus comprise the tuberomammillary nucleus (histaminergic neurons) and the posterior and lateral hypothalamus around the fornix (orexinergic neurons). The cholinergic neurons of the BFB are located mainly in the diagonal band of Broca, substantia innominata, and the medial septal area.

The NREM sleep-inducing system comprises neurons located in the preoptic area, which contains Gamma-Aminobutyric Acid (GABA) and galanin, and cells containing melanin-concentrating hormone located in the lateral hypothalamus and incertohypothalamic area. The latter is also involved in the regulation of

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REM sleep. Somnogens, including adenosine (formed mainly by the breakdown of adenosine nucleotides), prostaglandin D2 (which is mainly present in the leptomeninges, choroid plexus, and oligodendrocytes), nitric oxide (synthesized predominantly from L-arginine), and cytokine promote also sleep, mainly NREM sleep. Melatonin is a hormone secreted during the night from the pineal gland and has a weak sleep-promoting effect in humans.

The subcoeruleus nucleus has been proposed as the critical area for REM sleep regulation in the cat. Its equivalent in the rat is called the sublaterodorsal nucleus. The REM sleep generation region includes mainly glutamatergic and GABAergic neurons.

Sleep timing depends on two factors, sleep debt (process S; homeostasis) and circadian control (process C). When process S approaches the upper boundary, it triggers sleep. On the other hand, the markers of process C include melatonin and core body temperature.

Keywords

Circadian · Neurotransmitter · Polysomnography · Sleep · Two-process model

1.1 Introduction

Sleep is closely related to every facet of daily life. In this respect, disturbed sleep affects not only our health and well-being but also our quality of life. In humans, the sleep–wakefulness cycle can be characterized by the polysomnographic recording of three basic parameters: the electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). The American Academy of Sleep Medicine (AASM) scoring manual distinguishes a waking state, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep (Table 1.1) [1]. Active wakefulness (W) with eyes open is characterized by a low-voltage mixed-frequency EEG profile, high tonic EMG activity, and voluntary eye movements. In contrast, quiet wake with eyes closed is characterized by an EEG with sinusoidal waves of 8–11 Hz (alpha activity) and a relatively high tonic EMG. Concerning NREM sleep, the scoring manual distinguishes three stages (namely, N1, N2, and N3) mainly based on EEG criteria. Stage N1 is the transitional stage from wakefulness (W) and is characterized by the presence of relatively low-voltage waves with a prominence of activity in the theta range (4–7 Hz), slow and predominantly horizontal eye movements, and a decrease in EMG activity. Stage N2 is defined by the presence of sleep spindles and K-complexes, and stage N3 is characterized by the occurrence of slow, high-amplitude, or delta waves. During REM sleep, the subject is flaccid. In addition, it is more difficult to wake up a subject from REM sleep than from stage N3. During REM sleep, the individual's eyes periodically move rapidly under closed lids. If the subject is awakened, he might say that he was dreaming. The polysomnogram is characterized by the presence of low-voltage mixed-frequency EEG activity that closely resembles that of stage N1. In this context, theta activity is often observed in

Table 1.1 Electroencephalographic correlates of sleep stages

Sleep stages	Tst (%)	Characteristics			
		Eeg	Eog	Emg	Other variables
Stage awake (relaxed wakefulness)		Alpha activity (8–12 Hz) or low-amplitude beta (13–35 Hz), mixed-frequency waves	REM (in sync or out of sync deflections), eye blinks	Relatively high tonic EMG activity	Alpha activity in occipital leads compared with central leads, eye-opening suppresses alpha activity, movement artifacts
N1, formerly known as stage 1	2–5	Low-voltage, mixed-frequency waves (2–7 Hz range), mainly irregular theta activity, triangular vertex waves	SEMs, waxing, and waning of the alpha rhythm	Tonic EMG levels are typically below the range of relaxed wakefulness	Alpha $\leq$50%, vertex sharp waves in central leads, the absence of spindles and K-complexes
N2, formerly known as stage 2	45–55	Relatively low-voltage, mixed-frequency waves, some low-amplitude theta and delta activity	No eye movement	Low chin muscle activity	Sleep spindles (7 to 14 Hz) and K-complexes occur intermittently
N3, formerly known as stages 3 and 4	5–20	$\geq$20–50% of epoch consists of delta (0.5–2 Hz) activity	No eye movement	Chin muscle activity is lower than N1 and N2	Sleep spindles may be present
Stage REM	20–25	EEG is relatively low voltage with mixed frequency resembling N1 sleep	Episodic rapid, jerky, and usually lateral eye movements in clusters	EMG tracing almost always reaches its lowest levels owing to muscle atonia	Phasic and tonic components, the presence of sawtooth waves, alpha waves are 1–2 Hz slower than waves occurring during wakefulness and non-REM sleep

EEG Electroencephalography, *EMG* electromyography, *EOG* electrooculography, *REM* rapid eye movement, *SEMs* slow eye movements, *TST* total sleep time

conjunction with bursts of rapid eye movements, which take the form of sawtooth appearance. Despite this neural activity, the muscles, except for the diaphragm, are completely relaxed and are only periodically interrupted by muscle switches.

1.2 Changes of Central and Peripheral Functions Across the Sleep/Wake Behavioral State

Several functions are modified when passing from one behavioral state to the other.

1. In this respect, we are conscious during W and have normal cognitive activity, whereas, during N3 sleep, ***cognitive activity*** (expressed as dreams during sleep) is scant. In contrast, dreams are the cognitive complement of REMS. It should be mentioned that cognitive activities (consciousness and dreams) are mainly engendered by the activity of cortical and thalamic neuronal networks [2, 3]. When hyperpolarized, the thalamic neurons tend to obstruct the sensory information that travels toward the cortex. In contrast, when the thalamic neurons are depolarized, sensory information is transferred to the cortex, such as during REM sleep and wakefulness.
2. Concerning ***motor functions***, movements, and high muscle tone typify wakefulness. During NREM sleep, the tone of somatic muscles is reduced, whereas REM sleep is characterized by profound muscle atonia, predominantly of antigravity muscles.
3. ***Autonomic activity*** is closely related to the behavioral state [4]. As an example, there is an increase in tonic parasympathetic activity during NREM sleep.

1.3 Brain Regions and Neurotransmitter Systems Involved in the Regulation of the Behavioral State

The brain regions involved in the promotion of W are located in the brainstem, hypothalamus, and basal forebrain (BFB) and use different neurotransmitters (Figs. 1.1 and 1.2).

(a) The nuclei found in the brainstem include the dorsal raphe nucleus, the median raphe nucleus, which are serotonergic (5-HT); locus coeruleus (LC) which contains norepinephrine neurons (NE); ventral tegmental area (VTA), substantia nigra pars compacta (SNc), and ventral periaqueductal gray matter (vPAG) that harbor dopaminergic neurons (DA); laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) and basal forebrain (BFB) that project neurons containing acetylcholine (ACh); and medial pontine reticular formation and BFB-containing glutamatergic neurons (Glu).
(b) The structures located in the hypothalamus include cells containing histamine (HA) in the tuberomammillary nucleus (TMN) and orexin (OX) containing cells in the posterior lateral hypothalamus around the fornix (LH).
(c) The cholinergic and glutamatergic neurons of the BFB are involved in the regulation of the behavioral state, which are located predominantly in the diagonal band, substantia innominata, and medial septal area [5].

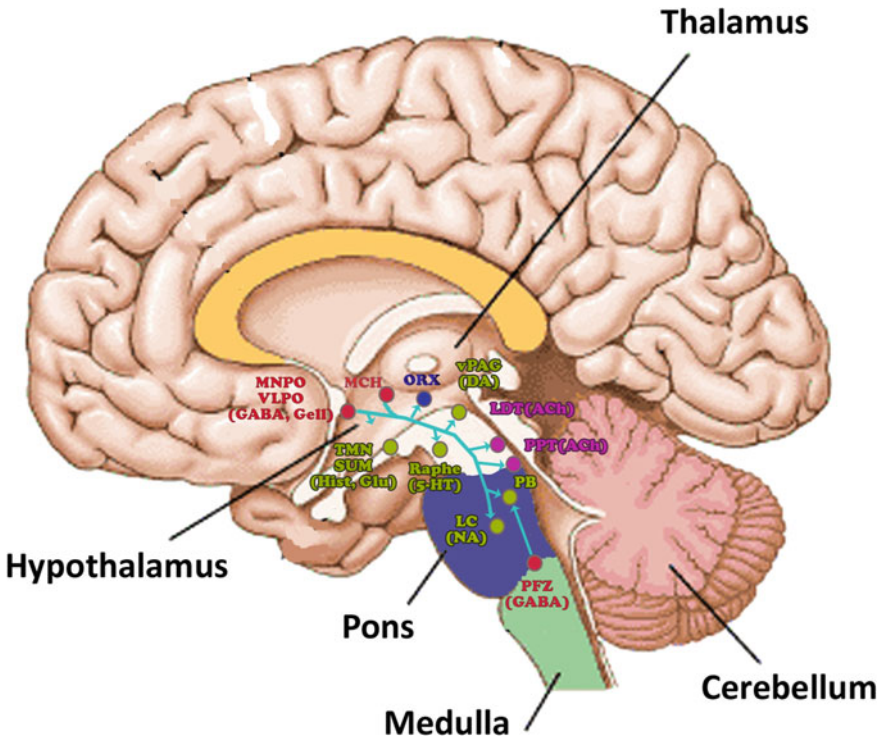

Fig. 1.1 Sleep tract

The 5-HT, NE, HA, and ACh-containing neurons that participate in the regulation of W give rise to mainly ascending projections to (1) the thalamus (dorsal route), which in turn projects to the cerebral cortex, and (2) the BFB (ventral route) where cells consecutively project to the cerebral cortex and the hippocampus. The DA-containing cells of the VTA and SNc project to the basal ganglia and the prefrontal cortex, while those corresponding to the vPAG project mainly to the BFB and midline thalamus. Moreover, OX-containing neurons carry projections to the whole forebrain and brainstem arousal systems [6].

It has been emphasized that isolated activation of each of the arousal systems already produces W. However, under normal conditions, they all partake in the occurrence of behavioral and EEG arousal [7]. This is mainly related to the interconnections of most of the W-promoting neurons. Notwithstanding this, from the functional point of view, different neuronal groups have a differential contribution to different circuitry of wakefulness. Accordingly, the noradrenergic system mainly supports attentional processes; the serotonergic neurons sustain W that is associated with stereotyped and automatic motor activity, while dopaminergic and orexinergic cells would support a waking state with high motivation [6].

Neurons of the preoptic area, anterior hypothalamus, and adjacent BFB compose the NREM sleep-inducing system. Slow-wave sleep (SWS) active neurons of the

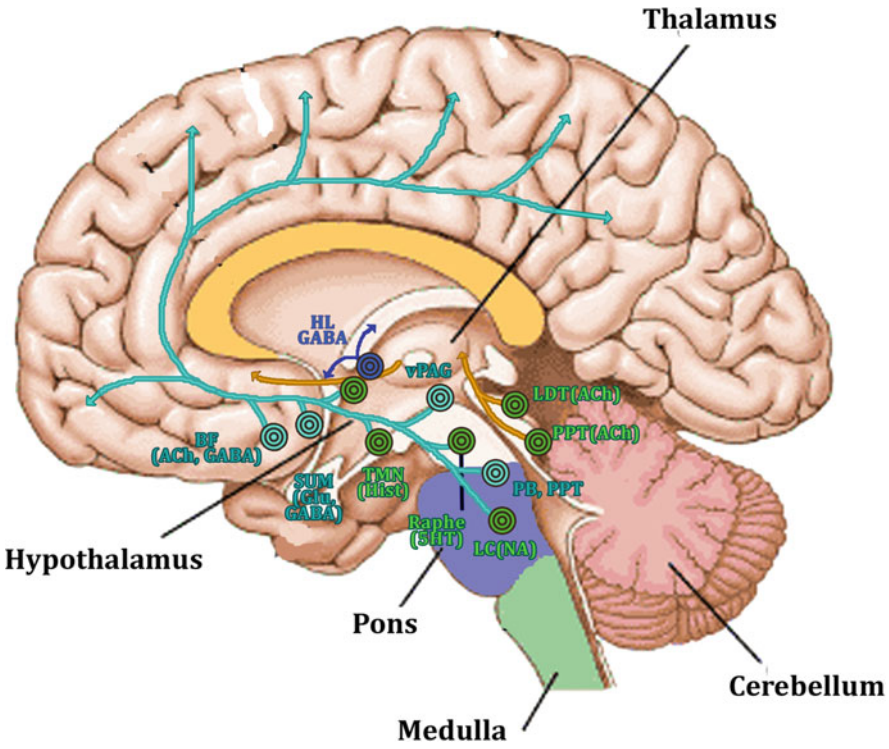

Fig. 1.2 Wakefulness tract

preoptic area are mainly located in the ventrolateral preoptic area (VLPO). Most of these neurons contain GABA and galanin and thus send inhibitory projections to the brainstem and hypothalamic areas involved in promoting wakefulness, namely, DRN, LC, LDT/PPT, vPAG, and LH. More recently, melanin-concentrating hormone (MCH) neurons located in the lateral hypothalamus and zona incerta have been proposed to participate in the regulation of NREMS as well as REMS [8]. It is worth mentioning that several other chemical factors present in the body, including adenosine, prostaglandin D2, nitric oxide (NO), and cytokines, promote sleep, mainly NREMS in humans and thus act as somnogens.

REM sleep is promoted by the activation of cholinergic REM-on neurons of the LDT/PPT. Moreover, the subcoeruleus nucleus (subC) has been proposed as the critical area for REM sleep generation in the cat. Its equivalent in the rat and mouse is called the sublaterodorsal nucleus (SLD). It should be mentioned that the parabrachial area, nucleus pontis oralis, and nucleus pontis caudalis also contribute to the occurrence of some REM sleep signs [9]. The REM sleep generation regions include predominantly glutamatergic and GABAergic neurons.

1.4 Wakefulness-Promoting Neurotransmitters

During quiet wakefulness, 5-HT, NE, HA, and OX neurons fire slowly and regularly. In contrast, during active wakefulness, the neuronal activity in these areas shows a significant increase. As the NREM sleep ensues, the mean discharge rate shows a progressive reduction, and during REMS there is a further decrease or even a cessation of neuronal activity.

1.4.1 Serotonin

5-HT predominantly promotes wakefulness and inhibits REM sleep. The 5-HT receptors can be classified into at least seven classes designated as 5-$HT_{1–7}$. The 5-HT_{1A} and 5-HT_{1B} receptors are linked to the inhibition of adenylate cyclase, while 5HT1A receptors increase potassium entry in the cell, leading to hyperpolarization. The 5-HT_{1A} receptor is located on the soma and the dendrites (somatodendritic autoreceptor) of presynaptic 5-HT neurons and also on postsynaptic neurons. The 5-HT_{1B} receptor is located at presynaptic (5-HT axon terminals) and postsynaptic sites. Mutant mice that do not express 5-HT_{1A} or 5-HT_{1B} receptors exhibit greater amounts of REM sleep than their wild-type counterparts without a knockout. Furthermore, direct infusion of a 5-HT_{1A} receptor agonist into the DRN enhances REM sleep in laboratory animals. The 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors are located on postsynaptic neurons, and their actions are mediated by the activation of phospholipase C, with a resulting depolarization of the postsynaptic cell. The 5-HT_6 and 5-HT_7 receptors are G protein-coupled receptors, and their primary signal transduction pathway is the stimulation of adenylate cyclase.

Systemic injection of full agonists of postsynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-$HT_{2A/2C}$, 5-HT_6, and 5-HT_7 receptor increases wakefulness and reduces both NREM and REM sleep [10].

The 5-HT_3 receptor is inotropic and is not coupled to G proteins. It directly activates a 5-HT-gated cation channel, which leads to the depolarization of monoaminergic, aminoacidergic, and cholinergic cells. Injection of a 5-HT_3 receptor agonist into the left lateral ventricle increases wakefulness, whereas both SWS and REMS are reduced [11].

1.4.2 Norepinephrine

In the central nervous system, norepinephrine (NE) is found almost exclusively in the neurons of the LC, located in the dorsolateral mesopontine region. During wakefulness, the norepinephrine neurons increase their firing rate in response to a novel stimulus. Furthermore, optogenetic stimulation of norepinephrine neurons awakes the laboratory animals, while their chemogenetic inhibition promotes the transition into NREM sleep. The NE receptors can be classified into at least three classes, designated α_1, α_2, and β. The α_1 receptor is related to the enzyme

phospholipase C and acts by increasing the Ca^{2+} concentration in the target cell. The primary signal transduction pathway of the β receptor is the stimulation of cyclic adenosine monophosphate (cAMP) synthesis. In contrast, the α_2 receptor is linked to the inhibition of cyclic AMP synthesis. The α_1 and β receptors are located at postsynaptic sites, and their activation results in the depolarization of the host cell. Stimulation of the presynaptic α_2 receptor leads to the hyperpolarization of the norepinephrine neurons, while activation of the postsynaptic α_2 receptor induces inhibitory responses on target structures. Systemic administration of the NE reuptake inhibitors, namely, amphetamine and cocaine or the selective α_1 receptor agonist, for example, methoxamine, significantly increases wakefulness and reduces both NREM sleep and REM sleep. In contrast, systemic or intracerebroventricular injection of the selective α_2 receptor agonist, for example, clonidine, produces profound sedation [11].

1.4.3 Dopamine

Two distinct groups of DA receptors, D_1- and D_2-like receptors, have been characterized in the central nervous system. The D_1 subfamily includes the D_1 and D_5 receptors, whereas the D_2 subfamily comprises the D_2, D_3, and D_4 receptors.

The D_1 and D_5 receptors are postsynaptic receptors linked to the activation of adenylate cyclase. Systemic administration of the selective DA D1 receptor agonist SKF 38393 induces desynchronization of the EEG and behavioral arousal in laboratory animals, increasing wakefulness and reducing both SWS and REM sleep. In contrast, the D1 receptor antagonist SCH 23390 produces sedation, which is seen as a reduction of wakefulness and increment of SWS and REM sleep on polysomnography.

DA receptors of the D_2 subfamily are predominantly coupled to the inhibition of adenylate cyclase. The D_2 receptors are located at postsynaptic sites in the basal ganglia. They are also found on cell bodies and dendrites in the VTA and SNc, where they function as autoreceptors. D_3 and D_4 receptors are also postsynaptic receptors.

Moreover, systemic or intra-nucleus accumbens injection of the selective D_2 autoreceptor agonist (-)3-(3-hydroxyphenyl)-N-n-propylpiperidine (3-PPP) is followed by a suppression of locomotor activity, which is accompanied by behavioral and EEG sleep in rodents. Interestingly, the D_2 receptor agonists such as bromocriptine and quinpirole give rise to biphasic effects. Low doses of these agents decrease wakefulness and enhance SWS as well as REMS, while large doses induce the opposite effects in the rat. In contrast, the D_2 receptor antagonist, for example, haloperidol, has been shown to reduce wakefulness and to increase SWS in rodents. The increase of wakefulness that follows the administration of relatively large doses of a D_2 receptor agonist has been related to (1) the activation of nonselective cationic conductance and/or (2) the disinhibition of monoaminergic cells synaptically related to GABAergic interneurons [12].

Dopamine antagonists have been shown to modify sleep variables in clinical studies as well. In this respect, several second-generation antipsychotic drugs,

including olanzapine, ziprasidone, and paliperidone that block DA D_2 receptors, cause a significant reduction in sleep onset latency and increase total sleep time of stage N2 when administered to schizophrenia patients [13].

1.4.4 Histamine

The histaminergic H_1, H_2, and H_3 receptors are prominently expressed in the central nervous system (CNS). A fourth HA receptor (H4) was recently cited in central nervous system structures, which is involved in the control of sleep variables. H_1 and H_2 receptors are present on postsynaptic sites. The H_1 receptor acts mainly by increasing the Ca^{2+} concentration in the target cell, while histamine acting through the H_2 receptor stimulates adenylate cyclase.

An optogenetic in vitro study showed that stimulation of histaminergic cells inhibits NREM sleep-promoting VLPO neurons, supporting a role for HA favoring wakefulness. Similarly, injection of α-fluoromethyl-histamine, a highly specific, irreversible inhibitor of histidine decarboxylase that reduces brain HA levels in rodents, augments SWS and REM sleep, whereas wakefulness is reduced. While the selective H_1 receptor agonist 2-(3-fluoromethylphenyl)-histamine increases wakefulness and reduces SWS, the H_1 receptor antagonists mepyramine, diphenhydramine, chlorpheniramine, and promethazine induce the opposite effects in laboratory animals and humans.

In contrast, the H3 receptor shows the attributes of a presynaptic autoreceptor, mediating the synthesis and release of HA, and a presynaptic heteroreceptor controlling the release of monoamines, for example, ACh, Glu, GABA, and several neuropeptides. Furthermore, H3 receptors are presynaptic inhibitory autoreceptors located in the cerebral cortex, hypothalamus, hippocampus, and basal ganglia [14]. Pitolisant, a new stimulant that has been approved for the treatment of narcolepsy, acts as a high-affinity competitive antagonist and as an inverse agonist at the human H3 receptor and mediates its pharmacological action at the presynaptic level [14, 15]. H3 receptors increase the reuptake of histamine at synaptic terminals and attenuate additional histamine release into the synapse [16]. By blocking H3 autoreceptors and raising the levels of histamine transmitters at the synapse, pitolisant magnifies the activity of histaminergic neurons and increases vigilance [17]. Inverse agonism of pitolisant at H3 receptors also enhances the synthesis and release of endogenous histamine above the basal level. The H3 receptor is negatively coupled to adenylate cyclase, and its stimulation induces a decrease of cyclic adenosine monophosphate. The effect of the H_3 receptor agonist R-α-methylhistamine (AMH) has been compared with that of the H_3-antagonist thioperamide. AMH increased SWS, whereas stage W and REM sleep were reduced. On the other hand, thioperamide induced the opposite effects [10].

The antidepressant drug doxepin has been approved for the treatment of insomnia disorder. The approved insomnia doses are just 3 and 6 mg. This is because, at low doses, the compound retains only H_1 receptor antagonism property [13].

1.4.5 Acetylcholine

Acetylcholine is synthesized from its precursor choline in a reaction that is catalyzed by the enzyme choline acetyltransferase and is metabolized by the enzyme acetylcholinesterase. This neurotransmitter acts on two different types of receptors referred to as nicotinic and muscarinic receptors. As mentioned earlier, cholinergic neurons are involved in the maintenance of wakefulness and are found in the LDT-PPT and the BFB. During wakefulness, there is an increase in cholinergic neuronal firing and an increment in the release of ACh at cortical levels. These neurons suppress their discharge during NREM sleep but are reactivated during REM sleep [18]. Optogenetic activation of the cholinergic neurons of the BFB reduces slow EEG activity during NREM sleep, while their inhibition increases the slow EEG rhythms [19]. Systemic administration of the muscarinic receptor agonist pilocarpine and arecoline evoke characteristic cortical arousal, which is reduced by atropine and related receptor antagonists. Furthermore, microinjection of the cholinergic agonist carbachol or the anticholinesterase agent physostigmine and neostigmine into the pontine reticular formation induces a long-lasting REM sleep-like state in the cat.

1.4.6 Orexin

The orexins A and B act on two types of metabotropic receptors, exerting postsynaptic and presynaptic excitatory effects. The intraventricular injection of orexins induces the occurrence of wakefulness [20]. Opto- and chemogenetic activation of these neurons also causes wakefulness. Caloric restriction has been shown to upregulate orexin gene expression in animal models [21]. Moreover, a recent study demonstrated that intermittent diurnal fasting increased orexin levels in the plasma during fasting hours [22]. It is thought that innervation of orexin neurons from regions that control metabolism and feeding, such as the hypothalamic arcuate nucleus, nucleus tractus solitarius, and ventromedial hypothalamic nucleus, is the likely mechanism enabling orexin neurons to react to the peripheral energy balance and stimulate arousal [23].

Of note, the degeneration of orexinergic neurons is on the pathogenic basis of narcolepsy with cataplexy. A newly approved selective dual antagonist of orexin receptors OX1R and OX2 is called suvorexant that reduces wakefulness and arousal, and enhances sleep. It has been approved for the treatment of insomnia [24].

1.5 Sleep-Promoting Neurotransmitters

1.5.1 ϒ-Aminobutyric Acid

GABA results from the decarboxylation of glutamate, a reaction catalyzed by the enzyme glutamic acid decarboxylase. Three different classes of receptors mediate the actions of GABA in the central nervous system, denominated $GABA_A$, $GABA_B$,

and $GABA_C$. The $GABA_A$ and $GABA_C$ receptors are ionotropic receptors, and their activation induces an increase in the permeability to chloride ions. The $GABA_B$ receptor is a metabotropic receptor that belongs to the family of G protein-coupled receptors. The $GABA_A$ receptor predominates at central sites and consists of α, β, and ϒ subunits, which contain multiple isoforms and variants. Interestingly, the $GABA_A$ receptor is the site of action of several hypnotic drugs, including benzodiazepine (temazepam), cyclopyrrolone (eszopiclone), imidazopyridine (zolpidem), and pyrazolopyrimidine (zaleplon) derivatives [25].

Flumazenil shares the inverse agonistic and antagonistic effects of the $GABA_A$ receptor. Its administration to healthy subjects produces an increase of stage W and N2 sleep latency and a reduction of stage N3. The $GABA_B$ receptor agonist baclofen has been shown to increase NREM sleep and REM sleep in humans. Contrarily, the $GABA_B$ receptor antagonist CGP 35348 reduces SWS and increases wakefulness in rodents.

Of note, the increase in synaptic GABA release in the sublaterodorsal nucleus, the executive area for REM sleep generation, is necessary to produce W. Additionally, a group of GABAergic neurons of the BFB is also involved in the occurrence of wakefulness. In this respect, optogenetic and chemogenetic activation of GABA-containing neurons that colocalize parvalbumin increase wakefulness and show fast activity in EEG.

1.5.2 Melanin-Concentrating Hormone

The melanin-concentrating hormone (MCH) is a peptide found in mammals, predominantly in neurons located in the lateral hypothalamus and incertohypothalamic area. The effects of MCH are mediated by two G-protein-coupled receptors named MCHR1 and MCHR2. It should be noted that the latter is found only in carnivores, primates, and humans. At central sites, MCH participates in several functions, including sleep–wake behavior. In this respect, MCHergic neurons project widely throughout the CNS to brain regions involved in regulating the behavioral states, including the VLPO, DRN, LC, TMN, BFB, vlPAG, and SLD.

MCH neurons are silent during wakefulness, and increase their firing rate during NREMS and still more during REM sleep. Studies in knockout mice for MCH have depicted a reduction of NREMS and increased wakefulness during the light–dark cycle. Optogenetic stimulation of MCH neurons and the intracerebroventricular injection of MCH increases and NREM sleep in rodents. An enhancement of REM sleep has also been observed following the infusion of MCH into the DRN, LC, and BFB (horizontal limb of the diagonal band of Broca). In contrast, the subcutaneous injection of selective MCHR1 antagonists suppressed REM sleep in the rat. It can be concluded that the marked REM sleep-inducing effect of MCH is likely to be related to the deactivation of neurons involved in the generation of wakefulness and the inhibition of REM sleep [11].

1.5.3 Melatonin and Circulating Factors

Melatonin receptors have been classified into MT1, MT2, and MT3 types. The former two receptors belong to the family of G-protein-coupled receptors linked to the inhibition of adenylate cyclase and have been detected in the suprachiasmatic nucleus (SCN), while MT3 is a melatonin-sensitive form of quinone reductase 2. MT1 mediates the inhibition of neuronal firing in the SCN by melatonin, while MT2 is involved in coordinating mammalian circadian rhythms. Ramelteon is a highly selective MT1/MT2 agonist. Compared to melatonin, it shows a sixfold higher affinity for the human MT1 and a threefold higher binding potency for the human MT2. Melatonin is available as a nutritional supplement in doses generally between 1 and 5 mg. On the other hand, ramelteon is presently administered for the treatment of an insomnia disorder.

Concerning the circulating factors, adenosine (AD) is formed inside cells or extracellularly by the breakdown of adenine nucleotides. The effects of AD on neuronal activity depend upon the activation of G-protein-coupled receptors. Stimulation of G_i-coupled A1 (A1R) and A3 (A3R) receptor inhibits adenylate cyclase, whereas activation of G_s couple A2a (A2aR) and a2b (A2bR) induces the opposite effect. In animals, sleeping ad libitum AD levels increase uniformly in several brain regions during W. Sleep homeostasis is impaired in conditional A1R knockout mice, resulting in the absence of the compensatory increase in NREM sleep following sleep deprivation.

Moreover, locomotor activity is decreased, and the caffeine-induced increase of W is absent in A2aR knockout mice. The facilitatory effect of AD on NREM sleep is partly related to the inhibition by A1R of HA- and OX-containing neurons. In contrast, activation of A1R in the lateral preoptic area facilitates the occurrence of wakefulness. Furthermore, activation of A2aR in the pontine reticular formation induces a marked increase of REM sleep related to GABAergic inhibition of local arousal promoting cells.

Prostaglandin D2 (PGD2), the most abundant PGD in the CNS of mammals, is produced by lipocalin-type PGD synthase, which is mainly found in the leptomeninges, choroid plexus, and oligodendrocytes, and released in the cerebrospinal fluid as a somnogen. Infusion of PGD2 into the lateral ventricle of wild-type mice during the dark phase gives rise to a significant increase of NREM sleep [26]. On the other hand, the microinjection of PGD2 into the preoptic area augments NREM and REM sleep [27].

Nitric oxide (NO) is synthesized in the CNS mainly from L-arginine by neuronal NO synthase (nNOS). Transgenic mice with an nNOS-targeted disruption exhibit a decrease in REM sleep compared with their wild-type littermates. Moreover, systemic or intracerebroventricular administration of NOS inhibitors is followed by a decrease of NREM and REM sleep in the rat. In contrast, L-arginine and the NO donor linsidomine induce the opposite effects [11, 28].

1.5.4 Human Circadian Timing System

A circadian clock is present in all cells of the mammalian body. It is an adaptation to the rotation of the earth to maintain a 24 h structure on processes at all body organs and cells. Circadian clocks can be broadly divided into peripheral and central clocks based on their anatomical location. The central clock is found in the suprachiasmatic nucleus (SCN), a specialized region in the hypothalamus. This central pacemaker is sensitive to light and obtains photic information through special receptors in the retina to synchronize its neuronal cellular clocks and conveys the information to the peripheral clocks network [29]. Peripheral clocks are located in other organs and tissues of the body [30]. These clocks are essential to preserving circadian tissue physiology by controlling tissue-specific gene expression [30]. The awarding of the 2017 Nobel Prize for the discovery of molecular circadian clocks stresses the importance of circadian clocks in both health and disease [30].

The timing of the circadian system must be reset regularly to ensure external synchrony between the body and the environment, as well as internal synchrony and correct temporal alignment between the central and peripheral clocks [30]. The primary entrainment factor or "Zeitgeber" for the SCN is light, whereas peripheral clocks are sensitive to neurohumoral modulation [31]. This is covered in detail in Chap. 3.

The terms "chronotype" or "morningness–eveningness" are used to describe individual differences in sleep–wake patterns. Individuals who go to sleep early, get up early, and feel and perform better in the morning are classified as morning types, while individuals who go to bed late, wake up late, and perform better in the afternoon are classified as evening types [32]. The intensity and timing of light exposure influence chronotype. For example, exposure to bright daylight in the morning and dim light in the evening encourages early bedtime and early rise time. On the other hand, exposure to bright artificial light at night may result in a shift delay in the circadian rhythm and a later bedtime and rise time making subjects of a later chronotype.

Certain behaviors such as sleep–wake patterns, fasting-feeding cycles, and mealtimes may disrupt the circadian rhythm [33, 34]. The cardiometabolic system is susceptible to the body's circadian system [35]. Indeed, disruption of this system causes cardiometabolic diseases. Misalignment of the circadian system results in several cardiometabolic dysfunctions, including impaired glucose tolerance, decreased insulin sensitivity, elevated inflammatory biomarkers, elevated mean arterial pressure, and decreased energy expenditure, which leads to weight gain [36]. Additionally, the circadian rhythm is essential for gene expression [37], immune [38], and endocrine function [39].

1.5.5 The Two-Process Model of Sleep Regulation

Three decades ago, the regulation of sleep had been proposed to be under the control of two processes called "the two-process model of sleep regulation" [40]. The timing

of sleep depends on two factors, sleep debt, which is reflected by how long we were awake (process S; homeostasis), and circadian control (process C) [40, 41]. Understanding these two processes is essential to understand the physiology of normal sleep and the pathophysiology of sleep disorders.

NREM sleep (slow-wave activity) represents the primary marker and upper range boundary of process S during sleep, while theta activity in the wake stage is a marker of the rising limb (lower boundary) of process S [42]. When process S comes close to the range's lower boundary, it enhances awakening, whereas approaching the upper boundary triggers sleep. On the other hand, markers of process C include melatonin and core body temperature. Sleep happens when the homeostatic process S verges on the upper threshold of process C, and waking occurs when process S reaches the lower threshold. The desire for nighttime sleep is triggered by melatonin release in the evening (which follows a circadian rhythm). Melatonin enhances distal limb vasodilation, which contributes to the drop in the core body temperature and hence enhancing sleep onset [43].

In animal models with disrupted process C by lesions of the SCN, sleep homeostasis was not disturbed [44, 45]. This suggests that the two processes are independently regulated. In humans, using a forced sleep/wake periodicity technique (forced desynchrony protocol) to move sleep timings outside the range of entrainment of the circadian pacemaker and in different circadian phases allows the assessment of both processes on sleep and performance variables [46, 47]. Data revealed an apparent sensitivity of many neurobehavioral functions to the circadian phase and the buildup of the homeostatic drive for sleep. Furthermore, Wyatt et al. demonstrated that the wake-dependent deterioration of neurobehavioral functions could be counterbalanced by the circadian drive for W [46].

Another interesting finding is the fact that process S and sleep homeostasis are not only a total (global) brain occurrence; the changes with sleep debt can be regional and limited to certain brain areas [42]. It has been shown that prolonged stimulation of the cortex limited to one hemisphere during wake increased slow waves over the stimulated brain area during subsequent sleep [48, 49].

These regional differences in sleep EEG have some implications. It is known that there is a distinct anteroposterior EEG power gradient of NREM sleep with a dominance of EEG low-frequency power in frontal derivations [50, 51]. Therefore, the EEG manifestations of the changes in process S are slowest in the frontocentral area [42]. This finding could be related to the functional specialization of different cortical areas, such as the involvement of the frontal cortex in cognitive functions [52].

Recent evidence suggests that both homeostatic and circadian factors may synergistically contribute to brain and synaptic plasticity [42, 53], where synaptic and cellular processes that had been exhausted during W are restored during sleep. Moreover, recently, it has been argued that both sleep homeostasis and the biological clock are needed for brain plasticity [54]. This is supported by a human-forced desynchrony protocol study, which showed that EEG slow-wave activity (reflecting sleep homeostasis) manifests pronounced circadian variation in central and posterior cortical regions [55].

It is interesting to know that process S does not influence the functioning of the circadian clock and that homeostatic sleep processes do not change with the circadian phase. Nevertheless, recent discoveries of the role of clock genes in sleep homeostasis indicate an interaction between process S and processes at the molecular/genetic level [56]. It has been shown that in animal models, knocking out one or more of the clock genes (Period Per1–3, Clock, Bmal1, Cryptochrome Cry1, and Cry2, Npas2) not only disrupts the circadian clock but also influences homeostatic sleep markers. Moreover, clock gene expression in the brain, particularly in the cerebral cortex, is significantly influenced by prior sleep/wake patterns [42].

1.5.6 Polysomnography

Polysomnography (PSG) is the gold standard diagnostic test for several sleep disorders. The test is usually performed at a sleep disorders unit within a hospital or a sleep disorders center. During PSG, several physiological parameters are monitored while the patient is asleep [57] (Fig. 1.3 (active wakefulness), Fig. 1.4 (Quiet wakefulness), Fig. 1.5 (Stage 1 sleep), Fig. 1.6 (Stage 2 sleep), Fig. 1.7 (Stage N3 sleep), Fig. 1.8 (REM sleep)).

These parameters include EEG brain waves, the oxygen level in the blood, heart rate and breathing, body position, eye and leg movements, and synchronized audiovisual monitoring. Moreover, additional parameters may be included in certain conditions, such as esophageal pH monitoring, esophageal manometry, and overnight blood pressure (BP) monitoring. In addition to its important diagnostic role, PSG can be used to adjust the treatment plan and to reach the optimal positive airway pressure setting for patients with sleep-disordered breathing (Table 1.2).

The placement of the EEG electrodes on the scalp follows an international system known as the 10–20 System of Electrode Placement (the International 10–20 system). The "10" and "20" refer to the 10% or 20% inter-electrode distance. The displayed EEG signal depends on the electrode derivation, which means from where the signals are being derived. A differential amplifier will measure and amplify the difference between the electro-potentials of two input sites (input 1–input 2). The AASM recommends three derivations for EEG recording: F4-M1, C4-M1, and O2-M1 (F: frontal, C: central, O: occipital, and M: mastoid) [1].

The electrooculograph (EOG) picks up movements of the eyeballs, based on recording the electro-potential difference between the cornea and the retina (the cornea has a positive voltage output, while the retina has a negative polarity). There are two reasons for recording EOG. The first is to record rapid eye movement (REM) sleep, and the second is to assess sleep onset, which is associated with slow rolling eye movements. Electromyography (EMG) is used to record chin muscle tone at the mentalis and submentalis muscles. It is a mandatory recording parameter for staging REM sleep and is essential to determine the onset of REM sleep. In general, muscle tone decreases during sleep, with maximal reduction occurring during REM sleep. Monitoring of the different sleep stages, sleep interruptions, movements, and the

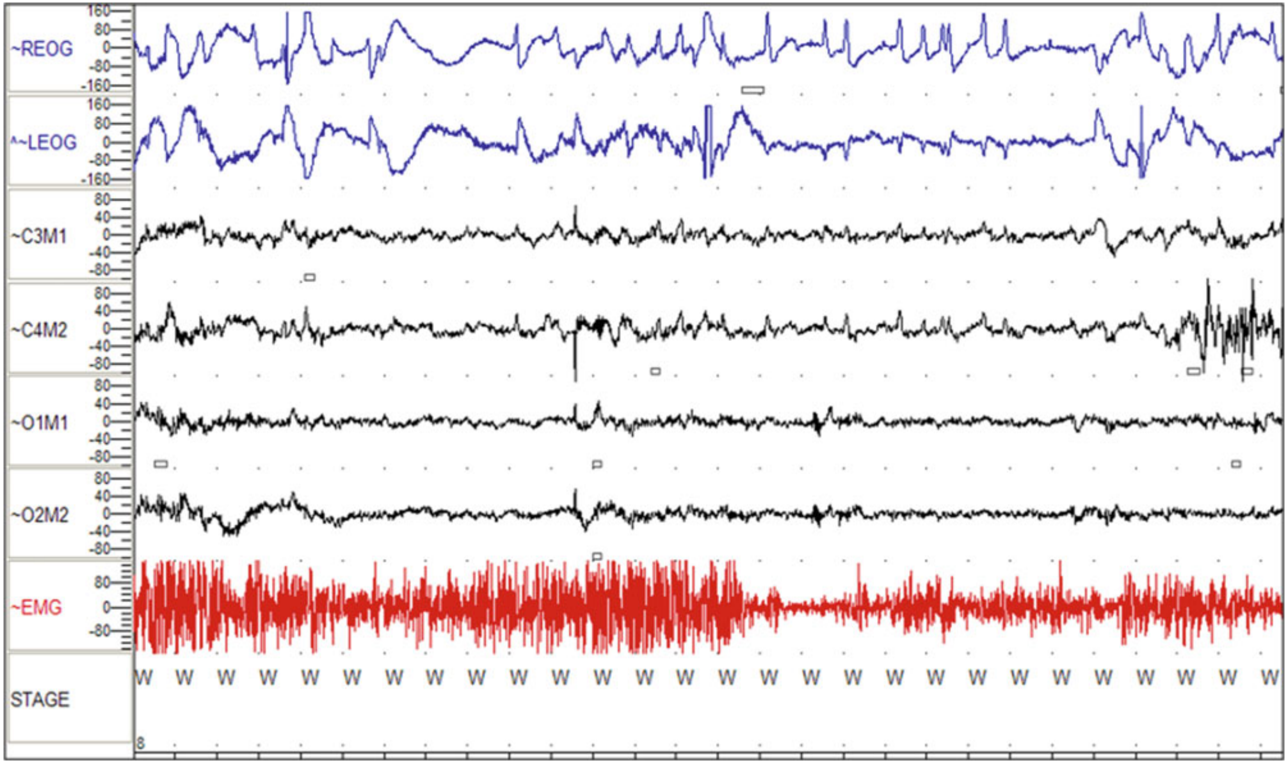

Fig. 1.3 (Active wakefulness): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage W (active wakefulness). Eye movements recorded in the EOG derivations consisting of the conjugate, irregular, sharply peaked eye movements with an initial deflection usually lasting <500 ms. While rapid eye movements are characteristic of stage R sleep, they may also be seen in wakefulness with eyes open when individuals visually scan the environment. With opening the eyes, low voltage, mixed frequency (chiefly beta and alpha frequency) is present

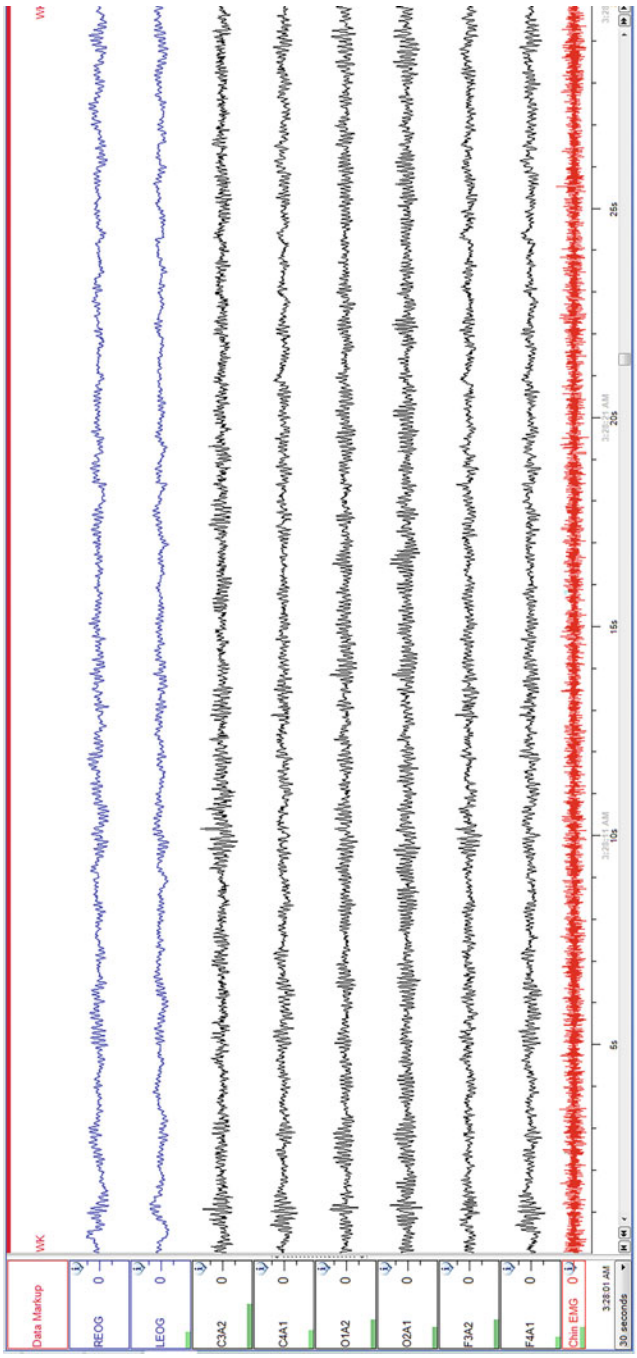

Fig. 1.4 (Quiet wakefulness): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage W (quiet wakefulness). An EEG pattern consisting of trains of sinusoidal 8–13 Hz activity was recorded over the occipital region with eye closure and high EMG tone

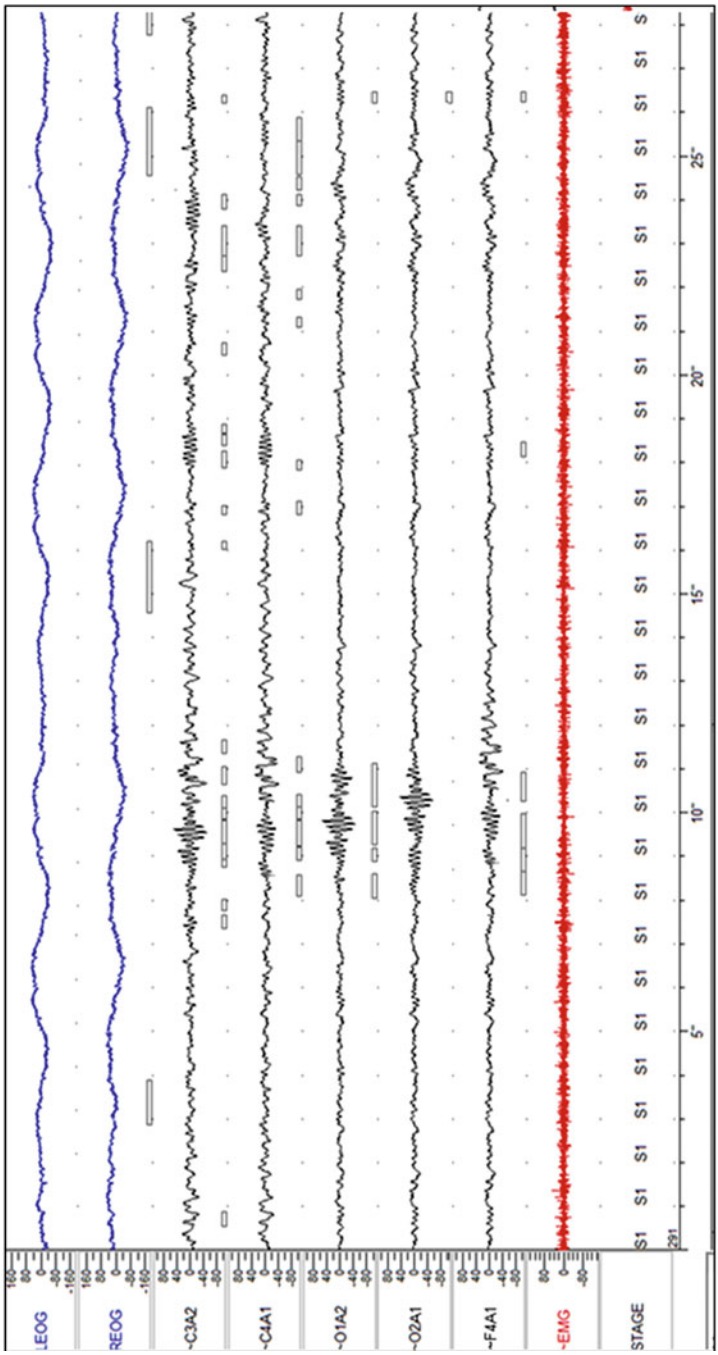

Fig. 1.5 (Stage 1 sleep): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage N1. The EOG shows the presence of slow eye movements (SEM), which is conjugate, reasonably regular, and sinusoidal eye movements, and the EEG shows low-amplitude, mixed-frequency activity, predominantly of 4–7 Hz (theta waves)

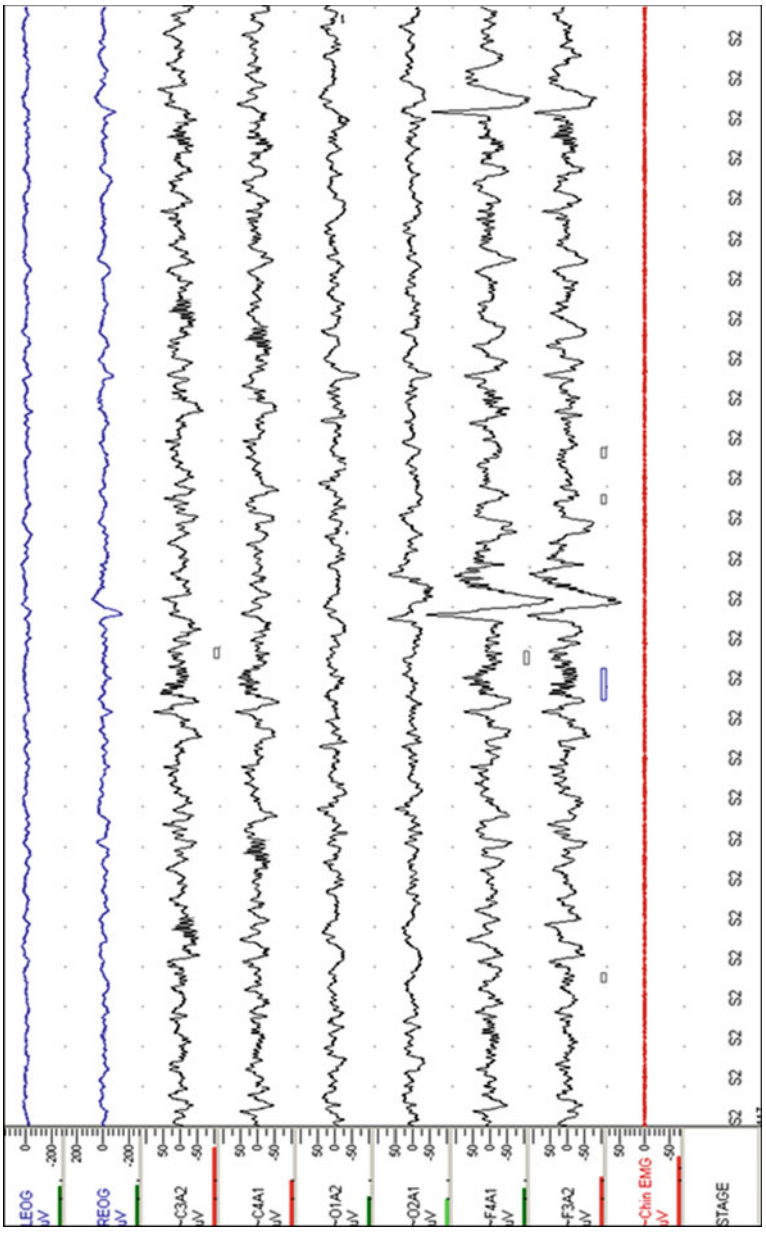

Fig. 1.6 (Stage 2 sleep): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage N2. EEG demonstrates sleep spindles (short rhythmic waveform clusters of 11–16 Hz), often showing a waxing and waning appearance with a duration of $\geq$0.5 s and K-complexes (sharp negative waves immediately followed by a slower positive component with a total duration of $\geq$0.5 s shown maximally in the frontal leads)

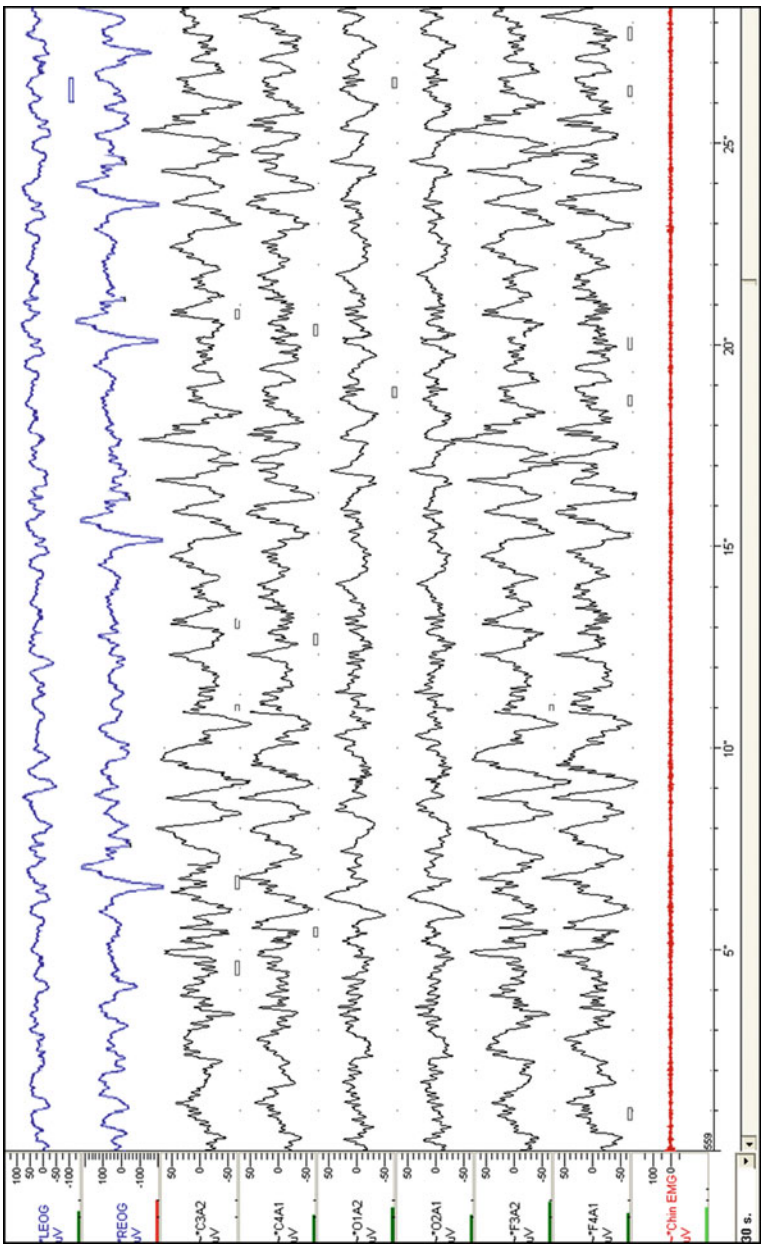

Fig. 1.7 (Stage N3 sleep): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage N3. The EEG shows slow-wave activity, which is the waves of a frequency of 0.5–2 Hz with a peak-to-peak amplitude >75 μV

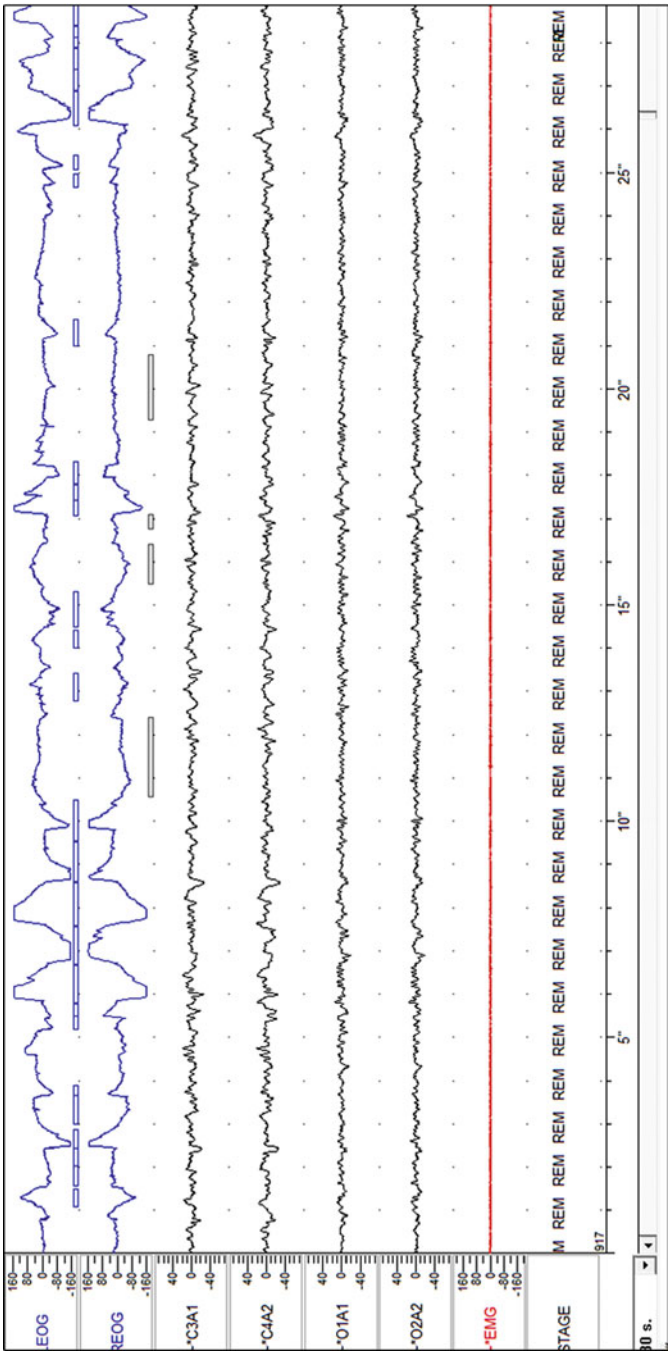

Fig. 1.8 (REM sleep): A 30 s Epoch consisting of the parameters of staging sleep (EEG, EOG, and chin EMG) showing stage R. The EOG shows rapid eye movements, and the EEG shows mixed-frequency low-amplitude waves. Chin EMG is absent

Table 1.2 Levels of sleep monitoring

	LLevel 1	LLevel 2	LLevel 3	LLevel 4
NNumber of leads	>7	>7	>4	1−2
TType of leads	EEEG, EOG, EMG, airflow, effort, oximetry	EEEG, EOG, EMG, ECG, airflow, effort, oximetry	AAirflow, effort, oximetry, ECG	OOximetry + other (usually airflow)
SSettings	AAttended usually in a sleep center	UUnattended	UUnattended	UUnattended

other respiratory and cardiac signals are clinically helpful for identifying the nature of the patient's sleep problems and assessing response to treatment.

After the test is completed, the recording is analyzed. A PSG recording of 7 h will be displayed in approximately 840 epochs (one epoch represents 30 s). These epochs are scored manually by an expert scorer. PSG is scored according to the AASM scoring rules [1]. The scorer may modify the duration of the epoch depending on the data to be scored. While EEG signals are scored in 30 s epoch, respiratory parameters and movements are usually scored in 2 min epochs. On the other hand, Cheyne–Stokes breathing may be scored in 5 min epochs, and ECG is usually scored in 10–15 s epochs.

Recently, unattended home sleep testing using portable sleep monitoring devices has become popular. The most commonly used portable sleep study devices are level-III devices, which allow for monitoring airflow, respiratory effort, oxygen saturation, and heart rate. Although more convenient for patients and less costly than the traditional PSG, portable devices have several limitations including the inability to monitor EEG signals, which prevents the determination of sleep duration and sleep stages, which may, in turn, underestimate the apnea–hypopnea index, particularly in REM sleep-related sleep apnea. Moreover, being unattended, this type of monitoring has a relatively higher rate of signal failure [58].

1.6 Conclusions

Wakefulness, NREM sleep, and REM sleep are prominent parts of the 24 h circadian cycle and are regulated by a complex interaction of neurotransmitter systems located in the brainstem, hypothalamus, and BFB. Thorough knowledge of the neurotransmitter systems involved in the regulation of wakefulness, NREM sleep, and REM sleep is essential to understand and treat insomnia disorders. Of note, currently used hypnotic drugs include $GABA_A$ and melatonin receptor agonists and histamine H_1 and orexin receptor antagonists.

Glossary

Circadian rhythm is a rhythm with ~24 h periodicity in all living organisms that are synchronized to an environmental light/dark (LD) cycle.

EEG (electroencephalogram).

EKG (electrocardiogram).

EMG (electromyogram) refers to recording muscle activity such as face twitches, teeth grinding, and leg movements; it also helps determine the presence of REM stage sleep.

EOG (electrooculogram) refers to the recording of eye movement that is particularly important in determining the different stages of sleep, particularly REM stage sleep.

Hypnogram is a visual depiction of overnight sleep, which shows the relationship between sleep stages.

MSLT (Multiple Sleep Latency Test).

MWT (Maintenance of Wakefulness Test).

PSG (Polysomnography or sleep study) is an attended overnight recording of overnight sleep (usually six or more hours) by means of sleep stages and cycles on a sheet of paper or on a computer screen via electrophysiological signals based on electrode and sensor recording in humans. It is a diagnostic procedure during which several different physiological and pathophysiological (cardiac, arousal, movement, and respiratory events) parameters (such as EEG, EMG, EOG, SpO_2, body position, blood pressure, penile tumescence, abnormal movement, and others) are continuously and simultaneously recorded across a sleep period to characterize sleep and identify sleep disorders. During overnight sleep, the following parameters are often recorded: Electroencephalogram (EEG); electromyogram (EMG; jaw, arm, and leg); electrooculogram (EOG); electrocardiogram (ECG); snoring; oro-nasal airflow (L/s) (liter/second) chest and abdomen movements (respiratory effort recordings); oxygen saturation (SpO_2); body position; and real-time-video-image recordings (video polysomnography). In addition, depending on the requirements, other parameters such as nocturnal penile tumescence, gastroesophageal reflux, and BP are other electrophysiological signals that can be recorded.

SpO_2 Pulse oximetry.

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Why Sleep Is Altered Across a Wide Range of Neuropsychiatric Disorders (NPD)?

2

Sourav Das and Vijay Krishnan

Abstract

Alteration in sleep timing or duration is common across a number of psychiatric disorders (e.g., depression, bipolar disorder, anxiety disorder, psychosis, and substance use disorders to name a few). However, despite the high prevalence, pathophysiological association between sleep and psychiatric disorders remains an enigma. This chapter tries to investigate it and describes the connection between the two based on neurotransmitters, neurotrophic factors, and shared neurocircuitry. In addition, role of circadian rhythm in increasing the risk of psychiatric disorders is also described.

Keywords

Insomnia psychiatric disorders · Neurobiology sleep psychiatry · Neurotransmitters · Neurocircuitry in sleep · Circadian rhythm psychiatry disorders

2.1 Introduction

Sleep problems are an integral part of psychiatric disorders, so much so that they are often a part of diagnostic criteria in the classification of psychiatric disorders, like in major depressive disorder (MDD), bipolar affective disorder, generalized anxiety disorder, post-traumatic stress disorder (PTSD), a major or mild neurocognitive

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disorder due to Lewy body, etc. There is a debate regarding whether sleep problems are a part of psychiatric illness. Recent findings point toward the existence of sleep problems as a separate entity coexistent with the psychiatric illness, warranting specific and separate management plan. The close association can be ascribed to shared genetics, shared neurobiological underpinnings, role of circadian rhythm in both sleep and psychiatric disorders, role of stress as a modulator of zeitgebers (time cues), role of psychiatric medications, and the role of psychiatric disorder in modifying behavior pattern which further alters sleep. Moreover, there are various sleep disorders that masquerade as psychiatric disorders and various psychiatric treatment-related practices which disturb the sleep of a patient with psychiatric disorder, thereby further compounding the problem. The present chapter intends to discuss in brief the assumed reasons for sleep alterations in various psychiatric disorders as per the current understanding.

2.2 Shared Genetics

The heritability of insomnia as a separate disorder has been proven in multiple studies [1–5]. A strong and statistically significant positive genetic correlation has been observed between insomnia and MDD. However, the covariance for lifetime MDD had only a modest impact on the strength of this association, favoring the idea that insomnia has a commonly shared but distinct genetic identity from depressive disorder [6–8]. The strongest genetic association with insomnia disorder was found at Chr 7 (q11.22), which is nearby AUTS2, a gene associated with alcohol consumption [8, 9]. Other candidate genes for insomnia disorder are related to brain development like RFX3 (transcription factor involved in development of white matter tracts including corpus callosum and thalamocortical tract), NTF3 (neurotrophic factor involved in cortical development and synaptogenesis), DEC1/DEC2 (circadian clock modulator, DEC2 linked to short sleep phenotypes), CACNA1D (L-type calcium channel gene, previously associated with bipolar disorder), CACNA1I (T-type calcium channel gene, mediates sleep spindles and thalamocortical oscillation in stage 2 sleep, was previously associated with schizophrenia) [10–20].

Thus, insomnia has close links to various psychiatric disorders at the genetic level, often sharing genes with disorders such as schizophrenia or bipolar disorder or having a locus in physical proximity to disorders like alcoholism and depression. Therefore, the coexistence of insomnia and various psychiatric disorders together in a single individual is not unexpected at all.

2.3 Neurobiological Underpinnings Are Common to Both Sleep and Psychiatric Disorders

Adequate good quality sleep is essential for optimal brain function, and lack of it has a negative impact on mood, cognition, and overall health. Poor sleep is found to be comorbid with psychiatric disorders like major depression, generalized anxiety disorder, social anxiety disorder, panic disorder, etc. in the range of 50–83% for major depression and 60–90% for anxiety disorders [21–27]. Moreover, depression and anxiety disorders are also frequently comorbid with each other [28, 29]. Naturally, the question comes if all these disorders share a common neural substrate.

2.3.1 Role of Neurotransmitters—Dopamine

Dopamine (DA) is a catecholamine neurotransmitter considered to be a key neurobiological substrate of reward and has been consistently linked with various psychiatric disorders like psychotic disorders (including schizophrenia), mood disorders, depression, anxiety, attention deficit hyperactivity disorder, movement disorders, etc. [30, 31]. DA has also been found to be integral in promotion and maintenance of arousal states [30, 31]. Mesolimbic DA neurons arise in the VTA and substantia nigra pars compacta and project to both subcortical and cortical structures including the nucleus accumbens, striatum, prefrontal cortex (PFC), and anterior cingulate cortex, all of which are highly relevant to the sleep–wake cycle [32, 33]. Also, DA receptors are abundant in key structures of the ascending reticular activating system, which are critical in modulation of sleep [34, 35]. Depletion of DA in the key structures provokes sleepiness, and the experimentally/pharmacologically induced arousal states are associated with altered dopaminergic neurotransmission [36]. DA neurotransmission (via D1 and D2 receptors) has been proposed as the primary mechanism for the arousal-promoting effects of stimulants like cocaine, amphetamine, methamphetamine, modafinil, etc. [37–40]. This has been confirmed in animal studies and positron emission tomography (PET) studies done in humans [40, 41]. Moreover, an SNP val158met on the catecholamine-O-methyltransferase (COMT) gene has been associated with differences in alpha wave oscillations in rapid eye movement (REM) and non-REM (NREM) sleep. The met/met genotype, associated with decreased DA metabolism is associated with higher peak amplitude alpha waves during wakefulness and greater 11–13 Hz activity in sleep (both REM and NREM) and thus a heightened state of arousal during sleep relative to the val/val genotype. This genotype has also been linked with depression and chronic pain [42]. Also, a variable number tandem repeat polymorphism on the D4 receptor gene (DRD4) is associated with insomnia-like symptoms in people with Alzheimer's disease and nicotine withdrawal [43, 44]. Furthermore, Vgontzas et al. in a polysomnographic study in primary insomnia patients reported positive correlations between indicators of sleep disturbance like sleep latency and wake after sleep onset with urinary levels of dihydroxyphenylalanine (dopamine precursor), dihydroxyphenylacetic acid, and dihydroxyphenylglycol (dopamine metabolites)

[45]. The dopamine variables were found to be stronger predictors of sleep disturbance than plasma cortisol in regression analysis [45]. These findings provide a general basis for DA neurotransmission involvement in sleep abnormalities through excessive central nervous system arousal and functional alterations observed in brain regions associated with the mesolimbic dopaminergic system. Hence, DA appears to be a common neurobiological substrate underlying both psychiatric disorders and sleep problems.

2.3.2 Role of Neurochemicals—BDNF

Brain-derived neurotrophic factor (BDNF) is a neurotrophin protein belonging to the family of growth factors which have a pivotal role in neuroplasticity [46]. There is ample evidence to suggest that BDNF synthesis is decreased by psychological stress and BDNF deficit leads to cognitive impairment and also various psychiatric disorders like major depression, anxiety, PTSD, etc. [46–48]. Chronic stress leads to dysregulation of the hypothalamic–pituitary axis (HPA), leading to sleep deprivation and reduced BDNF. BDNF appears to be a common denominator in various psychiatric disorders and sleep abnormalities. BDNF secretion is closely related to slow-wave sleep [49].

Patients with insomnia have shown low serum BDNF levels [50]. Many studies directly examining the effect of BDNF on slow-wave sleep (SWS) found a close association between the two. They also found that intrahemispheric BDNF infusion increased SWS and perceptual learning and memory consolidation [51–53]. A fairly large study of 250 participants done by Zaki et al. found that BDNF Val66Met polymorphism is linked with insomnia and depressive symptoms [47]. Various psychiatric disorders, by virtue of BDNF deficit, also present with sleep problems or insomnia. However, the exact direction of this association in terms of which comes first (which one is causative) is yet to be ascertained.

2.3.3 Role of Amygdala

Individuals with anxiety or depression frequently show excessive amygdala reactivity to salient, neutral, or negative stimuli compared to healthy participants [54, 55]. Similar findings have also been replicated in sleep-deprived individuals [56]. Amygdala-rostral anterior cingulate cortex (ACC) coupling was found to be diminished (signifying diminished top-down control of emotion regulation) in patients with primary insomnia and those with generalized anxiety disorder compared to good sleepers when the three groups were compared in resting-state functional connectivity (rsFC) studies [57]. Generally, altered amygdala-frontal lobe rsFC is found in depression and anxiety disorders, particularly in circuits encompassing emotion, cognition, emotion regulation, and sensorimotor processes (e.g., decreased amygdala-rostral ACC rsFC in social anxiety, reduced amygdala-ventral medial PFC rsFC in high trait anxiety, decreased amygdala-dorsolateral PFC

rsFC in adolescents with generalized anxiety disorder, reduced amygdala-medial PFC rsFC in adolescents with major depression) [58–61]. Similarly, worse sleep quality predicted increased left amygdala-subgenual ACC functional connectivity and reduced connectivity with posterior cerebellar lobe and superior temporal gyrus and increased connectivity between right amygdala and postcentral gyrus [62].

2.3.4 Interhemispheric Functional Connectivity

Yan et al. in an interhemispheric functional connectivity study found that primary insomnia patients showed higher voxel-mirrored homotopic connectivity (VMHC) in the anterior cingulate cortex (ACC) bilaterally than healthy controls [63]. Further, increased functional connectivity was noted between the left ACC and right thalamus (and the right ACC and left orbitofrontal cortex) in primary insomnia patients, revealing abnormal connectivity between the two cerebral hemispheres [63]. The VMHC values in the ACC were positively correlated with the self-rating depression scale scores and time to fall asleep [63].

A similar study by Qi et al. showed that irritable bowel syndrome patients had higher interhemispheric functional connectivity between bilateral thalami, cuneus, posterior cingulate cortices (PCC), lingual gyri and inferior occipital/cerebellum lobes, and lower interhemispheric functional connectivity between bilateral ventral ACC [64]. Inclusion of anxiety and depression as covariates, however, abolished the VMHC difference in the ventral ACC [64].

Thus, it can be safely concluded that interhemispheric functional connectivity in certain areas like the ACC and thalamus do play an important role in the neurobiology of insomnia as well as anxiety and depression.

2.3.5 Role of the DMN

The recent discovery of dynamic functional interconnectivity of large-scale brain networks in the process of human cognition has revealed the existence of various "networks" like Default Mode Network (DMN), salience network, central executive network, etc. These networks are basically highways between pre-designated brain areas that facilitate signaling along preferred pathways in the service of specific cognitive functions [65]. Now DMN is the one which remains active in the absence of overt behavior and plays in role in sustenance of conscious awareness [65]. Role of DMN alteration has been observed in various psychiatric disorders like anxiety, depression, Alzheimer's dementia, schizophrenia, etc. [66–70]. Deactivation in medial PFC and posterior cingulate cortex (PCC $>$ mPFC) were observed for patients with anxiety disorder [69]. Likewise, elderly individuals with depression and anxiety showed increased functional connectivity in the posterior regions of the DMN and decreased functional connectivity in the anterior regions of the DMN [66], whereas individuals with amnestic mild cognitive impairment (aMCI) and Alzheimer's dementia showed increased DMN activity in the PCC [71]. aMCI

patients also showed increased functional connectivity between right parietal cortex and left insula, while Alzheimer's patients showed increased connectivity between left hippocampus and dorsolateral prefrontal cortex [72, 73]. Recently, a substantial number of researches have been done on the role of DMN and insomnia, which found similar alteration in primary insomnia patients. Dong et al., in 2017, found significant decrease in functional neural connectivity between anterior DMN and posterior DMN in patients of primary insomnia, while Wang et al. found abnormal spontaneous activities in emotion-related areas of the DMN and Chen et al. found increased activation of the insula region of the DMN [74–76]. Brief description of earlier research in DMN in primary insomnia patients has been tabulated in Table 1 in our earlier publication [77]. Thus, it can be hypothesized that insomnia has similar neural substrates to various psychiatric disorders.

2.4 Role of Circadian Rhythm in Sleep and Psychiatric Disorders

2.4.1 Role of Circadian Profile

All the human organs and most human functions demonstrate circadian rhythmicity, due to which there is a profound influence of biorhythm regulating endogenous machinery on physical and mental functions [78–80]. Disruption of endogenous circadian rhythm has been strongly associated with psychiatric disorders, particularly mood disorders, and has been first demonstrated more than two decades ago [81, 82].

Disruption of circadian clock genes impairs sleep–wake cycle and social rhythm, which in turn affects cognition, mood and affect, emotion, and behavior, giving rise to psychiatric disorders [83]. Various mental disorders like seasonal affective disorder, depression, bipolar disorder including mania, nocturnal eating syndrome, schizophrenia, dementia, etc. have been related to temporal disorganization of biological functions [84].

There is increasing evidence now to conclude that blunted amplitude of the circadian profile is the main chronobiological abnormality in depression [85]. This may lead to depression in one of three ways [86, 87]:

1. Biological clock alterations at the molecular level could lead to neurobiological dysfunctions.
2. Primary circadian disturbance of the sleep–wake cycle may lead to insomnia which may precipitate, facilitate, or exacerbate a depressive episode.
3. Chronic stress, life events, or disease may bring unpredictable changes to the individual's circadian profile leading to depression.

The chronobiological model of depression is shown in Fig. 2.1 [79]. Various symptoms of depression, particularly the somatic symptoms like altered sleep–wake cycle, early morning low, evening slump, impaired daytime vigilance, and

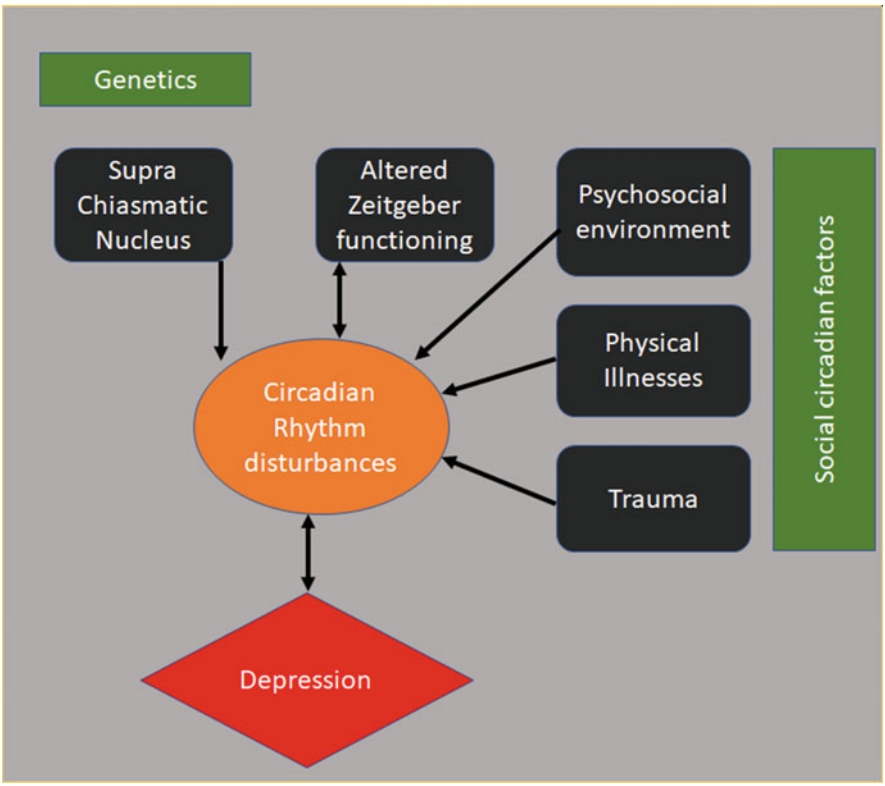

Fig. 2.1 Chronobiological model of depression

functioning, loss of appetite during physiological meal times, etc. have strong circadian underpinnings [79, 88].

Patients with schizophrenia showed blunted circadian variation of melatonin secretion, and forced desynchrony experiment in schizophrenia patients revealed an abnormal circadian propensity for sleep suggesting a disturbed circadian regulation [89, 90]. Furthermore, phase advances of prolactin, melatonin, and tryptophan secretion have been demonstrated in schizophrenia patients [91].

Patients with Alzheimer's dementia have shown reduced amplitude and increased fragmentation of the circadian rhythm of activity and reduced amplitude of the rhythms of melatonin and its metabolite 6-sulfatoxymelatonin [92–95].

2.4.2 Common Neurotransmitters and Pathways Underlying Circadian Processes and Psychiatric Disorders

The suprachiasmatic nucleus (SCN) is regarded as the circadian master clock which regulates the chronobiological rhythmicity of all the bodily organs and biological

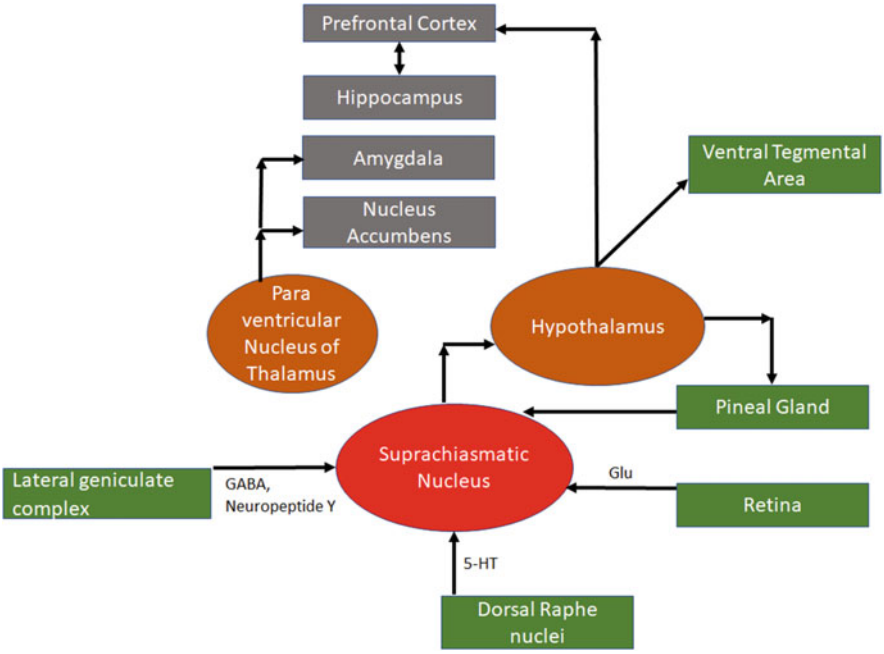

Fig. 2.2 Afferent and efferent connections of SCN

processes [96, 97]. The detailed process is described in Chap. 1 of this book. Light stimuli arriving at the retina are transmitted to the SCN, which further stimulates various processes downstream via various connections [98–100]. Figure 2.2 schematically describes the afferent and efferent connections of SCN [100].

Light stimuli arriving at the non-visual photoreceptive retinal ganglion cells are transmitted by the retinohypothalamic tract to the SCN via glutamatergic transmission [100]. Another tract runs from the lateral geniculate complex to the SCN and indirectly conveys light stimuli via GABA and neuropeptide Y [100].

Another strong synchronizer of the SCN is the serotonergic transmission from the raphe nucleus [98, 99]. The serotonergic system in the SCN is involved in entrainment and rhythm modulation through its receptors 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, and 5-HT7 and plays a key role in circadian clock resetting. 5-HT2C is the most important receptor in this regard having a circadian rhythm of expression and has the highest concentration in the SCN. It helps in potentiation of photic resetting along with photic-like effects (along with 5-HT3), while 5-HT1A and 5-HT7 receptors are implicated in the non-photic effects of the main clock [101–104].The efferent connection from the SCN reaches the amygdala and nucleus accumbens via the paraventricular thalamic nucleus, which may function as the circadian regulator of emotion and reward processing [100]. Another novel efferent pathway has been recently described from SCN to the ventral tegmental area (VTA)

via the median preoptic nucleus, which may function as the circadian regulator of behavioral processes like arousal and motivation [105].

Another circadian regulator is the hippocampus, which shows rhythmic gene expression relatively independent of the SCN, and has a pivotal role in neuroplasticity, learning, and memory [106].

These relevant neurotransmitters and receptors of the serotonergic system, GABAergic system, and the brain regions like hippocampus, amygdala, nucleus accumbens, hypothalamus, and thalamus are critically involved in the plethora of psychiatric disorders ranging from depression and anxiety to schizophrenia and Alzheimer's dementia, and their involvement in the circadian system does justify the hypotheses of shared underpinnings relevant to both psychiatric and sleep disorders.

2.4.3 Circadian Gene Variations Associated with Psychiatric Disorders

Another postulation is that the alterations of the molecular components of the endogenous clock system have a role in patients with psychiatric disorders, particularly mood disorders. The cellular machinery responsible for the circadian timing of the SCN is believed to be under genetic control and has largely been identified [107].

The essential elements of the clock include period (per1, per2, per3), circadian locomotor output cycles kaput (CLOCK), neuronal PAS domain protein-2 (NPAS2), cryptochrome (Cry1, Cry2), and brain and muscle ARNT-like-1 (bmal1) gene products. These proteins form a circadian autoregulatory loop by acting as activator and suppressor of genes. The activity of such genes therefore oscillates within a circadian period and generates the endogenous rhythmicity of the SCN neurons [100, 108].

Both animal and human studies have provided preliminary evidence for the role of circadian genes in the development of psychiatric disorders, particularly mood disorders [109–114].

CLOCK gene-mutated mice show behavior consistent with human mania, including decreased sleep, hyperactivity, lower anxiety, increased reward value for cocaine, and sucrose. Moreover, these behaviors are reverted by expressing a functional CLOCK protein in the VTA or by chronic lithium administration [114]. The "blind drunk" (Bdr) mouse line, which presents symptoms like schizophrenia, shows phase-advanced rest–activity cycles and a fragmentation of their circadian cycles [115].

In human studies, T3111C single-nucleotide polymorphism (SNP) of the CLOCK gene CC genotype has been associated with a higher recurrence of bipolar episodes and a reduced need for sleep in bipolar patients along with a greater severity of insomnia during antidepressant treatment [112, 113]. A family-based study of 46 SNPs in eight CLOCK genes revealed a modest but significant association of Bmal1 and time (TIM) genes with mood disorder [111]. A haplotype analysis study confirmed association of Bmal1 and per3 gene with bipolar disorder [110]. Also,

SNPs of per2, NPAS2, and Bmal1 genes are associated with an increased risk for seasonal affective disorder, and some of their effects were found to be additive [109]. Similarly, it has been observed that bipolar patients with the T/T allele of *GSK3* show an earlier age on onset of bipolar disorder and enjoy less improvement from lithium therapy than patients with the T/C or C/C alleles [116, 117].

Copy number variant in genetic coding for VIPR2 (Vasoactive intestinal polypeptide receptor) in the SCN has been found to increase the risk for the development of schizophrenia [118].

Likewise, three separate polymorphisms in the CLOCK gene have been associated with an increased risk of Alzheimer's disease [119–122]. Moreover, post-mortem pineal tissue of Alzheimer's patients did not show any evidence of day–night differences in CLOCK gene expression, pineal melatonin, melatonin synthesis activity, or β1-adrenergic receptor mRNA levels [123, 124].

Therefore, the genetic variations responsible for coding the molecular components of the endogenous clock system may be another important factor uniting the sleep problems and various psychiatric disorders.

2.5 Role of Stress as Modulator of Zeitgebers

The internal circadian clock is generated by the coordinated actions of a number of gene products, as described in Sect. 2.4.3. In sum, the transcription and translation of these genes are regulated positively or negatively by the sequential secretion of other gene products, creating a feedback loop whose net effect is a rhythmic oscillation in circadian protein levels in all nucleated cells in the body. As a whole, this feedback loop is "entrained" to the external environment by the influence of environmental factors which function as time cues (zeitgebers). The most important of these zeitgebers is light. Others include temperature, eating or drinking timings, and exercise.

The interaction of the body's stress response system with the circadian system continues to be elucidated [125–127]. The most important element in this interaction seems to be role played by the HPA, and particularly glucocorticoids.

Glucocorticoids such as cortisol have a well-demonstrated role in governing the stress response. Acute stress is associated with an immediate spike in CRH and adrenocorticotrophic hormone (ACTH) levels, which then leads to the synthesis of cortisol which peaks in the bloodstream around 30–60 min after the onset of stress. Serum cortisol also shows a diurnal variation, with a peak that is tightly coupled with an individual's habitual waking time [128–130]. Aside from there is also a phasic pattern of peaks and lows throughout the day, with individual peaks and troughs being 30–60 min apart.

At the low levels that persist through the majority of the daytime period, the secreted glucocorticoid is usually too low to bind with glucocorticoid receptors. Instead, the primary binding site is to the mineralocorticoid receptors that have a much smaller distribution within the body, but a greater binding affinity for circulating glucocorticoids.

It is hypothesized that these peak levels are a strong signal to maintain the circadian rhythm, and that glucocorticoids are as much a "circadian signal" as a signal of stress [128]. Under this hypothesis, one of the primary purposes of the HPA may be to convey time of day information from the SCN to the rest of the body, thus entraining peripheral tissue clocks to synchronize with the master clock in the SCN.

At a molecular level, cell cultures exposed to cortisol initiate cyclical production of CLOCK proteins, which are previously absent. At the organismal level, diurnal variations show a cortisol-mediated variability in stress responses. High cortisol levels protect against circadian phase changes induced by changes in certain time cues (e.g., food timing changes). Cortisol actions are also central to phase resets that occur in relation to rapid shifts in circadian phase (e.g., jet lag or shift work). Hypercortisolism is often seen as a result of such shifts and may be implicated in the increased risk of metabolic effects (hypertension, dyslipidemia, insulin resistance) seen in shift workers.

HPA abnormalities have been extensively studied in the pathophysiology of mental disorders [131], and this has been shown to have distinct patterns in different disorders, for example, schizophrenia and other psychotic disorders [132], bipolar affective disorder [133], and PTSD, with abnormalities being maximal with periods of illness exacerbation, but persisting into periods of remission for the mental disorder. These illnesses are also associated with sleep disturbances that are most prominent during illness exacerbations but persist into remission in a significant proportion of patients. Circadian rhythm disturbances are also noted across the range of these conditions.

A second system that has been implicated in the relationship between circadian rhythms and stress is the orexins (also called hypocretins). These excitatory neuropeptides are localized to neurons in parts of the hypothalamus, and the levels of activity of these neurons and the neuropeptides themselves are known to vary in response to circadian rhythm. The ramifications of these orexinergic neurons are wide, including the thalamus, cortex, brain stem, and spinal cord; inputs are important for arousal in response to stressors. Orexinergic neurons also project to the paraventricular nucleus of the hypothalamus and regular the release of CRH. Orexin abnormalities, particularly in the locus coeruleus, have a role in the organism's ability to control arousal and sleep cycles—blocking these effects leads to narcolepsy, characterized by pathological fragmentation of wakefulness. Similarly, blocking actions on the dorsal raphe nucleus lead to cataplexy. Orexin hyperactivity plays a role in causing insomnia.

Orexins have also been linked to the pathophysiology of MDD, with lower overall levels and reduced diurnal variation in cerebrospinal fluid (CSF) levels being reported. These effects improve with antidepressant treatment. Hyperactivity of this system may cause panic-like symptoms in animals, and a Val380Iso polymorphism in the orexin2 receptor has been linked to panic disorder in humans.

Orexins have also been implicated in drug-seeking behavior and addiction, with activation of these symptoms increasing preference for reward cues.

2.6 Behavioral Correlates of Psychiatric Disorders Impacting Sleep

Besides the characteristic sleep abnormalities associated with psychiatric conditions, sleep disturbance in those with mental illness may be attributed to behavioral symptoms that are seen in psychiatric illness.

Anxiety disorders are associated with states of autonomic hyperarousal. The elevated levels of norepinephrine and epinephrine associated with this state are inhibitory to sleep. Behavioral/cognitive manifestations such as restlessness and ruminations prevent the individual from winding down and may serve to maintain the hyperarousal. Similarly, psychotic states, fearfulness, may lead to similar hyperarousal. This state of hyperarousal is also associated with a specific alteration in sleep architecture. For example, in PTSD, there are changes in REM sleep as a proportion of total sleep time, as well as the overall phasic stability of REM, which may be related to the duration of the illness [134]. These changes may be responsible for the nightmares and frequent awakenings in this condition.

Interference due to psychiatric phenomena (such as hallucinations in psychosis or obsessions in OCD) may also interfere with sleep onset, as cognitively demanding activities are known to delay sleep onset [135].

Mental disorders are also known to disrupt routine in a number of ways. Certain aspects of these conditions cut across diagnostic boundaries but have profound impact upon the person's day—Social withdrawal, amotivation, and disorganization of food intake patterns, all have a final common outcome of disrupting Process S and Process C (described in Chap. 1) via complex pathways. As a result, many patients with these conditions have poor nighttime sleep with daytime somnolence, with a net reduction in sleep quality.

2.7 Role of Psychotropic Medications

Psychotropic medications may have impact on all three neuronal systems that play a part in sleep–wake regulation (i.e., the wake-promoting system, the REM-promoting system, and the NREM-promoting system).

The cholinergic, noradrenergic, dopaminergic, serotonergic, or histaminergic systems are all involved in promoting wakefulness. These systems are also targets of the actions of psychotropic medication, and thus changes to sleep are frequently associated with their use. Medications that act to promote NREM sleep also have sedative actions.

2.7.1 Sedative Hypnotics

At present, these medications are among the most prescribed psychotropics in multiple surveys of prescribing practices in primary care, among specialist physicians and psychiatrists [136]. Benzodiazepines or related drugs are often the

most commonly prescribed (alprazolam, diazepam, and lorazepam being most commonly used).

Insomnia is a frequent indication for these prescriptions, aside from anxiety disorders. In addition, they are often prescribed for symptomatic relief from agitation and anxiety associated with other mental disorders.

These medications exert their action by reducing arousal levels and promoting sleep (mostly by acting on the NREM-promoting systems) [137], through an increase in the inhibitory actions of GABAergic transmission. As a consequence, there are increases in total sleep time, sleep efficiency, and the proportion of slow-wave sleep. These are experienced by the individual as an increase in refreshing sleep.

However, longer term prescription of these medications engages adaptive responses that counteract these actions, reducing their effectiveness. These opponent processes also contribute to the withdrawal states experienced on sudden stoppage of these medications, limiting the effectiveness of these medications for chronic insomnia.

2.7.2 Antidepressants

Antidepressant medications have a range of effects on sleep. So-called "activating" medications such as fluoxetine and venlafaxine are associated with sleep disruptions, while others such as sedating tricyclic antidepressants are associated with an increase in total sleep time.

Actions that disrupt sleep are primarily related to these medications' actions on the 5-HT2A serotonin receptor, and increased norepinephrine and dopamine reuptake. Medications associated with these mechanisms, such as the serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and the activating tricyclic antidepressants (TCAS; e.g., imipramine, desipramine).

Other antidepressant medications have additional activity as histamine receptor blockers, including sedating TCAs (e.g., amitriptyline, doxepin), mirtazapine, mianserin, or as 5-HT2A antagonists (e.g., trazodone, nefazodone). These medications are associated with sedation.

In prescribing practice, most of these medications are associated with both treatment emergent insomnia and somnolence, possibly via interactions with the condition for which treatment is recommended.

The sedating medications are also associated with an increase in slow-wave sleep without much alteration in REM parameters. This effect is closely related to the serotonergic activity of the molecule. Those antidepressants that do not act directly via serotonergic pathways such as mirtazapine do not have such an effect [137].

2.7.3 Antipsychotics

Antipsychotic medications exert their pharmacodynamic action by blockage of the D_2 receptors, with or without actions on the 5-HT2 receptors. While these effects have direct consequences for sleep and wakefulness, these medications have activity on a range of other neurotransmitter systems that contribute to their tranquilizing effects. These include antihistamine, anticholinergic, and anti-glutamatergic actions. As discussed at length in earlier sections, these actions impact sleep–wake cycles profoundly.

Additional variations in these effects may be attributed to differences in pharmacokinetics of these drugs. As most of these medications have half-lives that are close to 24 h, they continue to exert sedative actions during the daytime, which contribute to daytime sedation.

Another frequent observation is that patients on these medications, particularly those on second-generation antipsychotics, are at an increased risk of obstructive sleep apnea (OSA). This increase in risk may be related to the weight gain mediated by histamine antagonism. However, other pathways that are independent of weight gain may also be at work [138].

2.7.4 Other Psychotropics

A host of other medication types are used in psychiatric practice. While many have sedative actions related to monoaminergic, cholinergic, or GABAergic antagonism, there are some that have distinct mechanisms of action. It is important to discuss two such classes: first, melatonin receptor modulators such as agomelatine, which is licensed as an antidepressant; and second, stimulants having varying activity by increasing catecholamine release.

2.8 Sleep Disorders Masquerading as Psychiatric Illnesses

The presenting complaint of persons suffering from sleep disorders is frequently unrelated to sleep. Instead, patients may focus on daytime consequences of poor nighttime sleep. The presenting complaints of these patients may range from daytime sedation or somnolence, fatiguability, reduced concentration or distractibility, reduced appetite, body pains, or psychological distress expressed as worrying, sad or irritable mood, and so on [139–141]. These symptoms feature in most diagnostic systems as criteria for the diagnosis of sleep disorders.In such situations, clinicians may focus on these presenting complaints, and mistakenly make a diagnosis of mental disorders such as somatic symptom disorder, anxiety disorders, or depression. In such a construction, the sleep disturbance is construed as a symptom of this mental disorder [142].

Illnesses that are particularly susceptible to this form of masquerade include OSA, where the nocturnal awakenings are seen as a sign of anxiety; or circadian

rhythm disturbances, where sleep onset delays and fixed waking times lead to reduced total sleep time and daytime sleepiness. These conditions may further be exacerbated by the use of psychotropics which may impact the sleep architecture. As described previously, antipsychotics and antidepressants are associated with weight gain and metabolic consequences that may worsen OSA [138].

Differentiating these conditions requires a systematic approach, including

Careful delineation of the specific symptoms associated with sleep apnea (snoring, snorting, respiratory distress on awakening, observed apneic, or hypopneic spells);

Investigations such as polysomnography (PSG) which show specific findings;

Eliciting transient improvements in daytime symptoms that occur after nights of restful sleep;

Therapeutic trials of specific treatments (e.g., continuous positive airway pressure) that also resolve the daytime symptoms.

2.9 Summary and Conclusion

In this chapter, the extensive literature on connections between sleep disturbance and mental illness are reviewed, in order to better understand why a variety of mental illnesses with disparate presentations, all commonly share the feature that they adversely affect sleep. This association has repeatedly been shown to be far more than that would be expected by chance alone.

Insomnia is a heritable condition, and this heritability has been shown to have an overlap with that of a range of psychiatric disorders, without being completely explained by them. The strongest such associations are with MDD and alcohol use disorders. However, a number of candidate genes linked with neural development and synaptic function have been shown to be associated with bipolar disorder and schizophrenia. The shared pathophysiology has been attributed to the functioning of neurotransmitters such as dopamine, whose actions on the reticular activating system are essential for maintaining arousal, but whose abnormalities have been documented both in primary insomnia conditions, as well as in the pathophysiology of neuropsychiatric disorders such as addictions, schizophrenia, and bipolar disorder. Experimental and observational evidence shows that neurotrophic factors such as BDNF (linked to the pathophysiology is implicated in MDD, anxiety disorders, PTSD, and cognitive decline) also have a role in regulating slow-wave sleep.

In terms of cerebral connections, sleep deprivation has been associated with the resting-state functional connectivity in circuits involving the amygdala and encompassing emotion, cognition, emotional regulation, and sensorimotor processes. These changes are also shared by social anxiety and MDD. Other circuit abnormalities are reported in the connectivity between corresponding areas of the bilateral hemispheres (aka homotypic connectivity). Functional imaging shows higher connectivity between anterior cingulate cortices among patients with primary

insomnia, which correlated positively with scores of self-rated depression and sleep onset latency.

At the level of larger cerebral networks, abnormalities in the so-called default mode networks have been identified as being part of the pathophysiology of a number of psychiatric disorders, including anxiety, depression, schizophrenia, and Alzheimer's dementia. Similar findings to those seen in these conditions are observed among patients with insomnia.

Circadian processes, that is, the regulation of sleep and arousal cycles in relation to the external environment, include a complex interplay between the expression of specific gene products in each cell of the body, and neurotransmitter, hormone, and other trophic factors that provide interoceptive and exteroceptive feedback to the organism. Monoamine neurotransmitters such as serotonin and GABA have a role in the entrainment process. Those with mental illness may have blunted circadian responses and involve parts of the brain such as the hippocampus, the hypothalamus, and specific thalamic nuclei that are central to the regulation of circadian rhythm. It appears that stress acts via alterations of the HPA to make the person less responsive to circadian signals, thus linking stress to insomnia.

Aside from these more or less direct connections, behavioral alterations arising out of mental illness may have more complex relations to insomnia. These include interference by symptoms such as hallucinations, fearfulness, worrying, or negative emotional states; physical hyperarousal; agitation; and disorganized patterns of sleep and food intake that interfere with the individuals' abilities to respond to time cues.

Apart from the biological and other effects due to illness, many psychotropic medications have direct effects on sleep, as their substrates, dopamine and serotonin, are directly involved in this regulation. Moreover, due to receptor non-selectivity, these medications also affect the levels of histamine and acetylcholine, which are both central to sleep–wake regulation.

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Biological Rhythm and Neuropsychiatric Disorders

3

Karuna Datta

Abstract

This chapter describes the concept of circadian rhythm in detail. The molecular clock mechanism of the master circadian clock and its interaction with central and peripheral clocks are explained. The chronobiological basis of neuropsychiatric disorders with available evidence regarding the circadian disruption in them along with the probable mechanism for the circadian disruption in these disorders is discussed.

Keywords

Circadian disruption · Neuropsychiatry · Social rhythm · Endocrine

3.1 Concept of Biological Rhythm

Biological rhythms are ubiquitously found among species and are a rather universal feature. These rhythms fluctuate rhythmically over a function of time with a peak time of the rhythm called '*acrophase* Φ', the *amplitude* of the rhythm which is the difference between the peak and the trough levels. It has a mean level, *mesor* and comprises *period* 'τ' which is the time difference between two-phase reference points (e.g. the time difference between two subsequent peaks or two subsequent troughs). It involves particularly a periodic function which may be associated with release of chemicals, neuropeptides or neurotransmitters; transcription or translation processes and activation or inhibition of regulatory substances, to name a few.

The main aim of this rhythm is to optimise the function of the organism with respect to itself, its surroundings and the requirements of the species. This may be

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attained by a basic biological clock pre-existent in the organism which may correspond to or respond to environmental changes. In other words, it makes the organism able to adapt to the change by resetting the clock in such a way that the organism has a better chance of survival.

The biological rhythm would have an endogenous mechanism to make an existent rhythm, an input mechanism which will make it aware of the environmental change and an output mechanism which will bring about change in the organism and also may be responsible to adapt the endogenous rhythm to the change. A study by Fukuhara, Tossini and Aguzzi showed that continuous red dim light on rats could uncouple the serum melatonin from circadian locomotor rhythm [1]. Endogenous rhythms are developed in the species as a result of evolution where anticipated environmental changes (e.g. temperature, light, availability of food, etc.) are synchronised to get an optimum physiology and behaviour apt to the time window every day.

There are many biological rhythms in a human body which may be ultradian, infradian or circadian. For this chapter, we will focus on the circadian rhythm and neuropsychiatric disorders.

3.2 Human Circadian Rhythm—Concept of Central and Peripheral Clocks

Circadian rhythm is a biological rhythm entrained predominantly by light. The reason for this link is probably related to survival of the species on this planet. Availability of prey for the predator, risk of predator from the prey and balance of the ecosystem for the species as per the day–night rhythm are all interrelated to survival. Species evolution happened maximally between the two tropics, making this area the most diverse. Most of the types of species are seen in this area.

In 1929, Fulton and Bailey had postulated an area in the anterior hypothalamus which regulated the timing of sleep in the 24 h of the day–night period. Later in 1972, the suprachiasmatic nucleus (SCN) was considered the site of a mammalian circadian pacemaker. SCN is also called the master clock for circadian rhythm [2, 3].

The word ‘circadian’ comes from ‘circa’ and ‘dian’ meaning ‘around a day’. Circadian rhythm is maintained by the master clock which has an inherent periodicity of a little over 24 h, being slightly more in males than females. There is a distinct afferent and efferent pathway intricately balancing specific functions which modulate behaviour, metabolism, sleep–wake time, release of hormones, release of neurotransmitters and neuropeptides, and produces temporal synchrony with peripheral clocks available in various tissues and organs of the body.

3.3 Anatomy and Physiology of Mammalian Circadian Rhythm and Effect of Its Interaction on Other Body Functions

The SCN in the hypothalamus is considered the central molecular clock or the master circadian clock for the human body. The anatomy and physiology of this master clock can be understood by looking at the molecular clock anatomy, its afferents, efferents and the physiological machinery linking to specific functions.

Available literature suggests that the SCN synchronises the peripheral clocks as a result of direct neural control, for example, SCN efferents to paraventricular nucleus of hypothalamus (PVH) which secretes Corticotropin-Releasing Hormone (CRH). CRH increases secretion of corticosteroids mediated by adrenocorticotropic hormone secretion on adrenals. PVH efferents end on the superior cervical ganglion that innervates the pineal gland to secrete melatonin. Both corticosteroid and melatonin exert their functions via endocrinal mechanism. SCN also has efferent projections to intergeniculate leaflet (IGL). IGL receives inputs from dorsomedial nucleus of hypothalamus (DMH), sub-paraventricular zone (SPZ), locus coeruleus, brain stem cholinergic area and midbrain raphe nuclei, and therefore IGL comprises non-photic stimuli and photic stimuli in the form of inputs from retina directly. IGL plays an important role as a modulator of circadian rhythm since its output goes to SCN itself, thus creating a feedback loop. SCN, as reported, also has another way of exerting its effects by secreting direct diffusible substances which probably controls locomotor activity, the exact mechanism of which is not clearly elaborated.

SCN acts on DMH directly and indirectly via SPZ. DMH activates the lateral hypothalamus which promotes arousal via wake-promoting neurons including orexin. DMH also inhibits ventrolateral preoptic area whose function is to inhibit the ascending arousal system. So, as a result of action of SCN on DMH, arousal occurs which alters the physiological state of the individual both physiologically and behaviourally including activation of the autonomic nervous system. DMH lesions produce elimination of the circadian rhythm of sleep–wake, feeding, locomotion and plasma corticosteroid levels, thus disrupting the intricate balance of central and peripheral clock harmony. DMH thus plays an important role in integrating circadian timing with physiological processes.

Apart from transmitting non-photic cues via serotonergic projections, midbrain raphe nuclei help glucocorticoids influence its output by driving the daily rhythm of tryptophan hydroxylase (enzyme required for serotonin synthesis) and also through geniculo-hypothalamic projections from IGL to SCN.

The necessity of integrating the circadian cues to physiological processes like sleep–wake state, feeding, metabolism, arousal, etc. are important to the species for survival. There are endogenous rhythms acting as biological clocks in tissues and organs (e.g. in adipose tissue regulating lipoprotein kinase, leptin, etc.), hepatic clock regulating blood glucose levels. These clocks are synchronised by SCN giving it the most important cue of light–dark and thus day or night, respectively. The effect of artificial lighting during night as well as long periods of darkness during winters thus affects the SCN and in turn the biological processes including both physiological and behavioural states.

Factors of internal milieu like metabolic state, plasma glucose levels, states of feeding or fasting, jet lag and core body temperature changes can make these peripheral clocks uncouple from the SCN. It implies that though the most potent stimulus which entrains these peripheral clocks is photic stimulus, they are also entrained by non-photic stimuli and can even desynchronise from SCN in case of aberrations between photic stimuli and non-photic information.

3.3.1 Role of Melatonin

First isolated in 1958 [4], melatonin is mainly secreted from the Pineal gland. Extrapineal sources of melatonin are also known, of which gut is of interest here. Tryptophan ingestion can affect secretion of melatonin in the gastrointestinal tract leading to an increase in melatonin level in blood causing a periodicity ascribed to food-related intake of tryptophan [5, 6].

In a normal human adult, the melatonin level starts to rise with dim light, also called as Dim Light Melatonin Onset (DLMO). It reaches its peak at about 2–4 a.m. and then tapers gradually in the latter part of the night. In the human foetus, maternal melatonin reaches through the placenta, and after birth it is provided through human milk and colostrum. Circadian rhythm of melatonin settles by the third to sixth month postpartum in the infant at which time the infant starts to develop continuous phases of sleep and wakefulness.

Melatonin acts on its receptors MT1 and MT2 to exert its effects. With melatonin, pronounced effects on sleep–wake cycle, namely, promoting sleepiness and shortening of sleep onset latency, are seen, associated with downregulation of core body temperature. Its effects are seen on circadian rhythm itself as it inhibits firing of SCN through MT1 receptors and MT2 receptors present on SCN, and help in phase setting of SCN master clock, thus completing the feedback loop. Melatonin acts as a time giver and causes endogenous synchronisation and reinforces oscillations and timing of circadian biological clocks all over the body [7] including synchronisation effects on cortisol and insulin secretion.

3.3.2 Role of Corticosteroids

Corticosteroids influence the circadian clock and also change the expression of clock genes in peripheral clocks. It plays an important role of ‘Time giver’ or ‘Resetting’ the clock. It can also explain the physiological and behavioural changes that occur in acute and chronic stress where corticosteroid levels are increased or in shift work or sleep deprivation where the corticosteroid rhythm gets altered.

On the other hand, corticosteroid can be altered by sympathoadrenal innervation (SCN) [8, 9]. ACTH can stimulate epinephrine secretion [10], and because of the effect of SCN, circadian oscillation of serum epinephrine and norepinephrine is documented [11]. This implies a crosstalk between hypothalamic–pituitary axis and autonomic system. This highlights the need for human studies for effects of acute

and chronic stress on circadian rhythm and the effect of circadian aberration or dysfunction on the autonomic system.

3.3.3 Molecular Mechanism of SCN

The molecular clock mechanism in any cell is primarily a transcription-translation feedback loop (TTFL). The core of the clock TTFL comprises genes—Brain and muscle arnt-like 1 *(Bmal1)*, Circadian locomotor output cycles kaput (*Clock*), Cryptochrome (*Cry*) 1–2 and Period (*Per*) 1–3.

In drosophila, core clock proteins primarily found are TIMELESS (TIM), CLOCK (CLK), CYCLE (CYC) and PERIOD (PER). The CLK/CYC heterodimer activates the transcription of hundreds of genes, including *tim* and *per* [12].

The BMAL1 and CLOCK proteins dimerise and enter the nucleus and bind to E box regulatory elements within promoters of *Cry* and *Per* genes. They also activate expression of clock-controlled genes. PER and CRY protein levels peak at dusk, and as it increases it inhibits BMAL1 CLOCK dimerise-mediated transcription of its genes. Recent studies have shown post-transcriptional regulation of these proteins which might help in buffering of the levels and the timekeeping mechanism as such [13].

PER and CRY phosphorylation can lead to its degradation. This phosphorylation of PER is done by Casein Kinase 1 (CK1) delta and epsilon-CK1δ and ε. CK1 regulates PER stability, influencing the period of the clock. Similarly, CRY can undergo phosphorylation which causes its degradation too.

In SCN, this molecular clock mechanism receives inputs from retinohypothalamic tract which innervate SCN core. Glutamate signalling causes CREB-mediated transcription of *Per* genes in SCN. Arousal influences can abruptly reduce *Per* expression.

Retinohypothalamic tract originates from melanopsin-containing ganglion cells in the retina which end on the SCN, anterior hypothalamus and IGL in thalamus. IGL projects to the SCN core and secretes Neuropeptide Y (NPY) and GABA. NPY causes phase shift in locomotor activity, and its action is attenuated by light. Midbrain raphe nuclei projecting to the SCN core releases serotonin which inhibits light effects on SCN. SCN core is predominantly for collating afferent information for pacemaker entrainment, and the shell has self-sustaining generation of circadian timing. The master clock then acts as a time information giver to all peripheral clocks and non-SCN clocks [14].

3.4 Chronobiological Basis of Neuropsychiatric Disorders

Observational studies report that circadian dysregulation is seen in many neuropsychiatric disorders. In seasonal affective disorder (SAD), a shift in melatonin release timing is seen and therefore leads to misalignment of the sleep–wake cycle and melatonin. In these cases, it is also postulated that there is a reduced sensitivity to

light as compared to normal controls. Reduced nocturnal melatonin secretion is seen in major depressive disorder, bipolar disorder and schizophrenia [15, 16] with a delayed melatonin peak secretion seen in major depressive disorder and bipolar disorder [15, 17, 18]. Schizophrenia was also called 'low melatonin syndrome' [16].

In depression, changes in DLMO and core body temperature are seen. These patients show early morning awakenings and reduced rapid eye movement sleep latency. The exact mechanism, though, is not certain. Bipolar disorders are known to show evening preference with reduced sleep–wake stability and reduced amplitude of activity.

A large number of studies have reported genetic modifications in the molecular clock genes among patients having psychiatric disorders. Studies using genome-wide associations have found CLOCK, BMAL1, PER3, and REV-ERB associated with bipolar disorder, major depressive disorder and SAD [19–21]. Single-nucleotide polymorphisms in core clock genes have been found to be associated with neuropsychiatric disorders [22].

3.4.1 Role of Social Rhythm and Its Association with Neuropsychiatric Disorders

Social rhythm includes social zeitgebers (i.e. demands and tasks which require interaction with person/persons, meal timings, bedtime, work time, exercise, etc.). Brown et al. [23] in 1996 had reported that sleep impairment was inversely proportional to the stability of social rhythm. Sleep disruption is found to be a common precipitant of manic and depressive episodes [24]. These disruptions in unipolar depression and bipolar disorders are also found to be linked with abnormality in the circadian rhythm pacemaker [25, 26]. Stetlar et al. [27] concluded that changes in activity patterns in the day changed biological rhythms, thus by altering the activity timing and pattern biological rhythm may be manipulated. Moreover, disease state and biorhythms influence the hormone secretion in the body that is associated with disease state. Patients with depression often have higher cortisol levels compared to controls. This is further manifested by the fact that non-depressed individuals showed greater reduction in cortisol levels with increase in daily activity as compared to depressed patients. There was evidence to suggest that depressed individuals have weaker circadian rhythm [28]. Considering an inherent weakness in the circadian function and a need to increase the amount of social activities to correct it made a foundation converge on to a theory of both internal and external triggers being implicated in affective episodes in vulnerable populations [29].

3.4.2 Circadian Rhythm Disruption in Neuropsychiatric Disorders

Circadian disruption at molecular and systemic levels is linked to sleep disorders, obesity, heart disease, cancer, psychiatric disorders and neurodegenerative disorders. The disruption may be in the molecular mechanism of the master clock itself, its

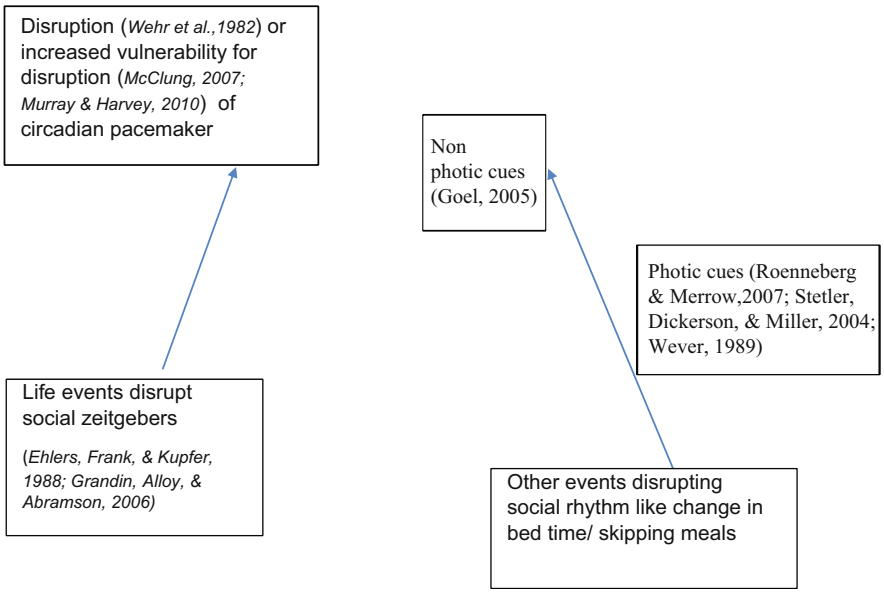

Fig. 3.1 Concept map showing the impact of social rhythm on circadian pacemaker with available literature

inputs, outputs or its effect on the peripheral clock. Further disruption of the regulators of this balance can also result in circadian disruption.

The social zeitgebers disrupt circadian pacemaker via photic and non-photic cues. Figure 3.1 shows a concept map of the available studies suggesting the impact of social rhythm on the circadian pacemaker.

In bipolar spectrum disorder patients, similar intensity life events are reported to produce more social life disruption [30]. Social rhythm irregularity is quite commonly seen in bipolar disorder type II patients and predicts the onset of depression episode [31] or first onset of bipolar spectrum disorder among at-risk adolescents [32]. Reduced regularity of social rhythm is also reported to predict the occurrence of major depression and hypomania or mania in bipolar disorder type II patients [33].

In fibroblasts from patients suffering from bipolar disorder, an increase in variance in period and amplitude in circadian rhythm was seen with deficits in entrainment of rhythm. Lithium carbonate, the drug of choice in these cases, targets Rev-erbα, which is an important promoter of Bmal1 [34]. In bipolar disorder, there was a difference found in the circadian system during mania and depression where melatonin levels were found to be higher in mania than in depression or normal controls. The *Per1* and *Nr1d1 (that encodes* Rev-erbA α) profiles were advanced in patients in mania, and expression of *Nr1d1* had a higher amplitude [35]. The circadian clock not only showed disruption but also varied in the different phases, probably implying an increased vulnerability. Evidence suggests that there is

an association to circadian genes such as CLOCK, ARNTL1, NPAS2, PER3 and NR1D1 for bipolar disorders, recurrent depressive disorders and seasonal affective disorders [17]. Per3 gene mutation is associated with seasonal depression. Light therapy works well in these patients which acts as zeitgeber and entrains the circadian rhythm. Abnormalities in the circadian clock and neuropsychiatric illness form a feedback loop where one gets disrupted and exacerbates the other.

There is a disruption of circadian rhythmicity and phasing of core clock genes in major depressive patients [36]. Agomelatine, melatonin agonist, is found to be effective in major depressive disorders implying the presence of a component of circadian dysregulation in this disorder which is corrected by melatonin agonists.

Dysregulation of circadian outputs has also been reported in schizophrenia. A loss of rhythm in CRY1 and PER1 expression was seen in the fibroblasts obtained from skin samples of chronic schizophrenia patients. In their leukocytes, reduced expression of CLOCK, PER3, CRY and functional clock homologue NPAS2 was found as compared to healthy controls. Majority of these patients reported to suffer from poor sleep [37]. This study showed that genetic aberration in the circadian system may be responsible for the sleep problems in schizophrenia patients.

It is also seen that neurodegenerative disorders like Parkinson's disease show sleep abnormality and also have non-motor symptoms which have an affective component. Recent studies showed that the circadian system not only directly or indirectly controls the sleep–wake timing but also had an effect on dopamine levels [38].

3.4.3 Probable Mechanism of Circadian Disruption and Neuropsychiatric Disorders

Circadian disorders and mood disorders were found to have a clinical association. A molecular link which can explain this association has been identified. The circadian genes have a role in dopamine synthesis and in its biodegradation [38].

Tyrosine hydroxylase is a rate-limiting step in conversion of L-tyrosine to L-DOPA. REV-ERBα directly reduces tyrosine hydroxylase expression, thus having a direct effect on its synthesis and in turn, reducing dopamine synthesis. Genetic deletion of Rev-erbα produced mania-like behaviour, and this was associated with increased midbrain dopaminergic tone. Dopaminergic tone in the ventral tegmental area leads to manipulation of CLOCK activity in this area. Per2 mutant mice show a less depressive state and have increased dopamine in the mesolimbic dopaminergic pathway by reducing monoamine oxidase (MAO A), an important enzyme for biodegradation of dopamine [39]. Core clock genes *Bmal* 1, *Per2* and *Rev-erbα* have circadian oscillation in the ventral tegmental area [40]. Thus, tyrosine hydroxylase shows circadian pattern [40, 41], and ventral tegmental area also shows diurnal variation in electrophysiological activity [42, 43].

Evidence available suggests that sleep impairment is an important predictor of onset of neuropsychiatric episodes. Circadian disruptions do occur in these disorders and can result from any of the or a combination of different phenomena that include

the alterations or deletions in circadian molecular clock genes as direct effect or indirectly manipulating circadian clock by sleep impairment or social zeitgebers affecting the clock. There is an association of genetic aberrations in molecular clock and dopamine release in the mesocorticolimbic area, implying the association of affective disorders to circadian aberrations.

Future studies and research will possibly aim at finding pharmacological and non-pharmacotherapeutic options where the exacerbation of neuropsychiatric disorders could be controlled by controlling zeitgebers like light, exercise time, bedtime, time of feeding, type of meals, temperature and self-awareness strategies. Considering inter-individual variations in the sensitivity to each of these, there is also a need to highlight an important role of individualised prescriptions in the future.

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Neurophysiology of Dreams

4

Nasreen Akhtar

Abstract

The first systematic accounts of dreams were made by Aristotle in 350 BC. In 1957, Dement demonstrated the occurrence of dreams during REM sleep. Numerous "theories" of dreams have been postulated in the twentieth century. Functional brain imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have begun to provide a spatial correlation between specific brain areas activation and deactivation and particular dream features. Activation of hippocampus and amygdala cause replay of memories and encoding and retrieval of emotional memories, respectively. Visual association areas exhibit a higher activation than the primary visual area during dreams, implying higher order processing without a primary visual stimulus. Anterior default network areas such as the dorsomedial prefrontal cortex show complete inactivity during REM sleep-dream states and are postulated to be responsible for the lack of insight during dreams. Emotional content of dreams is directly related to the extent of activation of the amygdala. Frontal alpha asymmetry has been reported as a correlate of anger during dreams. Combined evidence from neurophysiological, neuropsychological, neuroimaging, and intrinsic connectivity networks analysis have aided in the generation of a neurobiological model for REM sleep-dream generation.

Keywords

Dreams · Functional neuroimaging · REM sleep · Dorsomedial prefrontal cortex · Frontal alpha asymmetry · Amygdala

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Table 4.1 Historical aspects of the study of dreams

Year	Scientist	Finding
350 BC	Aristotle	First systematic account of dreams
1900	Sigmund Freud	Dreams have latent content and meaning
	Cartwright	
1938	Loomis et al	Dreams can occur with any type of sleep
1953	Nathaniel Kleitman and Eugene Aserinsky	Discovered REM sleep
1957	William C. Dement	Co-occurrence of dreams and REM sleep
1962	Foulkes	Dreams can occur in any stage of sleep
1962	Dement and Roffwarg	Scanning hypothesis
1977	Allan Hobson and McCarley	"Activation-synthesis" theory of dreams
1978	Rechtschaffen A	Dreams are not amenable to willful manipulation
1996	Calvin S. Hall	A "cognitive" theory of dreaming and dream symbolism
2000	Solms	REM is generated in the pons, dreams are generated in the forebrain
2013	Cartwright R	History of the study of dreams

Dreaming is a state of consciousness associated with visual imagery coupled with emotions, mimicking a story and punctuated with hallucinatory and bizarre experiences during sleep [1]. Most mammals manifest an identical state during dreaming [2]. In both dreaming and wake states, there is activation of the forebrain by the brainstem, the hypothalamus, and the basal forebrain ascending arousal system. However, the pattern of activation is what differentiates the wake state from the dream state. The limbic areas are activated more in contrast to that of the higher level cognitive areas during dream state, resulting in emotionally laden random experiences during dreams. On the other hand, wakefulness is characterized by rational thinking that usually overrides emotions.

The historical aspects of the study of dreams have been depicted in Table 4.1. The earliest accounts of dreams started with Rig Veda in 4000–6000 BC where nightmares as well as waking dreams are explained. In 1500 BC, Atharva Veda describes the significance of the content of dreams [2]. Later, Aristotle also described the theory of dreams in 350 BC. In the modern period, Freud elaborated a complex dream theory to understand the unconscious mind to interpret the "manifest" appearance of a dream in terms of its "latent" content and meaning. Even though this theory remains largely discredited today, it brought the focus from dreams being a voice of gods or prophecies of the future to a place where they belong based on current understanding-in the brain. Cartwright [3] summarized the history of scientific study of dreams starting in the 1950s by dividing the studies on the basis of their hypotheses. The scientific era of hypothesis-based biological, laboratory-based dream research can be said to have begun in 1953 when Rapid Eye Movement (REM) sleep was discovered by Nathaniel Kleitman and Eugene Aserinsky [4]. Its characteristic features were described as periods of rapid eye movements, wake-like

Table 4.2 Classification of common dream content

S. No.	Dream content based on the conceptions of
1	Self
2	Other people
3	The world
4	Impulses, prohibitions, and penalties
5	Problems and conflicts

low-voltage electroencephalogram (EEG) waves, and very low muscle tone that recurred through the night in cycles of one and half hours or 90 min and were associated with the occurrence of dreams. They reported 50 awakenings from REM sleep proving reliable and exclusive occurrence of dreaming during REM sleep. This led to the assumption for a considerable time to come that REM sleep provided an "objective measure" of dreaming and upon awakening a report on dreaming can be reliably collected. These reports showed negligible dreaming during non-REM (NREM) sleep, tying the dream state strongly to the REM state, shifting the focus to the causes of REM sleep and the areas responsible for its generation being responsible for generation of dreams. In 1959, Michael Juvet [5] established the origin of REM sleep in the pons through his work on chronic decorticate and mesencephalic cats. In 1966, Calvin S. Hall published a classification system for content analysis of dreams as depicted in Table 4.2 [6].

A "cognitive" theory of dreaming and dream symbolism was proposed by Calvin S. Hall [7]. William C. Dement [8] established firmly the co-occurrence of dreams and REM sleep. This has been a field where there has been substantial overlap of REM sleep and the dream state. And a fundamental question in this context has been whether REM sleep is a necessary or a sufficient condition of dreaming as an experience [9].

In 1938, much before the discovery of REM sleep by Aserinsky, Loomis and his group gave an alphabetic classification of the stages of electroencephalographic (EEG) sleep stages [10] and reported that "dreams may occur in association with any type of sleep potential pattern." It was subsequently reported in the research during 30s and 40s that non-REM sleep may also have dream manifestations, though their plots may be less elaborate [11]. Foulkes during his extensive research on the recall of dreams during REM awakenings [9] pushed awakenings back into pre-REM epochs of non-REM sleep and found no point at which dream recall ceased, thus concluding that dreaming might be more or less continuous during sleep. The "Scanning hypothesis" given by Dement in a collaborative study with Roffwarg [12] suggested that the pre-awakening eye movements and the dreamer's report were associated with each other. Later, it was proved as flawed in methodology and subsequently was explained in terms of phasic versus tonic differences of REM sleep mentation [13]. There were attempts to manipulate the REM dream content with both pre-sleep manipulations such as fluid deprivation and during REM sleep with a tone, some light, or sprays of water. The most general conclusion reached from the varied manipulations was that dreams are relatively autonomous, or "isolated" [14] and are not amenable to willful manipulation.

Allan Hobson and McCarley proposed an "Activation-synthesis" theory of dreams in 1977 [15]. They postulated that specific regions in the forebrain store memories in the wake state. During sleep, there is activity generation in the pontine brainstem, which in turn activates the forebrain region. In the absence of sensory input and motor output during sleep, the pontine activation of the forebrain creates spatiotemporal aspects of dreams imagery from the daytime stored memories. This is akin to a post-hoc version created by the forebrain of the signals generated from the pons during REM sleep. It stressed the bizarreness of dream experience and traced this property to phasic activity unique to REM sleep. The activation-synthesis theory formed the neurobiological model for a considerable length of time. It was subsequently modified to the "activation-input-modulation" theory [16]. Solms [17] reported almost 1000 cases of forebrain lesions where the patients reported no dreams. In these patients, the REM generating areas of the pons were intact. He even attempted to localize brain areas to certain features of dreams like color or people by comparing large samples of dreams in post-surgery or post-lesion patients with normal dream reports. He concluded that the mechanism of REM sleep generation and that of dreams are different. REM is generated in the pons, whereas dreams have a generator in the forebrain. The Solms group recorded 23 dream reports from 8 cases of a very rare genetic disorder called Urbach–Wiethe Disease (UWD) [18]. The disease causes bilateral calcification of the basolateral amygdala. They have compared this to 52 reports collected from 17 controls. They found that the UWD patients' dreams were more pleasant, shorter, and less complicated than dream reports from controls. Based on observations, it was concluded that the basolateral amygdala has a role in emotional and affect aspects of dreams and dream reports. This has raised doubts over the dream theories that disregard the role of amygdala in sleep, then followed the era of neuroimaging and cognitive neuronal networks that will form a part of the theories of dreams in subsequent sections.

4.1 Functional Neuroimaging

Functional neuroimaging of dreams poses certain challenges to the study of dreams. First, unlike the wake state, where the participant can signal the beginning of the event, for example, pain stimuli, this can be tied to the onset of the co-occurring physiological signs such as sympathetic activation, and during dreaming, external event markers such as electrooculogram or imaging changes cannot be linked reliably to the internal events like images or emotions transpiring during dreaming. Positron emission tomography (PET) studies began to provide data regarding neuro-anatomical activation during different dream characteristics in contrast to the awake state in the late 1990s [19–21]. However, structural imaging of brain also provided important information about the neuro-anatomical basis of dreaming.

Microstructure analysis and Diffusion Tensor Imaging (DTI) analysis of the magnetic resonance images have been used extensively [22–24] to delineate the structures underlying the dream process. Recently, it has been used in assessment of

the activation of hippocampus and amygdala during sleep. The hippocampus plays a role in partial replay of memories of wakefulness, which have long been held responsible for the content of dreams [19]. Control of encoding and retrieval of emotional memories may be mediated by amygdala, explaining its activation during sleep [20]. Fear memories are especially triggered during dreams by the involvement of both amygdala and hippocampus. The differences in brain tissue of the hippocampus–amygdala complex are related to inter-individual differences in emotional content and bizarreness of dreams [1].

Functional brain imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have begun to provide a spatial correlation between specific brain areas' activation and deactivation and particular dream features. Maquet et al. [21] have reported the areas activated and deactivated during REM and slow-wave sleep [25] by using PET scanning and statistical parametric mapping. They reported an increased activation in medial prefrontal, orbitofrontal and paracingulate cortex, basal ganglia, hypothalamus, pons and midbrain, thalamus, ventral striatum, and midline limbic and paralimbic areas [19, 26] during REM sleep as compared to non-REM sleep, whereas dorsolateral prefrontal cortex (dlPFC) has shown reduction in activation upon transition into REM from NREM state. Braun and Dang [19] reported decreased activity in primary visual cortex in contrast to increased activity in occipitotemporal visual cortex and visual association areas during dreaming. This implies a higher order processing of visual imagery during dreams without the primary visual stimulus and without activation of the primary visual area.

Functional imaging of dream state has been compared to resting wakefulness states during mind wandering and daydreaming and has been used to strengthen the neural correlates of dreaming. Some dreams like features such as visual imagery and bizarreness had been observed in states other than REM, in particular, during wakefulness with a resting mind, onset of NREM stage 2, in early hours of morning, and late in the night. In particular, increased activation of dorsomedial prefrontal cortex (dmPFC) was seen during unfocused thinking in contrast to task-focused thought processes [27]. Some PET studies have reported decreased activity in posterior parietal default network areas including lateral inferior parietal and posterior part of cingulate cortex during dreaming [28]. Areas that are part of anterior default network areas, ventromedial prefrontal cortex (vmPFC), and portions of dmPFC, hippocampal, and parahippocampal areas express incomplete activity during REM sleep-dream states [28]. In different studies, default mode network (DMN) has exhibited both increased [23] and decreased [24] connectivities between its nodes. There are two subsystems of the DMN, postulated to serve particular functions during dream generation. The simulation subsystem or the medial temporal lobe subsystem is centered around the hippocampal formation. Increased activity in this area during REM sleep as compared to non-REM may indicate its active role in dream generation [1]. In contrast, the dmPFC shows complete inactivity during REM [24] and is postulated to be responsible for the lack of insight during dreams,

Table 4.3 Areas responsible for specific features of dreams

Cortical areas	**Dream component**
1. Anterior cingulate cortex and orbitofrontal cortex	Emotional content of dreams
2. Activation of occipitotemporal visual cortex	Visual dream imagery
3. Inactivation of dorsolateral prefrontal cortex	Lack of logical reasoning, altered working memory, episodic memory, and executive functions
4. Mesiotemporal areas like the hippocampus	Access to episodic memory from wake state
Frontal alpha asymmetry	Anger
Subcortical areas	**Dream component**
1. Amygdala complex	Emotional load of dreams and dream recall
2. Rhinal hippocampus area	Consolidation of dream content and memory access

causing a lack of rational and logical thinking during dreaming, an activity fully functional during waking cognitive state [29].

Subcortical nuclei have also been found contributing to dreaming in neuroimaging studies. Limbic and paralimbic areas show enhanced activation during REM sleep [21], indicating a complementary role for hippocampal nuclei and amygdala complex in dream phenomenology.

Emotional content of dreams is directly related to the extent of activation of the amygdala [30]. MRI study with diffusion tensor imaging (DTI) analysis among healthy subjects reported direct correlation of the emotional content and bizarreness of dreams reports to the differential mass of hippocampal amygdala complex [31]. Thus, dopaminergic mesolimbic dopaminergic system changes the qualitative aspects of the dream phenomenon.

In order to assess the dream effect, Sikka et al. [32] have examined frontal alpha asymmetry and the difference in alpha power between left and right frontal cortex. Dream report was analyzed by awakening after REM episodes and analyzing previous 5 min of EEG. Frontal alpha asymmetry has been reported as a correlate of anger during sleep. It is of interest to note that during wake state, frontal alpha asymmetry has been used as a marker of emotional processing and regulation. During dreaming, anger is associated with increased alpha power implying decreased activity in right frontal cortex. Kamitani et al. [33] have used machine learning models to decode the visual imagery of dreams. They have compared patterns of brain activity during specific visualizations during wake state and used the same to deduce the dream content from patterns of brain activity during dreaming.

A neurobiological model of dreaming has emerged from neuroimaging studies. These models provide an insight into the areas responsible for the specific feature of dreams [1, 34, 35]. The areas are summarized in Table 4.3 [26].

4.2 Neurotransmitters of Dream Generation

Neuromodulation related to sleep–wake cycle within the brain is regulated mainly by at least five different neurotransmitters—acetylcholine, serotonin, norepinephrine, dopamine, and histamine, with modulating effects from adenosine and orexin [16], which are described in detail in Chap. 1.

Acetylcholine, serotonin, and norepinephrine play the major role in transition from wake to NREM and then to REM sleep. Dream state and wake state are differentiated by three neurochemical hypotheses. First is proposed by Hobson and colleagues—activation-synthesis [15] and activation-input-modulation (AIM) hypothesis [16]. In the AIM model, Hobson et al. [16] have proposed a marked physiological difference between wake, REM, and NREM states. There is a marked shift in modulatory balance from an aminergic dominance in wakefulness to cholinergic predominance in REM sleep of animals. They called this modulatory factor M and defined it as the ratio of aminergic to cholinergic influence upon the brain. Hobson et al. [16] also suggested that the dream consciousness originates from the substantial increase in cholinergic (relative to noradrenergic and serotonergic) activation from ascending reticular activating system during REM sleep. In the second hypothesis, Solms [17] explained dream initiation by the "reward activation model." According to this model, stimulation of limbic and prefrontal reward networks by dopaminergic projections from ventral tegmental area (VTA) in the midbrain activates the amygdala, anterior cingulate gyrus, and frontal cortex. This dopaminergic stimulation leads to dreaming. Various forms of cortical activation occur in both REM and NREM, and the final common pathway is activation of cortical circuits. Thus, according to Solms [17], dreaming is not exclusive to REM. The third model, proposed by Gottesmann [36], is "monoaminergic disinhibition hypothesis" suggesting that dopaminergic stimulation of the cortex during REM sleep is responsible for the psychotomimetic aspects of dream consciousness, particularly in the absence of the inhibitory serotonergic and noradrenergic modulation of the wake state.

These three models propose neurochemical hypotheses of dream generation with each theory propagating a different chief modulator of dream occurrence.

4.2.1 Acetylcholine

The activation-input-modulation model by Hobson et al. [16] suggests that the increase in activity of the forebrain during REM sleep-dreams is mediated by ascending activation of the mesopontine cholinergic nuclei. There is ample evidence that acetylcholine concentrations in thalamus and lateral geniculate nucleus are higher during wake and REM states as compared to NREM and are derived from mesopontine and brainstem cholinergic activity [37]. As a further evidence, REM sleep with dreaming can be induced by cholinesterase inhibitors. They also increase nightmares and hypnagogic hallucinations [29].

4.2.2 Dopamine

The effects of dopamine on dreams are dependent upon its dosage, type of receptor-stimulated, and its location. The reward-based theories of dreaming suggest that the prominent memories are first replayed and prioritized by the hippocampal–ventral striatal circuits during NREM sleep and subsequently selectively processed during dreaming. The support for this comes from the fact that there is selective consolidation of prominent memories during sleep and elimination of this selectivity by administration of dopamine agonists [29]. L-Dopa enhances dreaming in Parkinson's disease patients [38]. Remarkably, the effects of dopamine are varied and could be related to a subtype of dopamine postsynaptic receptors in a specific brain area. For example, psychostimulants do not increase dreaming; neuroleptics do not prevent dreaming and dopamine agonists and antagonists have variable effects.

Animal studies have also provided the basis for the role of dopamine in dreams. Dopamine concentrations in medial PFC and nucleus accumbens are greater during REM sleep than NREM sleep, and enhancing REM sleep intensity increases the c-Fos expression in the VTA [39]. Thus, animal studies have helped to firmly establish the role of dopamine in sleep.

4.2.3 Serotonin

Evidence connecting the influence of serotonin on the cortex is still ambiguous. The naturally occurring lowest levels of serotonin are seen in REM sleep, and transitions of sleep stages are associated with a fluctuation of these levels [29]. Hallucinosis during dreaming may be associated with the low serotonin levels.

In the AIM model [16], Hobson et al. referred to modulation as the comparative rate of firing or quantity of neurotransmitter release from locus coeruleus (norepinephrine) and raphe neurons (serotonergic) to that of ponto-geniculo-occipital (PGO) burst cells (cholinergic). Animal models have demonstrated state-dependent shifts of this activity extensively [40–42]. Human studies have failed to provide direct evidence due to methodological constraints, but indirect evidence is quite confirmatory [43]. Awake experiments with neuromodulating drugs administration have provided evidence of this effect [44]. Cholinergic drugs [44] enhance REM sleep and aminergic modulators [45] suppress REM and have alerting effects. Overall, the evidence suggests that neuromodulation of REM sleep is homologous to that in animals.

Gottesmann [36] has given an equation for mentation in dream state as

Dopamine alone cannot explain the psychotic-like mental functioning of dreaming because of identical firing of dopaminergic neurons during waking without such pathological mentation. The silence of noradrenergic neurons during REM sleep could exaggerate the cortical dopaminergic influence. Cortical disinhibition linked to the silence of serotonergic neurons seems to be accompanied by decreased dopamine release due to suppression of an action on postsynaptic 5-HT_{1A} receptors.

4.3 A Descriptive Neural Model of Dream Phenomenology and Function

A neurobiological model will assume the premise that the events in the brain at molecular and cellular levels produce the conscious state differences between the wake, REM, and non-REM. Combining the evidence from neurophysiological, neuropsychological, neuroimaging, and intrinsic connectivity networks, analyses have aided in the generation of a neurobiological model (Fig. 4.1) for REM sleep-dream phenomenology. Originally proposed by Hobson and Pace-Shott [16] in 2000, it has been updated with recent evidences [29].

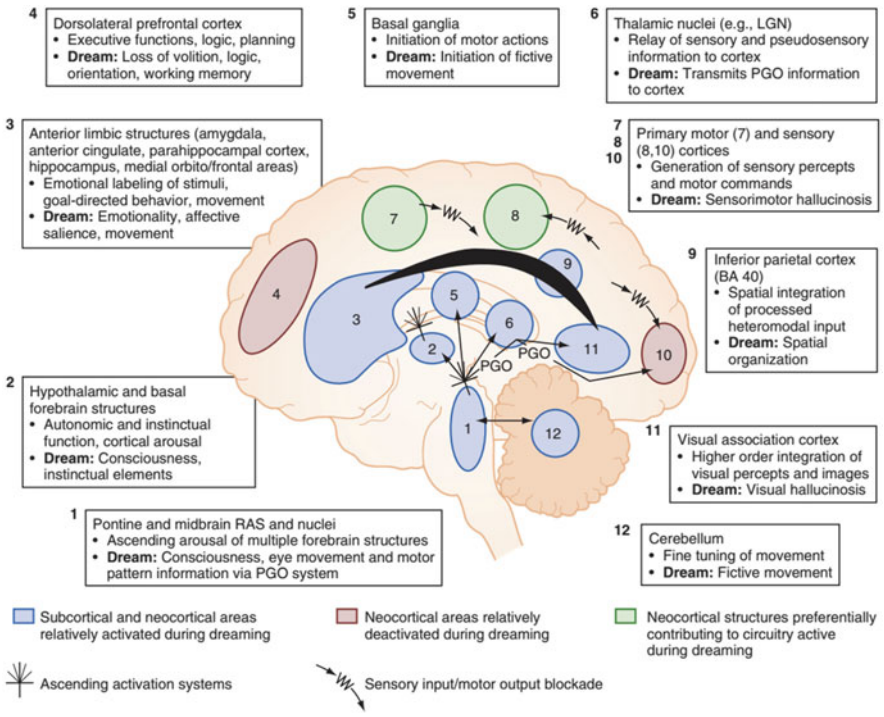

Fig. 4.1 Cortical and subcortical areas in dreaming. Areas 1 and 2, ascending arousal systems; area 3, subcortical and cortical limbic and paralimbic structures; area 4, dorsolateral prefrontal cortex; area 5, motor initiation and control centers; area 6, thalamocortical relay centers and thalamic cortical circuitry; area 7, primary motor cortex; area 8, primary sensory cortex; area 9, inferior parietal lobe; area 10, primary visual cortex; area 11, visual association cortex; area 12, cerebellum. *BA40* Brodmann area 40, the temporoparietal junction, *LGN* lateral geniculate nucleus, *PGO* ponto-geniculo-occipital waves, *RAS* reticular activating system. (With permission, from Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Sixth edition. Philadelphia, PA: Elsevier; 2017. 535 p)

4.4 Areas 1 and 2: Ascending Arousal Systems

Ascending arousal systems of the brainstem [46], basal forebrain [47], and hypothalamus [48] cause activation of the forebrain in both REM and wakefulness (regions 1 and 2, Fig. 4.1). The difference between the two states lies in preponderance of ascending cholinergic activation from the thalamus and the basal forebrain and attenuation of the aminergic systems during REM [16]. Pedunculopontine nuclei in upper part of pons and laterodorsal tegmental nuclei activate the thalamus and basal forebrain via cholinergic pathways [49]. Thalamus and basal forebrain structures in turn activate the cortex via glutamatergic and cholinergic pathways. These ascending arousal systems may be transiently activated during NREM and manifest as NREM dreams. A recent PET study has shown that pre-awakening REM sleep is directly related to dream recall on awakening [29].

4.5 Area 3: Limbic Areas

Activation of region 3 in Fig. 4.1 occurs selectively during REM sleep in PET scans. These are the limbic and paralimbic cortical and subcortical regions [19, 20, 25]. This may imply a role for REM sleep in processing of emotionally charged memories [50], integration of hypothalamic and basal forebrain reward mechanisms with cortical functions, or internal processing between visual association areas and limbic regions [20]. Such a process may form the basis of emotionality and social nature of dreaming [51].

4.5.1 Emotional Regulation and Dreaming

Dreams have a high activation of the areas involved in experience and expression of emotions: the anterior paralimbic regions. Dreams have been allocated the role of maintaining the emotional homeostasis by dual mechanism: One, resolution of intrapersonal conflicts, and the other by moderating emotional extremes by the processes of habituation and extinction [52]. This emotional regulatory function of dreams may be disrupted in mood and anxiety disorders and can cause nightmares. Mesolimbic and mesocortical dopamine is released by VTA sources upon activation of ascending cholinergic pathways [53]. They form a part of the anterior paralimbic REM sleep activation region as a part of reward systems. Social skills development and refinement may be occurring in sleep as evidenced by the activation of residual self-referential subsystem during dreams. The “rehearsal” of difficult emotions, difficult people, and difficult circumstances during dreams may help to deal with similar difficulties during daytime.

4.5.2 Differential Processing of Episodic and Declarative Memory

There is paucity of access to episodic memories during dreams. This may be attributed to cholinergic mechanisms mediating an informational barrier between hippocampus and cortex during REM sleep [54]. But the ease of access to another form of declarative memory—"familiarity" or "recognition"—is common in dreams. There is disconnection of temporal lobe face recognition from prefrontal reality monitoring regions during dreams. In cognitive neuroscience, double dissociation is an experimental technique by which two areas of neocortex are functionally dissociated by two behavioral tests, each test being affected by a lesion in one zone and not the other. A double dissociation between recognition and familiarity has been shown in fMRI studies during memory formation [55]. This may contribute to familiarity with persons in dreams despite a lack of facial recognition and a clear access to episodic memory.

Entire memories may not be incorporated in dreams but based on the emotional cues attached to them, parts of the memories may be accessed in dreams. Activity in DMN suggests that dreams rehearse or simulate anticipated future events to prepare for them [56].

4.6 Area 4: Dorsolateral Prefrontal Executive Control Cortex

These areas remain deactivated during REM sleep, and their lesions do not cause alterations of dream experience. It appears that they may be inessential for the dream process. Their inactivation may be responsible for the lack of executive functions during sleep leading to lack of orientation, logic, working memory deficits, and memory loss for dreams [16]. EEG and magnetoencephalography studies also point to a deactivation of dlPFC area leading to disinhibition of the posterior sensory cortex areas, hence promoting dreaming [57].

Default mode network analysis provides similar findings. There is absence of dorsomedial prefrontal cortex (dmPFC) area activation during REM. The activation of dmPFC is associated with logical thinking and dreaming, during which REM is associated with lowest level of logical thinking among all arousal states. The bizarre nature of dreaming with illogical thinking as compared to waking cognition may be attributed to the incomplete reconnectivity of the dmPFC with other DMN network subsystems such as bilateral inferior/middle temporal gyrus during REM sleep [24].

The PFC aid in creation of a focus by attenuating the functioning of other simultaneously activated networks. This "top-down" influence can sensitize primary and association cortices to certain stimuli while attenuating the effect of others. Its deactivation during REM may lead to sensitivity bias of sensory cortices to hallucinatory constructs related to social and emotional processing [16]. The non-emotional imagery may fail to persist due to ineffective working memory.

4.7 Area 5: Basal Ganglia

Basal ganglia are responsible for motor initiation and control. They are extensively connected with motor cortex and pedunculopontine nuclei that contain gait circuitry and other motor pattern generators and REM sleep regulators. A strong activation of basal ganglia (region 5 in Fig. 4.1) may be linked to generation of movements during sleep [16]. Vestibular sensations, such as falling or flying, and the sense of motor control may be linked to the activation of brainstem vestibular nuclei and the associated cerebellar vermis [19].

4.8 Areas 6 and 11: Thalamocortical Relay Centers and Thalamic Subcortical Circuitry

All the sensory inputs except olfaction are relayed to the cortex via the thalamus. During REM sleep, primary and secondary association sensory cortices (region 11) may interpret the thalamocortical signaling (region 6) as incoming sensory signaling. This may activate the local stored cognitive representations and appear as hallucinosis of known entities or if it is unfamiliar, it will manifest as bizarreness of dreams. Thalamus is connected to cortex via a non-relay sensory route through pulvinar nucleus to visual association cortex or to limbic prefrontal regions through magnocellular portions of the mediodorsal nucleus, among others [58].

Endogenous activity of cortico-cortical and corticothalamic circuits form the oscillatory rhythms of NREM sleep. The upstates of these rhythms return the cortical neurons to a high level of activation. Striade et al. [46] attributed visual imagery in NREM to the transient elevation of regional cortical activity by the phasic thalamocortical bursts such as PGO waves during NREM-REM sleep transitional states. NREM sleep imagery may also be generated by activation of primary visual and visual association areas [59].

4.9 Area 9: Inferior Parietal Lobe

Studies have reported no dream reports in patients with selective lesions of the supramarginal and inferior parietal gyri of inferior parietal lobe, more prominently in the right hemisphere (Region 9 of Fig. 4.1). They are associated with visuospatial awareness. An imaginative dream space may be generated by these areas which is necessary for the organized hallucinatory experience of dreaming [60]. Self-centered reality simulation may be occurring due to the activation of the vmPFC and simultaneously, visual association areas give rise to hallucinatory images. Inferior parietal multimodal association cortical areas add different dimensions of sensory inputs to the ongoing dream scenario [29].

4.10 Area 11: Visual Association Cortex

Visual imagery of dreams may be arising from activation of visual association areas including medial occipitotemporal cortices during REM sleep [19] (region 11 in Fig. 4.1). Specific regional activation may sub-serve specific visual characteristics. Fusiform gyrus activation during REM may mediate face recognition. Braun and colleagues suggest that the neural basis of dreaming continues to be drawn largely from studies of REM and so far, no mechanistic models of NREM dreams have been proposed.

4.11 Summary

High emotional content of dreams arises from higher activation of limbic system in the absence of logical thinking. Deactivation of dlPFC and dmPFC leads to disinhibition of sensory cortices, leading to a sensory experience in the absence of external sensory inputs and lack of logical reasoning, respectively. REM state dreams consist of internal processing of visual information without the inputs from the primary visual areas and without the outputs through the frontal cortex to the external world. This internal processing occurs between the limbic areas and the visual association areas. The ascending activation onto visual and multimodal association areas in occipital, temporal, and inferior parietal areas may be giving rise to the formation of images during dreams.

4.12 Future Aspects

The elucidation of non-REM dream mechanisms needs to be done. The phenomenon of lucid dreaming is being extensively used to study and manipulate dream content and must be explored further. Another fertile field is reconstruction of the images and emotions crossing the mind during sleep from physiological signals arising from the brain.

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Dream Consciousness and the Brain: Relevance to Psychopathology

5

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"If we could imagine a dreamer walking around and acting his own dream as if he were awake, we would see the clinical picture of dementia praecox" (Carl Gustav Jung, The psychology of dementia praecox, 1909).
"The modalities of thinking of schizophrenic subjects are very similar to dreaming".
"Most of the characteristics of schizophrenic thinking (particularly delusional thinking) are explained by the differences between the dreaming and the wakefulness way of thinking" (Eugen Bleuler, Dementia praecox or the group of schizophrenias, 1950).
"In spite of a lifetime of discriminating between dreams and reality, we can make the discrimination only after awakening. Identifying the neural substrates that are responsible for critical self reflection during wakefulness, and that fail us

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while dreaming, is a major challenge for sleep and dream research" (Allan Rechtschaffen and Jerome Siegel, Sleep and dreaming in Principles of Neural Science, 2000).

Abstract

Dreaming has progressively been marginalized in modern clinical approaches to the mental health and psychopathology. Scientific interest in dreams survived, only partially in the field of sleep and consciousness research, where the study of subjective experiences when the brain is disengaged from environmental stimuli may contribute to investigate the neural correlates of consciousness. Nonetheless, progression of knowledge on the dreaming brain/mind was recently employed to model pathological mental phenomena such as psychosis. Indeed, a phenomenological overlap between dreams and psychosis has been described since antiquity. The loosening of associations and disorganization of speech, the pervasiveness of one's hallucinatory experience and lack of insight on the internal origin of incoherent and incongruous mental contents are among several shared phenomena between dreams and psychosis. Bizarreness quantified in dream and fantasy reports was found to be inversely proportional to the neural response of a right fronto-temporal network activated during the script-driven recall of these experiences in healthy volunteers, suggesting a role for these circuits in the dreamlike bizarreness of psychotic patients' waking mentation. Other available neuroimaging studies also suggest that self-monitoring failure experienced during dreams and lack of insight in psychosis share the disengagement of the same frontal circuitry. However, incorporation of consciousness, psychosis and dream research in a "neuro-phenomenological" or "multi-level" framework remains speculative, and further work is needed to overcome many methodological limitations and to rigorously approach this fascinating field of enquiry.

Keywords

Dreams · Psychosis · Sleep · Consciousness

5.1 Introduction

Dreams are subjective experiences recalled upon awakening. They include a broad variety of mental contents, ranging from simple fragments of thoughts or images to articulate storylines and complex, multimodal hallucinatory experiences. The dreamer is typically immersed and fully involved in a first-person perspective but may also be an external observer to the dream scene. This state of consciousness occurs during sleep, when the brain is detached from the environment. Largely

unaware of its surroundings, the dream "Self" is fully capable of generating a rich, complex, multimodal sensorimotor experience which encompasses emotion, thought, action and social interactions.

The question of how the human brain generates a conscious "Self" remains elusive and open to remarkable speculations [1–3]. The clarification of functional brain dynamics underlying dreams is considered fundamental to the process of uncovering the so-called neural correlates of consciousness and is described in detail in Chap. 4 [4]. Indeed, some contemporary philosophers consider dreaming to reveal consciousness itself "in a very special, pure, and isolated form" [5] and define it as "immersive spatio-temporal hallucination" [6].

The phenomenological overlap between dreaming and hallucinations sustained research on a shared neurobiology [7–9], but insufficient evidence exists to fully support the hypothesis that waking hallucinations reflect intrusions of sleep-related neural activity into waking consciousness [10]. Indeed, similarities between physiological dreams and the experience reported by subjects with psychosis have been described at least as far back as classical antiquity. In the modern age of psychiatry, a broad scope of qualitative analogies has been reported by pioneers such as Carl Gustav Jung, Eugen Bleuler and Emil Kraepelin. These include but are not limited to the distortion of time and space parameters, the incoherence and absurdity of one's subjective experience, the loosening of associations and disorganization of speech [11–13]. More recently, the possibility of studying the dreaming brain–mind to model pathological mental phenomena, such as psychosis, has been explored [14]. Although appealing, the relative lack of knowledge on the neurobiology of dreaming itself, and the limited accessibility of patients with acute psychotic conditions in experimental settings, has somewhat hindered progression in this area. Nonetheless, bidirectional comparisons between dreams and psychosis have generated novel hypotheses to guide future research.

In this chapter, we will describe the role of dreams in understanding complex mental dysfunctions and clearly identify open questions that remain unanswered.

5.2 Sleep and Dreaming in Psychotic Disorders

Schizophrenia is a heterogeneous disorder defined by a complex interaction of cognitive, behavioural and emotional dysfunctions. Despite intensive research in several fields, the core dysfunction remains elusive [15].

The clinical phenomenology of this syndrome, originally termed Dementia Praecox, was studied at the turn of the twentieth century by Emil Kraepelin and Eugen Bleuler [11, 13]. These two authors described signs and symptoms and defined the course and prognosis of the disorder. The derived prototypical model is characterized by an insidious onset and progression, with episodic exacerbations and a residual outcome in which affective blunting predominates. Exacerbations are typically characterized by the emergence of so-called positive psychotic symptoms such as hallucinations, delusions and disorganization. Some patients may present

with "negative" symptoms such as alogia, anhedonia, diminished emotional expression or avolition during exacerbation.

In the 1970s, the similarity between positive symptoms and dreaming fueled several polysomnographic studies which aimed to identify intrusions of dream sleep in wakefulness to explain psychosis. Although this hypothesis was not confirmed, those studies began to reveal abnormalities in sleep rhythms and architecture that remain under scrutiny. Increased sleep onset latency, decreased total sleep time, decreased slow-wave sleep and prolonged wake time after sleep onset associated with an increased frequency of nocturnal awakenings [16] were reported in Schizophrenia patients compared to healthy control populations. Consistent reports of diffuse deficits of sleep-spindle activity recently sparked a new wave of research focused on microstructural features of non-rapid eye movement (NREM) sleep. Spindle density and integrated spindle activity were found to be reduced in prefrontal, centro-parietal and temporal regions [17]. A significant reduction of sleep spindles has also been reported in first-degree relatives and in the early-course, drug-naïve Schizophrenia patients [18]. However, spindle deficits are also commonly observed in neurodevelopmental disorders including autism, intellectual disabilities and inborn errors of metabolism, neurodegenerative disorders such as Alzheimer's or Parkinson's disease and in rapid eye movement (REM) or NREM sleep parasomnias [19]. Reduced spindle density and mean frequency of fast spindles have also recently been described in euthymic patients with bipolar disorder [20]. These findings suggest that spindle deficits might be a shared endophenotype rather than a disorder-specific biomarker [21]. Indeed, detailed characterization of both spindle and slow-wave deficits in first-degree relatives of Schizophrenia patients suggests a disruption of cortical synchronization mechanisms might increase the risk for Schizophrenia, but aberrant thalamic activity is necessary for the disorder to fully develop [22]. Although the function of spindling during NREM sleep remains open to debate, fast spindle activity has been associated with different measures of dream recall, indicating a possible link between this oscillatory thalamocortical activity, dreaming and memory mechanisms [23].

Another emerging field aims to define comorbid sleep disorders in patients with psychosis to improve overall health outcome. In a consistent cohort of early-course patients, 80% were found to have at least one sleep disorder, with insomnia and nightmare disorder being the most common [24]. Of note, although over half of these disorders had been discussed with a clinician, almost three-quarters had received no treatment. Common parasomnias such as nightmares and night terrors had previously been associated with psychopathology [25]. Furthermore, distressing nightmares are reported to be present across different mental disorders and specifically in patients with psychosis; in particular, nightmares are positively correlated with greater delusional severity, depressive symptoms, poor sleep quality and cognitive impairment and addressing nightmares might improve quality of life and decrease suicidal risk [24, 26, 27].

Cross-sectional studies also suggested that nightmares might be related to psychosis proneness or schizotypy [28, 29]. Recent data from the Avon Longitudinal Study of Parents and Children, a birth cohort study conducted in the United

Kingdom, have begun to shed new light on this relationship [30]. Within a vast examination of developmental issues related to the health and wellbeing from birth throughout childhood and adolescence, the quality of sleep and dream content of a large cohort has recently been reported. In one study, nightmares and night terrors during childhood were found to be associated with psychotic experiences at age 12, possibly suggesting that arousal and REM sleep disturbances could be early indicators of susceptibility to psychotic experiences [31]. In another study, a significant association was reported between the presence of nightmares at 12 and psychotic experiences at 18, which was confirmed when adjusted for possible confounders and psychotic experiences at 12 [32]. The authors conclude that nightmares and night terrors during childhood and early adolescence could have clinical significance in relationship to an evolving psychopathology, in individuals with additional risk factors such as a family psychiatric history or a past trauma exposure by adults or peers. Indeed, a significant increase in nightmare frequency was also recently reported in a group of patients with an at-risk mental state, a prodromal condition associated with an elevated risk of developing a psychotic disorder in the near future [33].

5.3 Consciousness in Dreams and Psychosis

5.3.1 The Phenomenological Overlap Across Mental States

The fundamental analogy between dreams and psychosis can be identified in the subject's failure to discriminate between environmentally driven and internally generated perceptions and beliefs. Patients who experience a psychotic episode misattribute self-generated perceptions of the environment. Likewise, dreaming subjects fail to distinguish vivid, self-generated perceptions from reality until awakening. During wakefulness, this failure leads to the subject's detachment from reality that is commonly termed psychosis. Affected patients experience hallucinations and maintain complex delusional beliefs, without acknowledging the internal origin of their experience. This lack of insight defines psychosis, no matter how bizarre the verbalized content may appear to an external observer. Likewise, the dreamer accepts incongruous and discontinuous transformations within the dream without developing doubts over the nature of the experience. While asleep, the dreaming subject is fully convinced of being awake, even when the plot is highly bizarre as often occurs during REM sleep [34]. Lucidity, defined experimentally as an increase in insight and control over one's dream, appears to restore the subject's waking source monitoring. Consciousness experienced in lucid dreams appears similar to waking cognition, exhibiting clear and coherent subjective experiences [35]. Whereas self-reflective awareness is physiologically lost every night while dreaming, only some subjects develop complex mental disorders in which the same loss severely compromises their everyday wake life [36].

Peculiar conditions exist where insight is preserved both in the context of hallucinatory experiences and dreaming. This is the case of sleep-related perceptual

phenomena (or hypnagogic/hypnopompic hallucinations) and lucid dreaming. While the first appears phenomenologically closer to so-called organic psychoses than to typical auditory hallucinations of Schizophrenia, and indeed involve only a portion of the circuitry underlying pathological hallucinations [37], lucid dreaming represents a window of particular interest into mechanisms of insight and self-monitoring in dreams. Efforts have been made to provide clarification regarding the overlapping cerebral dynamics underlying each of these phenomena, which share such phenomenological traits [38]. Despite some promise, incorporation of consciousness, psychosis and dream research in a "neuro-phenomenological" or "multi-level" framework has remained a speculative endeavour [39, 40].

5.3.2 Frontal Brain Activity and Insight during Dreams and Psychosis

Many authors described the shared patterns of brain activity between dreaming and psychosis [7–9]. The neurophysiological and neurofunctional underpinnings of dreaming have been partially clarified over the past few decades. For details on the neurobiology of dreaming, please refer to Chap. 4. In brief, a local decrease of low-frequency EEG activity in parieto-occipital regions has recently been found to predict the report of dream experiences upon awakening from any sleep stage [41]. This posterior cortical "hot zone" has been proposed as a neural signature of dream experiences. More specifically, dreaming appears to occur, most frequently when posterior regions present fast spindles and small, sparse and shallow slow waves and frontocentral regions present high-amplitude slow waves followed by local microarousals [42]. In terms of brain activation, a relative hyperactivation of cerebral regions related to emotional and affective life (i.e. amygdala and anterior cingulate cortex) combined with hypoactivity of frontal structures, mainly the lateral and rostrolateral regions of the prefrontal cortices, are commonly reported [43]. Many typical aspects of dream mentation, including the lack of logical thinking and self-reflectiveness and the strongly perceptual nature of the experience, have been attributed to the low regional cerebral flow observed in the prefrontal cortex throughout sleep [44]. Spectral EEG and functional Magnetic Resonance Imaging (fMRI) studies suggest that the retrieval of these higher order cognitive faculties depend on the engagement of frontal structures, such as the right dorsolateral prefrontal cortex (dlPFC), that are usually quiescent during REM sleep (Fig. 5.1) [45, 46]. Increased resting-state functional connectivity between the left anterior prefrontal cortex and the bilateral angular gyrus, bilateral middle temporal gyrus and right inferior frontal gyrus has recently been reported in frequent lucid dreamers [47]. Lucid dreaming (a state where the dreamer is aware that one is dreaming) has been verified through voluntary eye movements recorded in the electrooculogram during polysomnography, and it might prove fundamental to study the characteristics of visual imagery during sleep [48]. In general terms, reactivation of frontal structures during REM sleep is thought to underlie the experience of

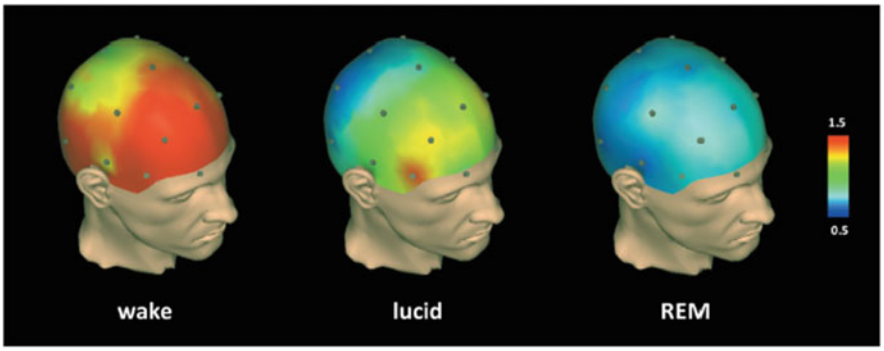

Fig. 5.1 Single-subject 40-Hz standardized current source density power during wakefulness, lucid dream sleep and non-lucid rapid eye movement (REM) sleep. Lucid dreaming is shown to have higher than REM activity in upper frequencies, peaking in the γ band frontolaterally at 40 Hz. (Reproduced from Voss et al. [45])

lucidity. Indeed, increased γ–band activity and coherence have been reported in frontal and frontolateral regions [49].

Frontal lobe dysfunction is a classical finding in patients with psychotic disorders, possibly also reflected by the relative lack of slow waves observed in the prefrontal cortex during sleep at disease onset [50]. Several neuroimaging studies point to an association between impaired insight and prefrontal, medial parietal and cingulate cortex abnormalities in psychosis. Intriguingly, increased activity within the same cortical regions has been reported when lucidity occurs during dreams [51].

In particular, the left medial prefrontal cortex, posterior cingulate cortex (PCC), frontopolar cortex and precuneus have been evidenced to show increased activation associated with good insight, while the dorsolateral prefrontal cortex (dlPFC) has been found to correlate negatively with poor insight in patients experiencing psychotic disorders [35, 52–54]. Furthermore, activation of the same areas has been associated with the lucid dreaming state [54–56], though findings regarding the dmPFC and PCC are limited and require further investigation. The striking overlap between brain activation patterns that are typically associated with lack of insight in psychotic patients and non-lucid dreaming warrants additional research into shared mechanisms that might lead to novel treatment pathways for complex mental disorders.

5.4 Dreaming in Patients with Complex Mental Disorders

Although many clinicians employed dreams in the diagnosis and treatment of patients with different mental disorders after Sigmund Freud [57], this type of content has progressively been marginalized by modern approaches so that competence to effectively respond to patients' dream material is now generally lacking [58]. According to the continuity hypothesis [59], several symptoms that patients

with different mental disorders experience while awake should be reflected in the reports of their dreams, and more negatively toned dreams should be present in their sleep. Recent reviews on dreaming in patients with mental disorders suggest that the majority of studies have been conducted in patients with Schizophrenia, depression, post-traumatic stress disorder and eating disorders [16, 60–62]. Furthermore, research on Schizophrenia provides us with a key example of what is meant by similarities between dream experience and waking life and insights on the relationship between sleep disturbance, dreams and psychopathological symptoms. Despite many methodological problems that limit dream research, different groups still pursue the rigorous investigation of dreams in clinical populations to study continuity and discontinuity between these two states [63]. We will describe two of the main approaches that have been used in the study of dreams: formal analysis and content analysis of dream reports.

5.4.1 Measuring Dream Recall Frequency

Despite the assumption that every sleeper dreams, the ability to recall dreams and their content is extremely variable. Of course, the possibility to successfully recall dreams and their content is a prerequisite in any dream research.

The ability to recall dreams refers to the capability of reporting any mental content that occurred during sleep, upon awakening. In order to be successful, a dream recall has to contain at least some memory or particular episode/image of the dream and has to be different from the feeling of having dreamt without remembering any content [64, 65].

Questionnaires, dream diaries and awakening during sleep in experimental settings are three of the main methods to record dream content and dream recall frequency (DRF). Within questionnaires, different questions can assess how many times a person dreamt during the previous month, week or night. A certain degree of consistency has been shown for DRF, and the rating scale proposed by Michael Schredl [66] shows a high retest reliability up to 3 years, indicating this scale can consistently measure inter-individual variability [67]. As compared to questionnaires, dream diaries often ask to not only report whether a person has dreamt or not, but also the dream content of the previous night. While no significant decrease overnights has been reported in DRF collected via checklist, dream content seems to depend more on personality traits and state factors in psychiatric populations. Therefore, DRF might be over- or underestimated when assessed via dream diaries in clinical samples.

Among several factors, other variables that might affect DRF are sleep quality and duration, psychotherapy, gender, cognitive factors and intelligence. This suggests that independent of clinical diagnosis, other variables must be considered when investigating dream frequency in complex mental disorders.

Awaking subjects during sleep is another option to assess dream recall, albeit more expensive in terms of experimental setting and compliance. Reported rates are between 80 and 90% for awakening from REM sleep and 40 and 50% for awakening

during NREM sleep when collecting dream reports in a laboratory (Nielsen 2000). Dream recall ability in experimental settings is specular to that of home settings, with participants who remember more than three dreams per week at home reaching 93% of dream reports after being awakened from REM sleep and low-rate recallers only reaching approximately 43% in laboratory REM awakenings [68]. Nevertheless, the advantage of the laboratory settings is the possibility to measure additional electrophysiological measures during sleep and awakenings [41].

5.4.2 Content Analysis of Dreams

The contemporary analysis of dream content evolved from Sigmund Freud's seemingly straightforward observation that all the material in dreams somehow derives from waking experiences. One commonly accepted basis for dream content analysis is that in the absence of external sensory input, memories with derived meanings and symbols must be the source material for dreams [69]. Indeed, some authors argued that memory sources are key to dream construction [70] and, more precisely, that such memory sources reflect emotional concerns [71, 72]. Memory elements are somehow merged and fused to construct visual scenes [73, 74], whereas the episodic replay of recent waking activities occupies only 1–2% of dream reports, declarative memories become more accessible for retrieval after REM sleep [69].

Early studies on spontaneous dream reports and those collected from sleep laboratory awakenings [75, 76] in Schizophrenia patients were characterized by an elevated frequency of male strangers with relatively more aggressive social interactions and more apprehensive emotions. An increased frequency of perceived threats has been intuitively related to paranoid thought processes during wakefulness [75, 77–79]. Generic delusional themes, such as persecution or grandiosity, appear to characterize patients' dreams rather than specific contents. However, one study found that all the differences between the dreams of Schizophrenia subjects and those of normal controls were dependent on the length of the reports [80]. Typical sleep stage-dependent style of dream reporting was also found to be preserved in Schizophrenia, with NREM sleep dream reports being more thought-like, less elaborate and less bizarre than REM sleep dream reports [81].

Other recent studies confirmed a relative increase of hostility directed at the dreamer, although subjects with Schizophrenia are rarely the main character in their own [16, 82]. Although some authors suggest a continuity between the waking life and dreams of patients with Schizophrenia [62, 83], very few studies analysed reports of waking life activity and symptoms of the patients and compare them with their dreams.

One study conducted in Israel recruited 20 adolescent inpatients with a diagnosis of Schizophrenia, 21 adolescent inpatients with other mental disorders and 31 age- and gender-matched healthy volunteers [84]. The control group demonstrated more involvement and emotional expression than Schizophrenia patients. In particular, elevated scores on the negative subscale of the Positive and Negative Symptoms Scale (PANSS, a psychometric scale that is commonly used to assess severity of

symptoms in Schizophrenia) were significantly correlated with lower scores on involvement, emotional expression and dream recall. No relationship was found between the positive subscale of the PANSS and content analysis of dreams.

In most studies, dreams were collected from chronic, stabilized Schizophrenia subjects with varying degrees of active psychotic symptoms, so that the continuity between dream mentation and waking thought processes during acute psychosis remains highly unclear. In a recent study, ten patients with a single fixed and recurring delusional content were asked to report their dreams during an acute psychotic break. Sixteen judges with four different levels of acquaintance to the specific content of the patients' delusions were asked to group the dreams. Most judges grouped the dreams only slightly above chance level, with no relevant difference between the four groups. Objective scoring of dreams for specific delusional themes suggested that at least some do migrate across wakefulness and dreams during an acute psychotic break (grandiosity and religion in the study sample) [22].

5.4.3 Formal Analysis of Dreams

The formal analysis of dreams encompasses a detailed evaluation of dream features such as general appearance, stream of talk, clarity, orientation in time, space and person, bizarreness, splicing, logic and authorship [85].

McCarley and Hoffman [86], for example, report that 67% of REM dreams exhibit bizarreness. Indeed, the word "bizarre" is used to characterize a person/object/place that takes on multiple (apparently inconsistent) elements. These considerations led to the construction and validation of a scale that proved to be a useful tool in the evaluation and assessment of bizarreness in dream reports [87]. Bizarreness can be viewed as a loosening of the formal structure of cognition, suggesting the sleeping brain is physiologically prone to the loss of logical reasoning observed during wakefulness [22].

Although conclusive theoretical observations on the basis of the available experimental data are perhaps premature [88], some studies reported high levels of bizarreness in dream reports of psychotic patients, independent of diagnosis [80, 89–91]. Equally high levels of cognitive bizarreness were observed in dream reports of patients and healthy controls, but also in the waking fantasies of patients and not of the healthy control subjects (Fig. 5.2).

The degree of bizarreness observed in dream and fantasy reports has been found to be inversely proportional to the neural response of a right fronto-temporal network (Fig. 5.3) that is specifically activated during the script-driven recall of these experiences in healthy volunteers [92]. This finding could imply that the high level of bizarreness observed in psychotic patients' waking mentation, at least partially, reflects the reduction of grey matter volumes which parallels the course of Schizophrenia across the same cerebral regions [93].

However, analyses conducted with different assessment tools yielded inconsistent results, so that bizarreness in the dreams of Schizophrenia patients has been

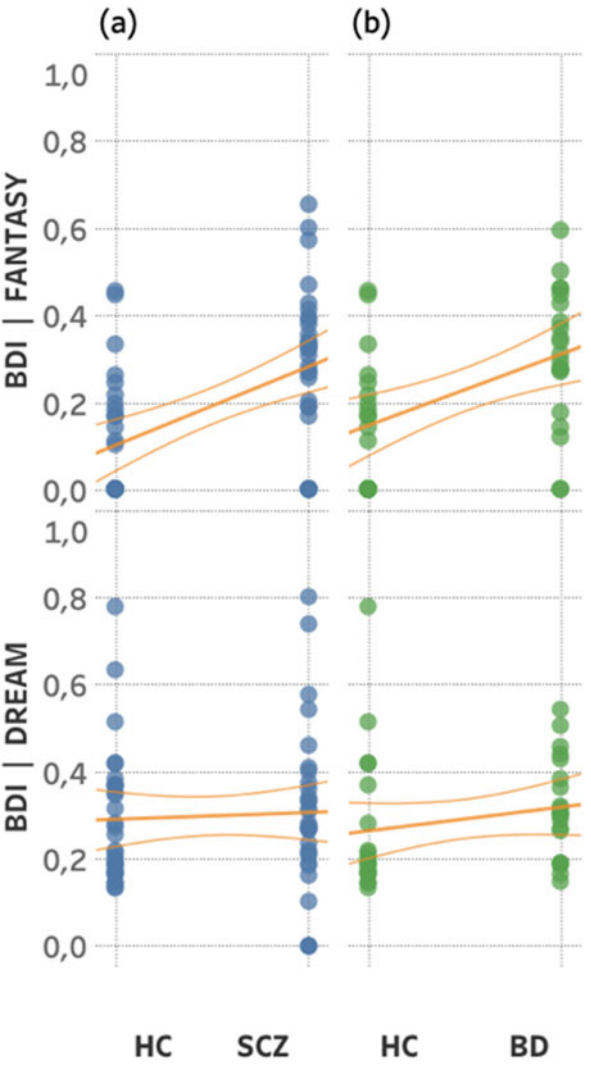

Fig. 5.2 (**a**) Mean Bizarreness Density Index (BDI) values in the dream and fantasy reports of acutely psychotic patients with Schizophrenia (SCZ) and healthy control (HC) subjects. (**b**) Mean BDI values in dreams and fantasy reports of acutely psychotic manic patients with Bipolar Disorder (BD) and healthy control (HC) subjects. Thematic Apperception Test (TAT) was used to elicit fantasy narratives. Bizarreness density was calculated by dividing Bizarreness Intensity (BI) by the report word count. BI is scored as the number of bizarre events in the domains of plot, cognition and affect according to the dream Bizarreness scale (Hobson et al. 1987). (Data retrieved from Scarone et al. [91]; Limosani et al. [90])

reported to be lower [75], equivalent [80] or even higher [94] than the bizarreness scored in dreams of healthy volunteers. Higher levels of bizarreness in the dreams of Schizophrenia patients have also been found in comparison to the dreams of groups of patients with other mental disorders [95].

More recently, a formal analysis of dream and waking reports investigating speech graph attributes in healthy volunteers and in patients with Schizophrenia and bipolar disorder suggested that dreaming significantly exposes differences across individuals [96]. The semantic and grammatical analysis of the most-frequent word loops and corresponding exit nodes yielded differences across dream and waking reports of patients and control subjects (Fig. 5.4).

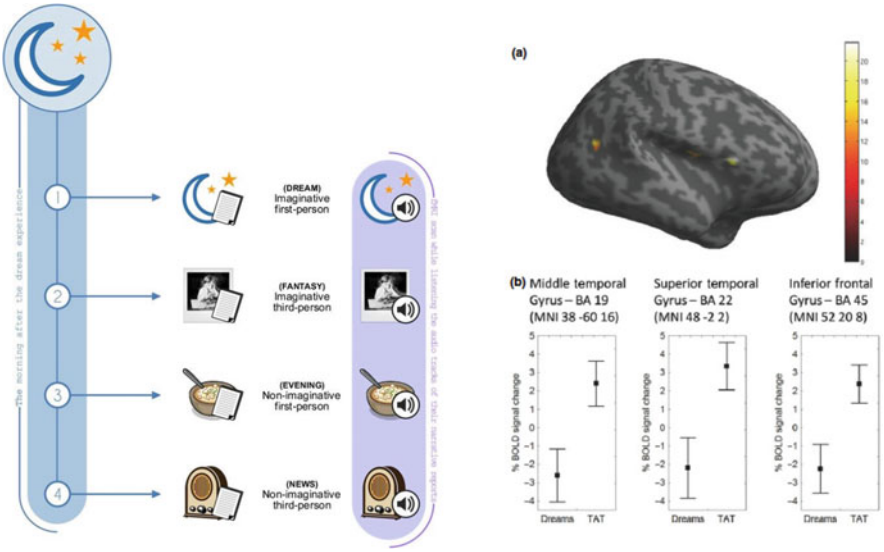

Fig. 5.3 Differentially activated grey matter areas during dream and fantasy (TAT) conditions, plotted on an inflated cortical surface of the human brain reconstructed from MRI scans (**right, a**). The BOLD signal change zero line marks the higher activation observed for both imaginative conditions (dreams and fantasies) compared to non-imaginative control conditions (narrative reports of daytime activities or news) (**right, b**). Participants were required to listen to a randomly presented sequence of scripts during fMRI acquisition. The scripts included their own dream reports (DREAM, imaginative first-person account); their own fantasy reports stimulated by a TAT table (FANTASY, imaginative third-person); their autobiographical reports of each evening prior to a reported dream (EVENING, non-imaginative first-person); their brief reports of an event heard from any news source on each day prior to a reported dream (NEWS, non-imaginative third-person) (**left**). (Figures reproduced from Benedetti et al. [92])

5.4.4 Methodological Considerations

Although very promising, the exploration of dreams to approach psychopathology has some methodological issues and drawbacks. The first limitation is the selection of patients: in one study [95], about 30% of the patients refused to participate because they could not remember dreams. This suggests that patients with a high dream recall rate are overrepresented in dream report studies, with a rejection rate similar to the one observed in healthy individuals [97]. Second, the heterogeneity of psychotic mental states limits the possibility to generalize. Indeed, several acute conditions are not easily accessible in experimental settings. Third, the effect of medication on dream recall can be another confounding factor when exploring dreams in patients with complex mental dysfunctions. Antipsychotics can have different effects on dream recall [98, 99], and antidepressants can reduce dream recall [100] and possibly interfere with the content of dreams (i.e. emotional tone) [101]. Furthermore, the dream report can depend on waking life events as well as

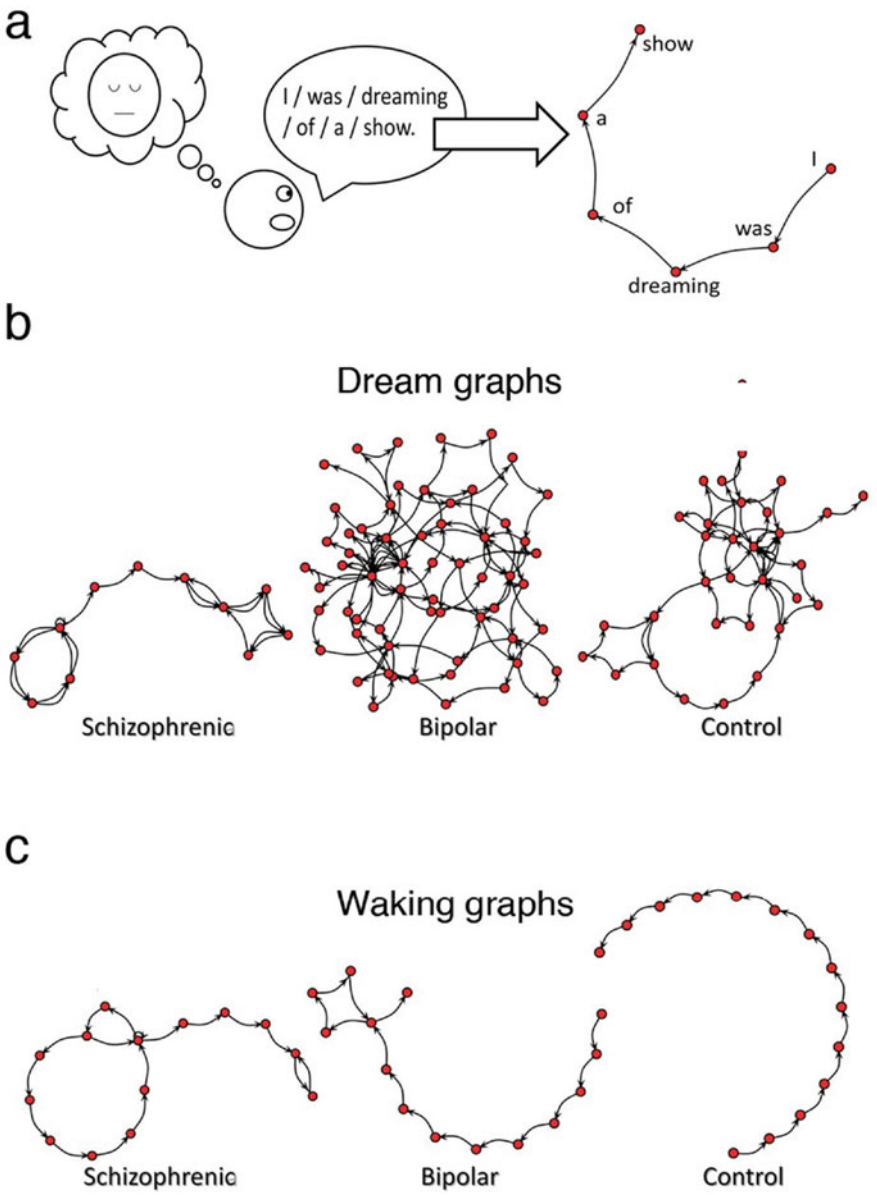

Fig. 5.4 Speech graphs of subjects diagnosed with Schizophrenia, Bipolar Disorder Type I and of a healthy control group. (**a**) Graphs were generated from transcribed verbal reports using custom-made Java software (http://neuro.ufrn.br/softwares/speechgraphs). (**b**) Representative speech graphs extracted from dream reports from one Schizophrenia, one bipolar disorder and one control subject. (**c**) Representative speech graphs extracted from waking reports of the same subjects. Differences between groups are more significant across dream reports than across waking reports. (Figure reproduced from Mota et al. [96])

waking life symptoms in patients with Schizophrenia. However, significant differences in the activation of specific brain areas have been reported when dreams, waking fantasies or mundane experience are recalled by healthy individuals [92]. These differences are thought to provide an argument supporting the reliability of dream reports [102], and neuroimaging techniques might in future also provide support for the preliminary findings in patients with psychosis.

5.5 Conclusive Remarks

For centuries dreams have been of particular interest to philosophers and scientists. They have been variously described as messages from gods to messages from the unconscious. The progression of neuroimaging techniques renewed interest in their neurophysiological substrate and links to sleep and mental illness.

Despite specific methodological issues, exploring dreams remains a unique opportunity to understand psychosis and consciousness. Similarities between psychosis and dreaming are supported by neuroimaging evidences indicating that self-monitoring failure experienced during dreams and lack of insight in psychosis share the disengagement of the same frontal circuitry. Future research might disentangle whether direct stimulation in these regions can not only modify dream experiences but also awareness in everyday life symptoms of psychotic patients.

Disruptions in sleep homeostasis, circadian rhythms and sleep architecture often precede the first clinical breakdown. Future research will need to address the relationship between such early disruptions of the sleep/wake equilibrium and the development of psychosis. In this context, the study of dream consciousness will perhaps contribute to bridge the neurobiology and phenomenology of affected individuals.

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Sleepiness, Fatigue, and Sleep Disorders

6

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Abstract

Sleepiness and fatigue are terms used interchangeably, but they are different concepts. For example, a person who runs up 15 flights of stairs may feel fatigued when reaching the top but would not inevitably fall asleep following the exercise. On the other hand, sleepiness is characterized by a tendency to doze off during work or while sitting idle. Establishing the underlying cause for sleepiness can be a challenging feat. Sleep disorders such as sleep-disordered breathing (e.g., obstructive sleep apnea), hypersomnias (e.g., narcolepsy), circadian rhythm disorders, restless legs syndrome, and periodic limb movement disorder have been shown to cause excessive sleepiness besides insufficient sleep-acute or chronic. In many situations, sleepiness as well as ability to stay awake needs to be ascertained. This can be measured using a multiple sleep latency test or maintenance of wakefulness test. Present chapter focuses on the etiological factors, clinical presentation, and laboratory assessment of conditions leading to fatigue and sleepiness.

Keywords

Sleepiness · Drowsiness · Fatigue · Tiredness · MSLT · MWT · PSG · ESS · FSS

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6.1 Introduction

The terms "sleepy" and "tired" are used interchangeably in various social, occupational, and clinical settings. Fatigue (i.e., mental and/or physical tiredness) may occur concurrently with, or may be independent of, sleepiness. For the purposes of this chapter, the clinical presentation and assessment of sleepiness will be distinguished from the clinical features and evaluation of fatigue. Briefly stated, sleepiness is an inability to stay awake or alert during activities that require wakefulness, whereas fatigue is a reduced ability to participate or engage in activity. For example, a person who runs up 15 flights of stairs may feel fatigued when reaching the top but would not inevitably fall asleep following the exercise. Treatment of both sleepiness and fatigue should target the underlying etiology, yet occasionally, symptomatic interventions may be paramount depending on the presenting problem and level of functional impairment.

This chapter will primarily address the salient features characteristic of both sleepiness and fatigue in the clinical setting. The etiology, assessment, potential causes and consequences, and best intervention and management practices are elucidated.

6.2 Sleepiness

6.2.1 What Is Sleepiness?

Sleepiness is more than just tiredness. The term "sleepiness" suggests having an actual propensity to fall asleep in situations that might not otherwise result in sleep (e.g., sitting and quietly reading, sitting relaxed in a lecture, watching television, watching a movie at the theater, or sitting and talking to someone). Other terms used to describe sleepiness are "drowsiness" or "somnolence." Sleepy individuals may experience heavy eyes or droopy eyelids, slowed breathing, frequent yawning, curbed responses, inattentiveness, and head nodding or "bobbing" during the transition into sleep [1]. These behavioral signs of sleepiness usually precede the dozing or sleeping episodes.

Sleepiness is a physiological drive state necessary for survival [1]. This homeostatic drive for sleep can occur after a prolonged period of sustained wakefulness, when awoken from the middle of the sleep period, or upon awakening from the main sleep period. Sleep drive is typically expressed within a 24-h rhythm, which is closely tied to the light–dark cycle of our environment [1]. Largely, the degree of sleepiness rises as time advances and naturally declines when sleep is attained. While physical activity has recently been shown to increase sleep drive in a positive way, light exposure also has a tremendous impact on sleep homeostat and can alter and/or influence the overall level of sleepiness on a given day.

Sleepiness serves as an essential biological function (i.e., to signal when it is time for sleep). When sleepiness is considered "excessive," sleep episodes occur frequently throughout the 24-period making a person unable to stay awake or alert in

situations where wakefulness may be obligatory. Usually, individuals with excessive sleepiness fall asleep during sedentary, inactive, or passive activities (e.g., reading a book, sitting at a lecture/church sermon, watching television). Episodes of sleepiness when more severe and recurrent may also take place during dynamic or lively activities (e.g., driving to work, eating dinner, talking to a friend). Excessive sleepiness can be a manifestation of a medical, neurologic, sleep, and/or psychiatric disorder, which may ultimately lead to impaired daytime functioning (e.g., social, occupational, and cognitive functioning, and/or overall functional ability).

When "excessive daytime sleepiness" (EDS) is present, there is usually an increased tendency to fall asleep during the daytime, or an augmented quantity of sleep time dispersed across 24 h. EDS can be seen in patients who present with clinical sleep disorders but can also be seen in otherwise healthy persons who are chronically deprived of sleep, or who do not have adequate opportunity to sleep. At the time a patient presents to the clinic with EDS, the clinician should immediately probe for more details, as this is a symptom highly associated with serious, potentially life-threatening, medical, and/or psychiatric conditions. For this reason, it is of the utmost importance to not only identify but also quantify sleepiness in vulnerable patients [2].

6.3 Epidemiology

Likely underestimated, sleepiness is a symptom exhibited by 10–25% of individuals [1]. Yet, prevalence rates vary greatly depending on the population studied and definition of sleepiness [1]. It should be noted that patients who present to sleep clinics are not necessarily representative of the general population. Even so, sleepy patients can provide insight into understanding the deleterious effects of EDS on daily functioning and overall quality of life.

Rates for sleepiness of 15% and up have been found for certain age groups (i.e., compared to middle-aged adults, both young adults and healthy older adults are sleepier; night shift or rotating shift work adults are sleepier than day workers) [1, 3–5]. Eleven percent of women and 7% of men endorsed EDS almost daily in a Finnish population study [6]. Prevalence of EDS in a random Michigan sample was 13%, as measured by multiple sleep latency test (MSLT), and Epworth Sleepiness Scale (ESS) scores 10 or higher made up 20% of the sample [7]. Higher rates were found in a Wisconsin study, with EDS rates and ESS scores 11 or higher at 25% [8]. Until further large-scale studies are conducted, the prevalence of sleepiness (and sleepiness severity) is relatively unknown in the general population.

6.4 Etiology

Establishing the underlying cause for sleepiness can be a challenging feat. Sleep disorders such as sleep-disordered breathing (e.g., obstructive sleep apnea), hypersomnias (e.g., narcolepsy), circadian rhythm disorders, restless legs syndrome,

and periodic limb movement disorder have been shown to cause excessive sleepiness [9] besides insufficient sleep-acute or chronic.

6.5 Measuring Sleepiness

To properly categorize and quantify sleepiness, the clinician should conduct a comprehensive clinical interview, including a detailed history, physical exam (if clinically indicated), and incorporate the use of both subjective and objective measures.

6.6 Subjective Sleepiness Measures

Questionnaires are effective tools that can be filled out quickly, determine the degree of sleepiness, and collect pertinent data on sleep–wake patterns. In addition to the objective measures mentioned above, subjective measures are beneficial clinical screening tools that can track progress over the course of treatment (e.g., pretreatment, sequential treatment visits, posttreatment) in addition to therapy response (Table 6.1).

Some data suggest that subjective measures may be more reliable when completed with the help of the bed partner or trained personnel. When nurse-administered Epworth Sleepiness Scale (ESS; outlined below) scores were compared to self-administered ESS scores in a study by Uqur et al. [10], the ESS scores were more sensitive and accurate when completed by a nurse. While this may not be clinically feasible due to time constraints and/or lack of trained staff, this tactic is meaningful to consider, especially since most individuals, when self-rating degree of sleepiness, will significantly underestimate sleepiness severity [1]. It may therefore be beneficial to ask the patient's bed partner or close family member/friend to help assist with the completion of the ESS [11, 12] and any other self-report sleepiness questionnaire. For instance, the severity level of subjective sleepiness before starting positive airway pressure (PAP) treatment was heavily underrated in a recent OSA study [13].

Table 6.1 Summary of widely used subjective measures of sleepiness

Subjective measures of sleepiness
Sleep diaries
Epworth sleepiness scale (ESS)
Stanford sleepiness scale (SSS)
Pittsburgh sleep quality index (PSQI)
Time of day sleepiness scale (ToDSS)
Morningness–Eveningness questionnaire (MEQ)
Sleepiness–wakefulness inability and fatigue test (SWIFT)
Visual analogue scale (VAS)
Karolinska sleepiness scale (KSS)

There are several potential reasons for underestimating sleepiness level. It appears that with chronic lack of sleep, the perception of sleepiness is diminished [1]. It is likely that most patients will adapt to chronic sleepiness and "forget" what it feels like to be completely alert. Accordingly, the higher the sleepiness level, the less likely the sleepiness severity can be accurately judged [1]. Howard et al. [14] illustrated this in a study of anesthesiology residents. The residents were not able to accurately determine when they had fallen asleep. In fact, the residents did not perceive themselves to be asleep approximately half the time they were truly asleep [14]. In sum, the sleepier the person, the higher the chance of disparity between subjective versus objective measures [1].

6.6.1 Sleep Diaries

Although not explicitly assessing level of sleepiness, individual sleep diaries or sleep logs can provide invaluable data for the clinician. Sleep tracking should take place over a period of at least 2 weeks to compile a proper baseline. Many providers will ask patients to continue tracking sleep over the course of treatment. Sleep diaries ask the patient to document total time spent in bed, time of lights off, time of sleep onset, number of awakenings during the night, total minutes awake, rise time, time out of bed upon final wake time, and total time spent napping during the day and/or dozing behaviors. Tracking sleep over the course of therapy can help discover any variables related to the potential symptoms (and subsequent consequences) of sleepiness (i.e., total sleep time (TST), napping/dozing, circadian patterns/misalignment, insufficient sleep), and therefore, the sleep diary can be utilized as a multipurpose clinical tool. It may also behoove the provider to provide a rationale to the patient about why filling out a diary is an important part of treatment. The clinician should emphasize that the diary does not have to be perfect; that it is an overall estimate of sleep. The sleep diaries should not be too time-consuming (e.g., a couple of minutes) or cause any distress to the patient when completing. The patient should also be advised to avoid watching the clock when awake at night, as this can increase worry related to sleep and further perpetuate the sleep problem.

6.6.2 Epworth Sleepiness Scale (ESS)

The ESS [11] is often cited as the most commonly used, well-validated subjective measure of sleepiness [15]. The scale has been translated into multiple languages and validated across clinical populations, with a 74% sensitivity and 50% specificity related to the MSLT [1]. Patients may be asked to complete the scale at the initial clinic evaluation, regardless of sleep complaint, and may be asked to fill it out again at future follow-up appointments. The ESS can be used to monitor the progression of or improvement in EDS over several months [12]. The ESS evaluates the severity of sleepiness over a period of 2 weeks [11]. The measure asks the patient to score the chance of dozing or falling asleep in eight everyday activities on a rating scale from

zero to three (i.e., zero "no chance" to three "high likelihood"). The maximum score possible is 24. A score of 10 or higher is considered excessive daytime sleepiness (i.e., abnormal), and a score of 15 or more qualifies as severe daytime sleepiness [11].

6.6.3 Stanford Sleepiness Scale (SSS)

The SSS [1, 16] is argued to be the best validated scale of sleepiness assessment, while the ESS is the most widely used across the globe [1, 16, 17]. The SSS evaluates sleepiness at any moment in time. In normal populations, scores on the SSS will typically increase in the afternoon, drop after 5:00 p.m., and augment again towards the evening [1]. The SSS uses a 7-point rating scale describing sleepiness severity, ranging from "feeling active, vital, alert, or wide awake" to "no longer fighting sleep, sleep onset soon, or having dream-like thoughts" [16]. The results are displayed on a scale of one to seven. A score of four or higher indicates EDS at a given moment in time.

6.6.4 Pittsburgh Sleep Quality Index (PSQI)

Like the ESS, the PSQI [18] measures sleep quality over a given interval of time. It is a 19-item questionnaire that measures seven distinct sleep components over a 1-month time frame. Items are rated from zero to three in areas such as sleep duration, sleep latency, awakenings during sleep, sleep disturbances, sleep medication use, daytime impairments, habitual sleep efficiency, and sleep quality. The total sum is computed to arrive at a global score ranging from 0 to 21. A score of five or higher is suggestive of poor sleep quality [18].

6.6.5 Functional Outcomes of Sleep Questionnaire 10 (FOSQ-10)

The FOSQ-10 [19] can assess the impact of excessive sleepiness on overall quality of life, and the ability to complete daily activities because of sleepiness severity. The original FOSQ is a 30-item scale, which may be too time-consuming for clinical practice. The reduced 10-item scale helps to differentiate between patients who do not experience EDS-related impairments from those who suffer daily limitations. The measure provides a global assessment of daily functioning in the subscale areas of general productivity (e.g., "taking care of financial affairs and paperwork"), activity level (e.g., "keeping pace with others"), vigilance (e.g., "driving long distances"), social outcomes (e.g., "visit in your home"), and intimacy and sexual relationships (e.g., "desire intimacy") [19].

6.6.6 Time of Day Sleepiness Scale (ToDSS)

The ToDSS [20] measures sleepiness at key points throughout the day (i.e., with a goal to address potential variation in day-to-day activities). The tool asks for an estimation of sleepiness severity in three separate columns (i.e., morning, afternoon, evening) and thus provides perceived sleepiness levels throughout the daytime [20].

6.6.7 Horne and Östberg Morningness–Eveningness Questionnaire (MEQ)

The MEQ [21] is a convenient tool for identifying chronotype or "morningness" and "eveningness" tendencies. The so-called "morning larks" are usually the most alert during morning hours, and the so-called "night owls" have the most energy during evening hours. The measure splits chronotypes into three categories that is, "morning-type," "neither-type," and "evening-type." The original version is a 19-item questionnaire while the reduced version has five items [21]. Both versions assess variations in the time of day the individual prefers to engage in certain activities. Data measured by the MEQ has shown morning chronotypes to have earlier sleep schedules (or time-in-bed windows) and earlier circadian temperature phases (i.e., as measured by core body temperature). On the other hand, evening chronotypes have later sleep schedules and later circadian temperature phases. Discovery of polymorphism of the human PER3 gene has been associated with both morningness and eveningness [22, 23], and present-day genetic studies have supported the different chronotype preferences evaluated by the MEQ [21–23].

6.6.8 Sleepiness–Wakefulness Inability and Fatigue Test (SWIFT)

The SWIFT [24] is a newer measure that evaluates the inability to remain awake in addition to fatigue level. It is a 12-item test with a maximum possible score of 36. Six questions correspond to the ability to stay awake, and the other six questions ask about tiredness, or lack of energy. The items are rated between zero and three by "not at all," "just a little," "pretty much," or "very much." When compared to the ESS, the SWIFT was found to better differentiate patients with sleepiness from controls [24], but further validation for clinical use is still warranted.

6.6.9 Visual Analogue Scale (VAS)

Like the SSS [1, 16] which evaluates sleepiness at a given moment in time, the VAS [1] displays a sleepiness rating on a straight, horizontal, fixed-length 100-mm line, which lists the terms "wide awake" and "asleep" on opposite ends. The outcome can be expressed in millimeters (1–100 mm), or commonly displayed on a scale from

0 to 10. Patients write in a line mark that is equivalent to how alert or sleepy they may feel across a given time [1].

6.6.10 Karolinska Sleepiness Scale (KSS)

The KSS [25] is a 9-point Likert scale of situational sleepiness that also records sleepiness at a particular time during the day. Items are scored from one to nine and list the terms "extremely alert" to "extremely sleepy, can't keep awake." Patients are prompted to convey sleepiness level experienced in the last 10 min using the nine progressive graduations of sleep intensity [25].

6.7 Clinical History

Obtaining a full clinical history is an essential first step toward evaluating (1) whether the patient is sleepy; (2) to what degree the patient is sleepy; and (3) how sleepiness may be impacting social, occupational, and/or daytime functioning. Typically, the clinical interview can be conducted between the clinician and patient, but it is important to be cautious when assessing sleepiness via the patient only, as many patients with EDS may not actually be aware that they are, in fact, sleepy [2]. It is common for patients to deny sleepiness either due to the lack of general awareness of what it means to be truly alert, or because it is challenging to be fully aware of the times sleep episodes occur. Some individuals with sleepiness may not admit to falling asleep at all [14]. Popular topics discussed during the clinical interview may include perceived cognitive complaints (e.g., difficulty remembering or concentrating, trouble focusing/paying attention, "cognitive fog"), mood concerns (e.g., irritability, negative mood, feeling down/sad, distress/worry about sleep, temper outbursts), performance impairments (e.g., inattention, lack of productivity, comments from supervisors or co-workers, negative work evaluations), and safety behaviors (e.g., canceling appointments (social and/or occupational), events, engagements, etc.). Thus, the provider should collect a collateral history from the bed partner, caretaker, or close family member/friend to corroborate the patient's report and to further evaluate the degree of sleepiness. A comprehensive assessment of sleepiness can be difficult to obtain by self-report only; hence, follow-up objective measures become valuable tools for diagnostic clarification.

6.8 Objective Sleepiness Measures

Objective, or unbiased measures, are effective at confirming and/or corroborating subjective findings and/or patient accounts. One of the principal features of using objective measures is the ability to demonstrate that sleepiness is present despite conflicting reports (i.e., between patient, bed partner, family, and/or clinician). The two most widely used objective measures of sleepiness are the Multiple Sleep

Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT). It should be noted that neither the MSLT nor the MWT should be used as a sole diagnostic confirmation of a sleep disorder. These measures simply confirm the (1) mere presence of sleepiness and the (2) probable severity of sleepiness [1].

Other central objective measures include polysomnography (PSG), Psychomotor Vigilance Test (PVT), Oxford Sleepiness Resistance Test (OSleR), pupillography, and actigraphy. Objective measures are fundamental in sleep medicine research yet warrant further validation for use in the clinical setting.

6.8.1 Multiple Sleep Latency Test (MSLT)

The MSLT [26] is argued to be the most commonly used objective test of sleepiness. The MSLT involves four or five brief opportunities to nap scheduled at 2-hourly intervals (i.e., usually during the daytime), with the initial nap opportunity taking place approximately 2 h after arising from the major sleep period. The MSLT is conducted immediately following an overnight polysomnography, which must obtain at least 6 h of sleep. The overarching premise behind the use of the MSLT is to determine the patient's actual propensity to fall asleep during the chief period of wakefulness [26].

During the MSLT, patients with suspected and/or explicitly reported sleepiness are asked to wear comfortable pajamas, lie in bed in a dimly lit room, relax, and allow sleep to naturally unfold. Twenty minutes is the time frame permitted to attain sleep across the four or five nap opportunities. Individuals with more sleepiness will fall asleep faster than those with less sleepiness. Once the chances to sleep are performed, the average time to fall asleep (i.e., mean sleep latency [MSL]), and the stages of sleep that were achieved across the four or five nap circumstances are recorded. Patients who possess the ability to fall asleep within 10 min (i.e., have an MSL of $\leq$10 min based on start and end times of each nap or nap opportunity) are characteristically considered to have excessive sleepiness [27]. When a sleep onset rapid eye movement period (SOREMP) occurs in up to one nap episode, it is within the normal range. On the other hand, when SOREMPs occur in two or more nap opportunities, this may be indicative of underlying pathology (e.g., narcolepsy) [26].

The MSLT is often utilized to help confirm the diagnosis of narcolepsy [26] or when assessing residual sleepiness in OSA patients with optimal PAP therapy. Nonetheless, there are no large systematic studies to date that accurately define normative MSLT data [28]. In a study of 2083 people, 170 of whom were previously diagnosed with narcolepsy, Aldrich et al. [29] found the sensitivity of the MSLT to be 70% with a specificity of 97% when using an MSL and SOREMP criteria of $<$5 min and two or more SOREM periods. Regardless of the cause, the severity of sleepiness may be empirically determined with the MSLT and quantify the degree of sleepiness on a given day. However, it should be clear that the MSLT is only validated for the diagnosis of narcolepsy (type 1 and type 2) with a bit of ongoing debate for other disorders of central hypersomnolence [26–32].

6.8.2 Maintenance of Wakefulness Test (MWT)

The MWT [32] is beneficial for (1) demonstrating the ability to remain alert during waking hours and (2) exhibiting the effects of treatment (if any) being used to alleviate EDS. It is important to note that the MWT is not diagnostic but rather more indicative of response to therapy and treatment. In other words, the MWT is not intended to confirm diagnosis but to assess treatment effect(s). Patients may come dressed in regular street clothes, sit comfortably in a semi-reclining seat position, and try to stay awake during four to five 40-min nap chances performed at two-hour intervals, the first attempt given an hour and a half to 3 h after awakening from the major sleep period. The testing room should be free of distractions and noise. Prior to the test start, it is important to ask the patient about his/her sleep from the night before. Because a preceding polysomnography is *not* required for the MWT, a description of the patient's previous night of sleep and whether it was satisfactory in quantity and quality is meaningful information. Accordingly, the time from the lights being turned off to the onset of definitive sleep (i.e., three consecutive epochs of stage N1 sleep, or any one epoch of stage N2, N3, or REM sleep) for each nap time is observed and documented [32]. Nap trials are concluded after 40 min if no sleep has transpired or immediately following sleep onset.

Large-scale normative values for the MWT are scant in the literature [33]. The current consensus posits that a person's ability to remain awake is robustly supported by the ability to stay awake for each of the four, 40-min nap periods (i.e., an MSL of 40 min) [32]. Additionally, an MSL of $<$8.0 min on the 40-min MWT is considered abnormal, and values between 8 and 40 min are of unknown significance [34]. The validity of the MWT to assess the risk of sleepiness on driving, operating heavy machinery, working, and/or potential involvement in an accident has not yet been substantiated [35]. Thus, the MWT should not be used as a standalone test, and the clinician should be cautious when interpreting its outcome [36]. One study attempted to tease apart the variables being measured by the MWT versus the MSLT and found that, unlike the MSLT, which quantifies sleepiness, the MWT considers the degree of arousal (i.e., as measured by heart rate), or the propensity to stay awake during nap opportunities, and the combined effects of sleepiness severity [1, 28, 37]. Neither test is diagnostic of a specific sleep disorder. The MSLT and MWT are designed to simply confirm the presence of sleepiness and its intensity [1, 26, 32].

6.8.3 Polysomnography (PSG)

PSG [16, 38] is designated in the assessment of sleepiness for most patients and is typically an overnight study of continuous sleep monitoring. The in-lab PSG is ordinarily videotaped to allow sleep center staff ample observation time of any abnormal sleep behaviors during the night. While the home sleep study can pick up on unusual events, it is not usually videotaped, so direct observation of the home night's sleep is unavailable. Regardless of the PSG method, the study is customarily performed at the time and for the duration of the main sleep period. It is imperative to conduct an overnight PSG before an MSLT [1, 26, 38]. PSG aims to monitor total

sleep time (TST), sleep efficiency (SE), sleep fragmentation, sleep architecture (i.e., the amount and percentage of each sleep stage attained during the night), cardiac activity, respiratory parameters, limb movements, body positions, and snoring sounds.

Multiple electrodes are applied to the scalp to record the electroencephalogram (EEG), to the lower limbs and chin to record the electromyogram (EMG), and near the eyes to record the electrooculogram activity during the night of sleep monitoring. Additional sensors are placed around the chest and abdomen areas to assess ventilation. Also, air pressure and airflow are monitored via leads placed at the nose and mouth. Other measures include infrared oximetry for oxygen saturation, electrocardiography, gastroesophageal Ph, and end-tidal carbon dioxide concentration. With both the in-lab and home PSG, any presence of abnormal sleep-related breathing events (i.e., apneas and/or hypopneas) or peculiar disruptive behaviors/movements are recorded. The presence of periodic limb movements and extremity activity, which may be suggestive of periodic limb movement disorder and/or restless legs syndrome is also obtained. Home sleep tests are becoming more accessible and convenient for patients, but depending on the home sleep kit, there are not as many leads or electrodes required for hook-up compared to an in-clinic study.

While not always clinically feasible, 24-h PSG monitoring has been shown to predict the overall degree of sleepiness. For instance, Pizza et al. [36] demonstrated an association between TST during waking hours and mean sleep latency on the MSLT. PSG plays an important role in the diagnosis of sleep and wake disorders as well as in the assessment of treatment effects.

6.8.4 Vigilance Testing

The degree of sleepiness, by way of measuring the ability to sustain attention, can be indirectly measured through vigilance testing. There are several versions of vigilance tests, but the Psychomotor Vigilance Test (PVT) [39] is more commonly known and used in various research settings.

During the test, the behavioral consequences of excessive sleepiness are documented by reaction time to digital cues. Consecutive stimuli are presented on a digital screen, and patients are asked to press a button to record reaction timing. The PVT specifically evaluates performance and/or attention impairments [39]. Every behavior, including omissions and commissions, is noted. Studies that have compared versions of the PVT demonstrate a positive relationship between hours of wakefulness and increase in reaction time [39, 40].

6.8.5 Oxford Sleepiness Resistance (OSleR) Test

The OSleR test [41] is an alternative to the MWT and often includes components of the MWT plus vigilance testing. Based on key data, the OsleR test has been found to be reliable for measuring sleep propensity [41]. This sleepiness test has a sensitivity and specificity of 85% and 94%, respectively, for identifying sleep episodes over 3 s

in length [42]. EEG sleep characteristics of 3 s or less duration are identified as microsleep episodes on the OSleR. Additionally, failure for the patient to respond to three sequential illuminations is classified as impaired attention because of microsleep events. Failure to respond to seven consecutive illuminations is considered sleep onset [41].

Upon exam, the patient is asked to sit in a dim-lit room, free of distractions and noise, for four 40-min periods over the course of 1 day. The patient is then asked to respond to a light displayed on a digital screen by pressing a switch, all while reaction time is assessed. The light is lit up for 1 s, every 3 s. The digital screen and switch button are connected to a computer that records correct responses based on the number of times the light is displayed on the screen. This scoring system allows for proper evaluation of the ability to sustain both wakefulness and vigilance [41]. For instance, Bennet et al. found that normal subjects (i.e., with an average MSL of 39.8 min) were able to be distinguished from subjects with sleepiness due to OSA (i.e., average MSL of 10.5 min) [43].

6.8.6 Pupillometry

Pupillometry is used to evaluate sleepiness by measuring eye pupil size and/or oscillations of the pupil [44]. Although pupillometry is less employed in the clinical setting, the use of this test can be clinically beneficial. Because of sympathetic activity, pupils will dilate normally when a person is fully awake and alert. When someone is sleepy, pupils are generally constricted due to parasympathetic activity. If placed in a dark room and fully awake, most individuals can sustain constant pupil size. Sleepiness in those who struggle with maintaining wakefulness will cause the pupil size to fluctuate. Some data have shown that increased pupil oscillations and corresponding decreased pupil size may be associated with subjective sleepiness level [44].

6.8.7 Actigraphy

An actigraph is a watch-like sleep monitoring device that can differentiate sleep versus wake across 24 h, estimate TST, determine circadian patterns, and assess sleepiness level based on movement. Actigraphy operates under the assumption that individuals move more when awake than when asleep. Movement is recorded, quantified, and plotted on a 24-h figure for interpretation. The absence of movement or decreased activity represents sleep time, and frequent movements represent wake time. While actigraphy provides ample rest/activity data, the biggest critique is when the device captures "sleep," but the patient is lying in bed wide awake with the lights off and is very still or not moving.

Objective actigraphy monitoring is recorded over at least a 1-week period, ideally for 2-weeks time. Usually worn on the non-dominant wrist, the amount of movement

Table 6.2 Summary of widely used objective measures of sleepiness

Objective measures of sleepiness
Multiple sleep latency test (MSLT)
Maintenance of wakefulness test (MWT)
Polysomnography (PSG)
Vigilance testing
Oxford sleepiness resistance (OSleR) test
Pupillometry
Actigraphy

throughout the 24-h period is documented. Actigraph devices are rest/activity monitors that work similarly to fitness trackers, wearables, movement devices, or pedometers. Nevertheless, actigraphy data have been clinically validated against PSG, while most consumer wearables data have not (i.e., no large samples to demonstrate efficacy against PSG yet). Validation studies on consumer wearables versus actigraphy versus objective PSG data are of recent interest.

The use of actigraphy can also be a useful cognitive reframing tool, as it provides clinicians an opportunity to demonstrate sleep state misperception, break down some of the common misconceptions about sleep (e.g., waking up is a normal part of sleep, movement during sleep is to be expected), and/or assist in identifying an underlying circadian rhythm disorder (Table 6.2).

6.9 Causes of Sleepiness

Sedentary activities (e.g., sitting in a boring class, watching television, long-distance driving) and other scenarios identified by both objective and subjective measures may reveal situations that unmask physiologic sleepiness when present, but these "at-risk" activities do not necessarily cause sleepiness [1]. For the purposes of this chapter, the most common causes of sleepiness are briefly outlined. Diagnostic and relevant clinical criteria for each of these disorders are detailed at length elsewhere in this text.

6.9.1 Obstructive Sleep Apnea (OSA)/Sleep-Disordered Breathing (SDB)

EDS is often the most cited complaint about patients with untreated OSA [1]. Patients may not report episodes of snoring or gasping/choking themselves; it is often the bed partner who complains of these events. Other common clinical complaints include but are not limited to snoring, mouth breathing, loud/heavy breathing, gasping/choking, witnessed apneas, fatigue, insomnia, frequent arousals, excessive movement at night, night sweats/temperature dysregulation, cold hands/feet, unrefreshing sleep, bruxism, dry mouth, sore throat, coughing, morning headaches, chest pain upon awakening, heartburn, discoordination, concentration/memory difficulty,

weight gain, and nocturia [45–47]. Of note, the symptom of nocturia is highly predictive of underlying sleep apnea and comparable to snoring as an initial screening differential [48].

OSA involves brief continual periods of breathing cessation (i.e., apneas) or partial cessation of breathing/upper airway obstruction (i.e., hypopneas), which usually coincide with significant sleep disruption and fragmentation, reduced blood oxygen saturation, and/or loud snoring [1, 45–47]. The sleep fragmentation (i.e., frequent nocturnal awakenings, changes in sleep architecture) and hypoxia (i.e., low blood oxygen saturation) associated with SDB typically leads to significant sleep deprivation and, as a result, may cause EDS. Chronic central nervous system changes, because of increased sympathetic activation during apneic episodes, may also contribute to sleepiness severity. Other forms of sleep-disordered breathing, including upper airway resistance syndrome (UARS) and central and mixed apneas, have been known to cause EDS [1]. Even after successful treatment of apnea (e.g., continuous positive airway pressure—CPAP), a small minority of patients continue to experience residual daytime sleepiness.

6.9.2 Hypersomnia

6.9.2.1 Narcolepsy Type I (with Cataplexy) and Type II (without Cataplexy)

Narcolepsy is characterized by EDS and abnormal REM sleep transitions [49]. Narcolepsy with cataplexy (type I) is caused by loss of hypocretin (or orexin) producing neurons [50]. Narcolepsy without cataplexy (type II) is more difficult to diagnose and associated with multiple comorbidities.

In narcolepsy type I, there is sudden muscle control loss after strong emotions without warning (i.e., cataplexy) in addition to sleep attacks, sleep paralysis, hypnagogic/hypnopompic hallucinations, and/or fragmented nocturnal sleep. All narcolepsy patients have EDS, but other symptoms are only present in some patients [50]. Individuals with narcolepsy usually indicate that brief naps are refreshing and help to alleviate EDS. There is a refractory period 1 h to several hours later until the next sleep episode occurs [50]. Sleep and wake boundaries are usually blurred causing both excessive sleepiness and fatigue to be present.

6.9.2.2 Idiopathic Hypersomnia (IH)

Unrelenting EDS (despite ample time to sleep), long and unrefreshing naps, extreme difficulty upon awakening (i.e., sleep inertia, which can precede automatic behaviors), and prolonged and undisturbed nocturnal sleep often characterizes patients with IH [51]. There is an insatiable need to sleep that is not alleviated by a full night's sleep, and PSG may show normal sleep architecture and sleep efficiency [51]. Those with IH may sleep normal hours or long amounts of time every night ($>$ 9 hours) but still experience EDS. Recent literature has shown differences between IH with and without long sleep time. Patients with IH and long sleep time

were found to have a lower body mass index, lower MEQ score, be younger in age, and have a higher sleep efficiency than subjects with IH without long sleep time [52].

6.9.2.3 Circadian Rhythm Disorders (CRD)

Patients who endorse symptoms consistent with insomnia and/or EDS but who can sleep relatively free of awakenings once asleep may have a CRD [9] (e.g., delayed or advanced sleep phase syndrome DSPS/ASPS, shift work). Sleep maintenance is usually not a problem for these patients. Those with DSPS, for example, will often have difficulty with sleep onset and may present in clinic with symptoms like sleep onset insomnia. However, once asleep, the patient has little to no difficulty staying asleep. The patient may then have to wake for school/work at an early hour, which is often outside of the patient's biologically determined rise time, and hence results in losing a few hours of sleep. Patients with ASPS may feel pressure to stay up past their early bedtime due to family or social pressure and may lose adequate opportunity to sleep. Similar effects apply when the patient is a shift worker or experiencing symptoms of circadian misalignment due to jet lag/travel. The misalignment with rise time versus biological rise time (and light cues based on time of work shift or light in a different time zone) and subsequent lack of sleep due to these constraints may cause a high degree of daytime sleepiness.

6.9.2.4 Insufficient Sleep Syndrome

Insufficient sleep, or sleep deprivation, occurs when an individual intentionally shortens the night's sleep to focus on another activity or commitment (e.g., social event, work deadline, television show binge). If the activities were not present, the person would otherwise be sleeping and getting the number of biologically predetermined hours of sleep. This intentional form of sleep deprivation frequently results in EDS.

Insufficient sleep and its consequences have been studied and found to be genetically linked. Because of EDS, patients may suffer from impaired cognitive performance (e.g., executive tasks, reduced accuracy, learning, and recall difficulties) and even require more time to complete assignments [1].

6.9.3 Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

RLS is characterized as a "creepy-crawly" uncomfortable sensation that is often accompanied by a deep aching sensation or pain in the arms and legs. This discomfort or pain that urges movement or motion of the extremities often makes it difficult to promote sleep onset.

RLS usually coincides with repetitive stereotypical movements of the extremities (i.e., more often legs than arms) that occur during sleep. Many patients with RLS also experience concurrent periodic limb movements during sleep, and a small percentage of patients with periodic limb movements will experience EDS

[1]. Having the above symptoms can significantly shorten total sleep duration, overall sleep quality, and as a result, contribute to sleepiness severity.

6.9.4 Other Untreated Medical Disorders

Numerous medical disorders have been shown to cause EDS. When the following disorders (note, this is not a conclusive list) are left untreated, not well managed by the provider, or the patient is non-adherent to medication/treatment, EDS may be present; patients with strokes, demyelinating diseases, traumatic brain injury, tumors, arthritis, anemia, acute and chronic pain, vascular disease, peripheral neuropathy, spinal cord injury, organ failure, diabetes, or hypothyroidism may endorse EDS.

6.9.5 Sedating Medications

Many prescription medications, even when taken at night, may cause daytime sleepiness. Central nervous system depressants, benzodiazepine hypnotics, and long-acting benzodiazepines may delay sleep onset, shorten sleep latency, and ultimately increase EDS by acting on GABA receptors [1, 53–55]. Second-generation antiepileptic drugs, dopaminergic agonists, antihistamines, and some antihypertensives have also been demonstrated to produce EDS [1, 54–60]. Whether the EDS is a result of direct sedative effects or due to sleep fragmentation/disruption is unclear and needs further investigation [1, 60].

6.9.6 Important Note About Insomnia

Patients with primary insomnia are not usually sleepy outside of the main sleep period. A clear majority of patients with insomnia are fatigued (e.g., mental exhaustion often having greater impact on perceived daytime functioning) but do *not* have the propensity to fall asleep during the day. If sleepiness is reported or observed (e.g., dozing off while watching TV every night), there should be a high suspicion for an underlying sleep disorder or other untreated medical/psychiatric conditions, as it is far less common for insomnia to cause EDS.

6.10 Consequences of Sleepiness

The more severe the level of sleepiness, the more the likelihood of adverse consequences. It is important to keep in mind that patients with sleepiness may not complain of sleepiness in and of itself but rather its consequences, which may include fatigue, low energy, lethargy, memory lapses, or concentration difficulty. Patients with EDS are subject to increased risk for motor vehicle accidents and accidents in the home or at school/work [61]. Sleepiness may also impact social

adjustment and pleasant activities, thereby creating a vicious cycle with mood disturbances. There is a domino effect when sleepiness invades daily life, as the consequences can lead to impaired performance and reduced cognitive dysfunction.

6.10.1 Fatigue

Sleepiness habitually coincides with daytime fatigue. While it is pertinent to tease apart the two, it may also be important to make sure the two are accurately evaluated simultaneously, if clinically relevant. In a study of narcolepsy type I patients, Droogleever et al. demonstrated that a vast number of patients suffered from severe physical fatigue in addition to EDS [62].

6.10.2 Cognitive Dysfunction

Cognitive changes can place the patient at risk for accidents at work or in the home [61]. Cognitive difficulties may also place the patient at risk for poor educational or work performance. Most commonly, patients will describe "cognitive fog" or difficulty with memory, recall, concentration, attention, and/or focus. These cognitive deficits (e.g., memory) are not specific to a certain sleep disorder but unique to the underlying sleepiness of the disorder [63]. This is becoming more important to screen for and identify, as several studies are now being conducted that show potential long-term effects of cognitive deficits (e.g., increased risk for dementia). Chronic hypoxia associated with SDB has also been hypothesized to lead to brain injury (i.e., chronic tissue loss) [60], thus resulting in further risk for cognitive consequences. When treated appropriately and sleepiness resolves, cognitive impairments typically improve or are rectified [64].

6.10.3 Mood Disturbances

Several mood disorders (e.g., severe anxiety, nocturnal panic, and depression) may clinically manifest with EDS [9, 65–68]. It is imperative that the clinician considers screening for mood symptomology alongside the use of other subjective sleepiness measures. Validated questionnaires such as the Generalized Anxiety Disorder Assessment (GAD-7) [68] and the Patient Health Questionnaire (PHQ-9) [69] may serve as quick and effective mood screening tools and invaluable adjuncts to the clinical interview process.

Sleepiness in the context of mood disturbances, and depression more specifically, is theorized to be either a non-specific homeostatic response mechanism [70] or a manifestation of anergic depression (i.e., also involving low energy, withdrawal from daily activities, lack of interest) [71]. Screening the patient for depression using a validated screening measure (e.g., PHQ-9) and explicitly asking about reduced appetite, negative/blunted/flat affect, hopelessness, and suicidal ideation are imperative to further determine depression severity. In addition, sleepiness and its

consequences may cause distress and worry in many patients. On occasion, when a patient experiences nocturnal panic attacks, which are recurrently due to disrupted nocturnal sleep, EDS may also be present.

6.10.4 Performance Impairments (Home, Work, School, Etc.)

Daytime performance may decrease or stop entirely when patients report EDS. Studies have documented the negative effects of EDS on occupational performance, earning capacity, promotion potential, and increased disability insurance [2]. Patients may report receiving complaints or unfavorable evaluations from co-workers/supervisors about their performance, which may also invoke actual job loss, or the fear of actual job loss. Accidents at home or work and adverse performance due to EDS are usually more common in patients with narcolepsy when compared to age- and gender-matched controls [2].

6.10.5 Safety Behaviors and Social Impact

Patients may allude to other consequences of sleepiness, but it is also relevant to distinctly ask about safety behaviors. Patients with EDS tend to cancel doctor appointments, events, engagements, activities, etc. that they otherwise would attend if sleep was not a major limitation. Patients will also skip out on social events or choose not to participate in activities they typically enjoy because sleepiness makes social activity feel draining or like a chore. Similarly, sleepiness has been shown to be disruptive to family and social life [72]. Patients may feel irritable or "cranky" with family, friends, or co-workers; be callous and uninterested in work or social activities; and have difficulty focusing on tasks around others [73].

6.10.6 Driving Safety/Operating Heavy Machinery Safety

As much as assessing sleepiness during everyday sedentary activities is important, it is equivalently, if not more imperative to identify sleepiness during more active, potentially dangerous situations like driving or operating heavy machinery. Nearly half of all patients will endorse life-threatening occupational incidents or automobile accidents, and many will lose their jobs because of excessive sleepiness [72]. As a sleep community, it should be deemed a medical emergency if a patient endorses the ability to doze off at the wheel when stopped in traffic, doze off while in slow moving traffic, or has the tendency to miss signs/exits as a result of dozing. Over a third of individuals reported dozing off while driving or falling asleep at the wheel in the National Sleep Foundation 2008 Poll of 1000 people [74]. Through verification of driving records obtained from motor vehicle agencies, there is a sevenfold risk of car accidents among patients with EDS [75] with the highest rate of accidents occurring in the early morning hours (i.e., when the greatest sleepiness is traditionally experienced) [61].

Table 6.3 Common causes and consequences of sleepiness

Causes	Consequences
Obstructive sleep apnea (OSA)/sleep-disordered breathing (SDB) Hypersomnia Narcolepsy type I (with cataplexy) Narcolepsy type II (without cataplexy) Idiopathic hypersomnia (IH) Circadian rhythm disorders (CRD) Insufficient sleep syndrome Restless legs syndrome (RLS) Periodic limb movement disorder (PLMD) Other untreated medical disorders Sedating medications	Fatigue Cognitive dysfunction Mood disturbances Performance impairments (e.g., home, work, school, etc.) Safety behaviors Social impact Driving safety Operating heavy machinery safety

Clinicians should routinely pinpoint the signs of EDS in patients who are drowsy while driving. Patients who endorse moderate to severe sleepiness and report a recent car crash or near miss due to sleepiness are considered high-risk drivers [76]. It is not uncommon for those afflicted with EDS to drift over from the lane while driving, miss important signs/exits, forget they drove the last few miles, yawn constantly, and/or doze off at a red light. It is imperative to continue reassessing driving risk during follow-up visits (Table 6.3).

6.11 Interventions and Management of Sleepiness

6.11.1 Pharmacological Management

Pharmacotherapy for patients with EDS should be personalized based on the underlying etiology. Traditional stimulants (e.g., methylphenidate, amphetamine) are no longer the drug class of choice for the management of EDS. Modafinil and armodafinil are wake-promoting agents that have replaced traditional stimulants for the management of EDS in patients with narcolepsy [77, 78]. Modafinil and armodafinil have been approved for EDS associated with narcolepsy, OSA, and shift work sleep disorder [78]. Solriamfetol was recently approved for EDS related to narcolepsy and OSA [79]. EDS may be present even after adequate treatment (e.g., residual EDS in patients using CPAP for OSA), and thus wake-promoting agents may be prescribed to alleviate daytime dysfunction. Oxybate and pitolisant are two medications that treat EDS and cataplexy in narcolepsy and are effective for first-line therapy for EDS in narcolepsy [79A Thorpy MJ. Recently Approved and Upcoming Treatments for Narcolepsy. CNS Drugs. 2020 Jan;34(1):9-27. doi: 10.1007/s40263-019-00689-1. PMID: 31953791; PMCID: PMC6982634.

6.11.2 Non-pharmacological/Behavioral Management

6.11.2.1 Bright Light Exposure

Patients with EDS may benefit from natural, bright light exposure, if feasible given weather and air conditions. Natural light, even if not "sunny," may help regularize and anchor the sleep–wake cycle in addition to improving alertness during the daytime. If natural light is unavailable, a portable light box may be helpful (i.e., at least 10,000 lux to be held approximately 12 inches from the face) in mimicking the brain's usual response to light exposure. For those patients who may not be able to afford a light box or are unable to hold the light box near them for maximum benefit, getting natural light exposure by going outdoors or sitting next to a well-lit window is the best recommendation to boost alertness first thing in the morning and throughout the day. Decreased light exposure and limited physical and/or social activity during waking hours may also be disadvantageous to achieving good quality sleep.

6.11.2.2 Scheduled Naps

For patients whose medications do not completely alleviate EDS, or for those individuals who would prefer not to take stimulants, scheduled preemptive naps may be beneficial. The patient has a few potential options; (1) schedule two 10–15-min naps at times that usually precede the hours where the patient has difficulty keeping alert/staying awake (80); or (2) schedule one single 120-min nap at a time that precedes the "sleepiest" part of the day, as a substitute for several, shorter nap periods [80–82]. This may become a trial-and-error process, as some patients may feel refreshed upon awakening while others may feel much worse and still sleepy/groggy.

The consensus when factoring in scheduled naps: Awakening from a nap feeling unrefreshed is more typical of naps that occur in individuals with OSA or IH. In narcolepsy patients, awakening from naps is customarily refreshing. Current guidelines do not support scheduled naps as the single method for managing EDS but as an adjunct intervention to first-line stimulant medications [80, 83, 84].

6.11.2.3 Caffeine

Caffeine has also been objectively shown to boost daytime alertness [85]. Caffeine may be preemptively scheduled in patients with EDS, which may be especially important for those driving, operating heavy machinery, and/or working the night shift/rotating shift. If possible, caffeine should be used in conjunction with scheduled naps (e.g., drink a cup of coffee 20–30 min before taking a nap, so upon awakening alertness is more likely); however, sensitivity to caffeine widely varies from person-to-person. A schedule that makes sense for the patient's work/school/social life, which includes scheduled naps and caffeine, should be a collaborative part of the treatment plan. It is crucial to take into consideration caffeine sensitivity, as most patients will be able to combat sleepiness, while others may experience withdrawal or caffeine rebound, which may, in turn, exacerbate the degree of sleepiness.

6.11.2.4 Schedule Regularization

Helping the patient set a regular bedtime and rise time is a crucial part of managing sleepiness. Ensuring that the patient maintains a consistent wake-up time is of the utmost importance. This helps with entrainment of the sleep–wake pattern across the 24-h day. Sticking to a regular schedule, not only during the week but also on non-work days and weekends, will only help to keep EDS "in check." It is equally important to enforce scheduled wind-down and wake-up routines. The wind-down period should take place at least an hour before bedtime, aim to be conducted in dim-light, and with a focus on reducing electronics. The wake-up routine should take place within 15–20 min upon waking and should ideally include the use of bright light exposure plus physical activity.

6.11.2.5 Extended Nocturnal Sleep Periods

Patients with narcolepsy or hypersomnia, untreated sleep-disordered breathing, or for those with residual EDS after Positive Airway Pressure (PAP) therapy may benefit from "prescribed" extended sleep periods. An example would be to allow at least an 8-h time-in-bed window every night for a period of 2 weeks. The goal is to ensure the patient allows ample time in his/her sleep window for an increased number of hours of sleep (i.e., to make sure the patient is not intentionally causing sleep deprivation) during the intended sleep period. This is also in an effort to sustain alertness after waking from sleep.

6.12 Fatigue

6.12.1 What Is Fatigue?

The term fatigue in clinical sleep medicine is demarcated from sleepiness as a symptom, as by definition, there is no physiologic drive for sleep, and instead, rest or a need to "de-stress" occurs (e.g., upon lying down in bed, the patient is unable to fall asleep but "feels tired") [86–88]. Therefore, fatigue is not linked to an increased propensity to fall asleep, which is characteristic of homeostatic sleepiness [1].

The perception of fatigue is highly subjective and challenging to describe among patients and clinicians. Subsequently, this makes it commonplace to mistake chronic, crippling fatigue from true sleepiness [89–91]. Fatigue can be either mental, physical, or both, and is most often related to perceived lack of energy and/or exhaustion [1]. Mental fatigue may be described as low mental energy or mental exhaustion due to frustrating mental tasks, intense concentration or vigilance, severe anxiety, and/or impaired cognitive/executive functioning deficits. Physical fatigue frequently occurs because of strenuous muscle activity (e.g., cardio exercise, weight training, etc.) and may also be described as low physical energy or physical exhaustion. In either case, fatigue may be debilitating, overwhelming, and contribute to lassitude, lack of energy, lack of motivation, and/or the feeling of tiredness. Fatigue has also been described as a reduced ability to start or continue various daily activities and/or difficulty with memory, concentration, and/or mood stability.

6.13 Epidemiology

Fatigue prevalence in the clinical setting is unclear, as the definitions of fatigue are inconsistent among clinicians, researchers, and patients. Both mental and physical fatigue may arise in the context of neurologic, medical, and/or psychiatric disorders, and fatigue tends to be more common in women [90, 91]. In one study by Rosekind et al. [92], approximately 55% of study participants (i.e., 4188 employees) endorsed a sleep disorder and/or sleep complaint, including experiencing fatigue [92, 93]. Fatigue rates appeared to be between 7% [92–95] and 45% in the primary care setting [90–92]. Prevalence rates in cancer patients ranged from 37 to 100% [95, 96], inflammatory bowel disease at 40% [97], and stroke patients from 40–70% [98]. Hence, depending on the population studied and definitions of fatigue (e.g., fatigue-related cancer may be described in a completely different capacity than fatigue-related insomnia), prevalence rates vary substantially.

6.14 Etiology

Sleep disorders associated with fatigue include insomnia, circadian rhythm disorders, insufficient sleep, obstructive sleep apnea, restless legs syndrome, and narcolepsy [92, 93]. Fatigue is usually one of several presenting symptoms indicative of the respective underlying disorder, especially when fatigue is due to an underlying medical or psychiatric disorder. Fatigue is not yet known to be hereditary, but some medical causes of fatigue (e.g., diabetes mellitus) may have a genetic predisposition. Sleep disorders (e.g., obstructive sleep apnea, narcolepsy) may be passed down from older generations, and thus make it quite possible that fatigue related to sleep conditions may be inherited too.

6.15 Measuring Fatigue

6.15.1 Subjective Fatigue Measures (Table 6.4)

6.15.1.1 Sleep Diaries

As mentioned above, sleep diaries can provide invaluable information regarding sleep habits and patterns. Although most sleep diaries do not directly assess for fatigue, diaries ask the patient to rate the quality of sleep, which may be influenced by overall fatigue level upon awakening (i.e., the usual time to complete the sleep log).

6.15.1.2 Epworth Sleepiness Scale (ESS)

While the main goal of the ESS [11] is to evaluate the severity of sleepiness over a 2-week period, the measure should be considered if fatigue is reported, as many patients with fatigue may not be sleepy. To aid the clinician in determining the etiology of the fatigue, it is crucial to see if EDS is also present.

Table 6.4 Subjective measures of fatigue

Sleep diaries
Epworth sleepiness scale (ESS)
Fatigue questionnaire (FQ)
Fatigue severity scale (FSS)
Multidimensional assessment of fatigue (MAF)
Vitality subscale (energy/fatigue) of the SF-36
Visual analogue scale to evaluate fatigue severity (VAS-F)

6.15.1.3 The Fatigue Questionnaire (FQ)

The FQ [99] is an 11-item screener used to evaluate the severity of fatigue in the clinical setting. Four items are associated with mental fatigue (e.g., "How is your memory?") while the other seven items are related to physical fatigue (e.g., "Do you need to rest more?"). The total possible score is 11, with a higher score indicative of more severe fatigue. Total score or scores for each category (i.e., mental versus physical fatigue) can be used to help identify chronic fatigue symptoms (CFS) [99].

6.15.1.4 Fatigue Severity Scale (FSS)

The FSS [100] is a 9-item measure that screens fatigue severity in the context of medical and neurologic disorders. In addition, the items are rated on a 7-point Likert scale, where "1" is listed as "strongly disagree" to "7" which indicates "strongly agree." The nine statements are calculated as a mean score (i.e., range 1–7) with higher scores indicating more severe fatigue. The questions ask about motivation, physical activity, carrying out duties, and interference with work, family, social life, etc. [100].

6.15.1.5 Multidimensional Assessment of Fatigue (MAF) Scale

The MAF scale [101] was originally designed to measure fatigue in patients with rheumatoid arthritis but has since been adapted for use in other chronic medical populations, like oncology [101, 102]. The patient is asked to think about fatigue over the past week. The items are scored using a numerical rating scale, and a global fatigue index (GFI) is calculated (only 15 out of 16 items are used to compute the GFI). The four dimensions of self-reported fatigue include (1) amount of distress, (2) timing, (3) degree of interference in daily life, and (4) severity level. The higher the score, the more severe the fatigue, distress, and/or interference with daily life [101, 102].

6.15.1.6 The Vitality Subscale (Energy/Fatigue) of the Short-Form Health Survey (SF-36)

The Vitality Subscale (Energy/Fatigue) of the SF-36 [103] is a 4-item measure which asks (1) "Did you feel full of life?"; (2) "Did you have a lot of energy?"; (3) Did you feel worn out?"; and (4) "Did you feel tired?" to determine global fatigue level.

Scores range from 4 to 24, and responses are scored on a 6-point Likert scale (i.e., "1" is "all of the time," to "6" or "none of the time"). The higher the score, the higher the overall vitality (i.e., increased energy and lower fatigue level). A lower score demonstrates overall lower vitality (i.e., decreased energy and greater fatigue level) [103].

6.15.1.7 Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F)

The VAS-F [25] is an 18-item fatigue rating scale that asks patients to circle the number that best corresponds to their level of energy before and after a night of sleep. Questions range from "not at all tired" to "extremely tired," and "I have absolutely no desire to lie down" to "I have a tremendous desire to lie down."

In sum, the FQ, FSS, MAF, vitality subscale of the SF-36, and the VAS-F have all illustrated excellent internal reliability and good to excellent validity [25, 104, 105] when screening for fatigue severity among diverse clinical populations.

6.16 Clinical History

Patients may commonly misattribute their fatigue-related impairments to poor quality sleep. It is vital for the provider to differentiate whether the fatigue is due to an underlying medical condition or due to an actual sleep disorder (e.g., insomnia disorder). As detailed above, it is valuable to not only ask the patient for a detailed history but also the bed partner, caregiver, or close family member/friend to help distinguish the patient's daytime complaints. A comprehensive sleep consultation including medical, psychiatric, social, and family history should be conducted in order to accurately identify the underlying cause of the fatigue.

As part of the evaluation, the clinician should have a good sense of the patient's daily activities during waking hours (e.g., ability/inability to nap), including level of physical and social activity to ascertain daily activity level. Because fatigue is a frequent by-product of insomnia disorder, asking about overall stress level and current stressors (e.g., family/romantic/professional relationships, marriage discord, work stress, financial hardships, etc.) may additionally provide insight into the underlying etiology of the fatigue. As with any clinical interview, an in-depth review of the patient's medications and supplements (i.e., both prescribed and over-the-counter) is warranted.

6.16.1 Objective Fatigue Measures (Table 6.5)

6.16.1.1 Laboratory Evaluations/Blood Work

In the absence of any revealing findings (i.e., on physical exam or history), and the provider remains clinically suspicious, extensive lab testing may be appropriate. Blood work (i.e., complete blood count and comprehensive metabolic panel) should

Table 6.5 Objective measures of fatigue

Polysomnography (PSG)
Vigilance testing
Actigraphy
Laboratory evaluation/blood work
Electroencephalogram (EEG)
Neuroimaging

screen for possible infection(s), anemia, liver function, electrolyte abnormalities, hormone levels, blood glucose, and vitamin D.

A serum ferritin level and iron study should be conducted if there is clinical suspicion for restless legs syndrome [106]. The ferritin level, which is more a measure of cerebral iron stores than iron saturation percentage, should not be less than 50 μg/L or no less than 16% iron saturation. Otherwise, this reveals a potential source of fatigue, and the need to begin iron replacement therapy.

6.16.1.2 Polysomnography (PSG)

While typically indicated for the assessment of sleepiness, PSG may be worthwhile when nocturnal sleep is disrupted, or when there is high suspicion for sleep fragmentation. The PSG is usually not recommended if insomnia is believed to be the underlying cause of the fatigue [107], but it is important to rule out any sleep-disordered breathing or disruptive nocturnal movements that may underlie the insomnia complaints. Although there are no consistent PSG findings that characterize the sleep of patients with fatigue, there are notable changes that have been documented (e.g., reduced TST, decreased sleep efficiency, more frequent night awakenings, alpha intrusion, decreased REM and slow-wave sleep, and longer sleep latency) [107–111].

6.16.1.3 Actigraphy

There is no direct indication for the use of actigraphy in assessing fatigue; however, actigraphy may help pinpoint any issues related to an irregular sleep–wake pattern and/or sleep fragmentation [107], which may in turn contribute to the overall degree of fatigue. In a study of patients with fibromyalgia using actigraphy, fatigue level was directly related to wake after sleep onset and sleep efficiency [112].

6.16.1.4 Vigilance Testing

Vigilance testing can measure the behavioral consequences of mental fatigue. To specifically assess for mental fatigue, the PVT [40] measures the ability to remain alert and attentive by calculating the reaction time to continuous stimuli. As a result, the test can measure fatigue-related attention and performance deficits [40].

6.16.1.5 Electroencephalogram (EEG)

Fatigue-related seizures have been known to impact daytime functioning and overall quality of life. If sleep-related seizures or subclinical seizures are suspected, a routine EEG should be considered with the use of sleep, hyperventilation, and photic

stimulation parameters. The EEG should be repeated after sleep deprivation if the original EEG result is nondiagnostic. If after three or so sequential EEGs are unrevealing, a long-term video-EEG for 24 h or more (or a prolonged daytime EEG) may be necessary.

6.16.1.6 Neuroimaging

Neuroimaging can help screen for neurologic-related fatigue (e.g., an MRI of the brain may help to identify stroke location(s), seizure foci, lesions, cysts, or tumors, all of which may cause periodic physical fatigue complaints [e.g., lethargy, lack of energy]) [113]. To date, there are no definitive neuroimaging markers specific to fatigue, yet a few recent studies have pinpointed anatomical fatigue-related brain changes. One such study located areas of brain atrophy in multiple sclerosis patients with fatigue [114, 115]. De Lange et al. [116] found areas of atrophy in patients with Chronic Fatigue Syndrome (CFS), and as a result, deemed that atrophy may be reversible with proper fatigue management.

6.16.1.7 Other Studies and Evaluations

Electromyography (EMG) or the nerve conduction velocity test may prove advantageous for identifying fatigue etiology. The results may aid in better screening of neuropathy/radiculopathy, which often mimics the symptoms of restless legs syndrome. Other studies include a pulmonary function test, which may help screen for pulmonary disorders responsible for the fatigue, or an endoscopic evaluation (i.e., performed by an otolaryngologist) to differentiate the airway anatomy, locate any obstruction, determine the severity of enlarged turbinates/adenoids/tonsils, or uncover a prolapsed epiglottis.

A neurological or vascular evaluation may also determine a possible source of sleep disruption contributing to overall fatigue level (Table 6.5).

6.17 Causes of Fatigue (Table 6.6)

6.17.1 Insomnia Disorder

Difficulty falling asleep, staying asleep, and/or waking up too early are the most typical insomnia complaints. Accordingly, it is common to hear complaints of fatigue related to disrupted sleep.

Patients with chronic insomnia are habitually in a hyperarousal state or have elevated sympathetic nervous system activation around the clock. Consequently, chronic insomnia is often a 24-h disorder in that patients not only have difficulty with sleep at night but also during the daytime. This heightened state of arousal makes it less likely to be able to fall asleep during waking hours. Patients may endorse feeling tired, fatigued, irritable, or "moody" throughout the day but are typically unable to take naps [9]. On occasion, however, some patients with insomnia may find

Table 6.6 Common causes and consequences of fatigue

Causes	Consequences
Insomnia disorder	Reduced quality of life
Obstructive sleep apnea (OSA)/sleep-disordered breathing (SDB)	Poor sleep quality
Hypersomnia	Cognitive deficits
Circadian rhythm disorders (CRD)	Performance impairments
Psychiatric disorders	Safety behaviors
Other medical conditions	Mood disturbances
Fatigue syndromes	
Other potential causes	

themselves briefly dozing off when seated and in a relaxed environment before bedtime (e.g., watching television on the couch). This may be a sign of conditioned insomnia in the bedroom, which subsequently reinforces the vicious insomnia pattern and its influence on daily fatigue level.

6.17.2 Obstructive Sleep Apnea (OSA)/Sleep-Disordered Breathing (SDB)

Daytime fatigue is often reported in patients with OSA or other forms of SDB, but the current data do not show a compelling direct association [117]. Women with certain types of fatigue syndromes may be more likely to have other breathing abnormalities like oxygen desaturation and UARS, rather than definitive OSA [117, 118]. In addition to EDS, many patients with a diagnosis of OSA or SDB will frequently endorse both mental and physical fatigue. Proper treatment with PAP therapy will ultimately improve functional outcomes and ensuing sleep-related fatigue complaints [117, 118].

6.17.3 Hypersomnia

In addition to excessive sleepiness, patients with disorders of central hypersomnolence (e.g., narcolepsy with or without cataplexy, IH) may also suffer from severe fatigue.

6.17.4 Circadian Rhythm Disorders (CRD)

Enduring circadian misalignment as a consequence of a CRD (e.g., delayed sleep phase syndrome, shift work) may not only generate sleepiness but also high levels of fatigue.

6.17.5 Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

The irresistible urge to move the legs or arms (i.e., occurring in the evening or during the night) may contribute to daytime symptoms of fatigue. Many patients with RLS will have difficulty falling asleep due to the limb discomfort and/or pain associated with RLS that forces movement in bed to alleviate symptoms. This often causes either a delay in falling asleep or a delay in being able to return to sleep during the night, unfortunately shortening TST.

Like chronic pain, RLS may significantly impact fatigue levels during the day and can present as mental or physical fatigue depending on RLS severity. The same premise applies to PLMD, although far less is known about the presence of PLMD and subsequent daytime fatigue.

6.17.6 Psychiatric Disorders

Fatigue is very common among patients with affective disorders, including anxiety and depression. When fatigue is impacting the ability to complete daily activities, the clinician should attempt to identify any mental health comorbidities. Darbishire et al. [105] demonstrated that about half of patients with chronic fatigue attribute their symptoms to psychological causes. Ordinarily, patients diagnosed with clinical depression tend to exhibit an abnormal lack of motivation, loss of interest or decreased pleasure in activities once enjoyed, negative/sad mood, temper outbursts, mood swings, and/or low energy/extreme fatigue. The fatigue (i.e., both mental and physical) is often debilitating, to the point where inactivity becomes normal. This chronic lack of activity (e.g., boredom, physical, and social activity) further perpetuates the level of fatigue. For instance, a patient who lies in bed for several hours on end (i.e., outside of the main sleep period) to "rest" during the day, or to escape having to attempt any activity may further maintain the feelings of tiredness, exhaustion, and/or anhedonia commonly associated with fatigue. Depending on the severity of the depression, patients may experience fatigue without excessive sleepiness [86–88].

Clinical anxiety, on the other hand, may facilitate both mental and physical fatigue due to overactivity. Chronic stressors (e.g., stress related to health conditions, family/social life, work, etc.), relentless negative thoughts/cognitive distortions, and/or too much physical activity/exercise may lead to a heightened level of daytime fatigue, and subsequently, lead to subpar sleep quality.

6.17.7 Other Medical Conditions

Several medical conditions have been known to directly or indirectly cause fatigue. A careful and cautious review of systems should be performed and screen for the following; chronic pain/pain disorders, eye strain, infections (e.g., urinary tract

infection, endocarditis, mononucleosis, other bacterial infections, etc.), low iron, autoimmune disorders, gastroesophageal reflux disease, hypertension, cardiovascular disease or heart failure, thyroid dysfunction or disease, diabetes mellitus, connective tissue diseases, endocrine abnormalities, malignancy, Parkinson's disease, multiple sclerosis, etc. This review will often disclose the source of the fatigue, but it may require patience from both the patient and provider to complete further testing.

Excessive daytime fatigue and associated lack of energy/motivation may be due to hematologic (e.g., anemia, vitamin B12 deficiency), cardiac (e.g., congestive heart failure, coronary artery disease), pulmonary (e.g., chronic obstructive pulmonary disease), endocrine (e.g., hypothyroidism), neurologic (e.g., multiple sclerosis), or rheumatologic (e.g., fibromyalgia, arthritis) conditions. When fatigue is a result of an underlying medical illness, it is with treatment specifically targeting the medical disorder that will likely ameliorate the associated fatigue.

6.17.8 Fatigue Syndromes

Although fatigue syndromes are common diagnoses of exclusion, the clinician should consider them and any potential impact on daytime functioning. Chronic fatigue syndrome (CFS) generally presents as unexplained fatigue associated with difficulty sleeping, cognitive complaints (e.g., "cognitive fog." difficulty concentrating), irritability, and flu-like symptoms for at least 6 months [119]. Sleep problems are customary (and to be expected) in patients with CFS [117]. If the fatigue is continuously disabling, persists for more than 6 months, and does not meet the criteria for CFS as deemed by the Center for Disease Control, it is likely that the patient has idiopathic chronic fatigue. Still not well understood, fatigue syndromes can be paralyzing and cause severe detriments to overall functional ability.

6.17.9 Other Potential Causes

Patients should be educated about other possible reasons for their fatigue. Quite often, the cause of fatigue may not be sleep-related (i.e., despite patients "blaming" sleep for their level of fatigue). Fatigue may be caused by several other potential sources including but not limited to; dehydration, boredom, insufficient diet, mental exertion, physical exertion, excess weight/obesity, lack of activity, medication side effects, and substances (e.g., excess alcohol, nicotine/tobacco, cannabis, caffeine).

6.18 Consequences of Fatigue

6.18.1 Reduced Quality of Life

Because there is still so much to be discovered about fatigue, the direct consequences are meager and inconclusive. Generally, fatigue negatively impacts sleep quality as well as overall quality of life [117]. The experience of fatigue is usually not a pleasant one, and the consequences can be utterly debilitating.

6.18.2 Poor Sleep Quality

Sleep disturbance and resulting diminished sleep quality may be a by-product of fatigue. Sleep quality and fatigue have a bi-directional relationship, one influencing the other (e.g., poor sleep quality leading to increased fatigue; severe fatigue impacting sleep quality). In 87–95% of CFS patients, unrefreshing or nonrestorative sleep is a common complaint [117–121]. Some patients with CFS may not have the best understanding of their sleep and may subsequently experience sleep quality misperception (e.g., overreporting of difficulty sleeping and underestimating sleep efficiency) [117, 119, 120]. Sleep disturbances may therefore contribute to fatigue, and vice versa.

6.18.3 Cognitive Deficits

The impact of fatigue-related cognitive dysfunction is also unclear, yet some objective tests have shown changes in attention, information processing, executive functioning, and motor functioning [117, 122–125]. Other cognitive complaints because of mental fatigue or mental exhaustion have been associated with difficulty completing daytime tasks (i.e., concentration, memory, and attention complaints).

6.18.4 Performance Impairments

Fatigue-related performance impairment is a relatively new phenomenon, and its consequences (e.g., in the workplace) may be multifaceted and complex. In one study, higher ratings of subjective fatigue were associated with slower decision-making and lower risk options [121].

6.18.5 Safety Behaviors

Patients with fatigue may engage in various safety behaviors (e.g., cancel/reschedule social events, engagements, doctor appointments, etc.). Patients may also skip or stop participating in physical activity. These safety behaviors, in an attempt to

alleviate the level of fatigue, in turn contribute to its disabling nature. Patients may have difficulty starting, carrying out, or completing their usual daily activities (e.g., household chores, assignments/projects related to school/work, etc.).

6.18.6 Mood Disturbances

Negative mood, irritability, distress/worry, etc. may be consequences of severe fatigue. Mood is negatively influenced by greater amounts of fatigue (e.g., the higher the level of fatigue, the greater the chance for poor mood). For patients with chronic insomnia and complaints of daytime fatigue, it is common to worry about their sleep during the day, which often results in further delay of sleep onset at night. This increase in sleep latency due to distress/worry may then negatively increase fatigue level during wakefulness.

6.19 Interventions and Management of Fatigue

Interventions (i.e., pharmacologic and nonpharmacologic) that directly target the underlying sleep complaints may help to improve fatigue severity [117].

6.19.1 Pharmacological Management

The guidelines for fatigue pharmacotherapy suggest that treatments should be specific and tailored to the patient depending on the underlying etiology. Because fatigue is most often a symptom of a primary disorder, there are numerous alternatives to managing the fatigue based on its cause. Additionally, the pattern of fatigue may help the provider determine its cause. An example is a patient with hypothyroidism as the underlying cause of the fatigue. This patient feels refreshed upon awakening in the morning, but in a short time after being awake develops sleepiness with activity. In this case, the fatigue may be best managed with thyroxine supplementation. Pharmacotherapy should therefore be personalized based on the distinct fatigue etiology and pattern. Also, if the fatigue is present in addition to EDS, the use of medications may prove advantageous. Therapies targeted at improving sleep symptoms and/or sleep complaints may help remedy daytime dysfunction [117].

The medication management of fatigue will most likely be individualized and on a case-by-case basis. Modifying the timing of medication, especially if sedating (i.e., taking medication at bedtime instead of morning or daytime), or avoiding sedating medications entirely may help increase daytime alertness and diminish overall fatigue level.

6.19.2 Non-pharmacological/Behavioral Management

6.19.2.1 Healthy Sleep Practices (a.k.a. Sleep Hygiene)

Basic behavioral principles regardless of etiology may help to at least partially improve fatigue. Interventions that directly focus on improving sleep quality may also help rectify daytime fatigue [117]. Healthy sleep practices (e.g., increasing physical activity, limiting large meals/heavy foods/excessive liquids before bedtime, reducing electronics, creating a sleep-conducive bedroom environment, etc.) and ensuring the patient is getting enough sleep at night are cardinal to improving fatigue symptoms. Avoiding alcohol, nicotine/tobacco, and/or recreational drugs will help minimize fatigue as well. Too much caffeine may lead to a withdrawal phenomenon and potentially contribute to or even exacerbate fatigue, and thus should be avoided if the patient is sensitive to its effects. Endless amounts of stimulating activities too close to bedtime or during wake after sleep onset may all be counterproductive to increasing energy and alertness.

6.19.2.2 Schedule Regularization

Ensuring the patient maintains a regular sleep schedule is paramount (i.e., helping the patient set a regular bedtime and rise time to manage fatigue level). This is especially important when insomnia-related fatigue is the primary complaint. For example, the patient may feel extremely tired during the day and get into bed earlier at night to get more sleep and remedy daytime fatigue the following day. The fate of this behavior makes sleep even more erratic and dispersed within a longer time-in-bed sleep window (e.g., in bed for 11 h but only sleeping 7 h). Following the bad night of sleep, the patient may have the urge to stay in bed late the next morning. As noted above, it is equally worthwhile to focus on relaxing, non-stimulating activities during the wind-down and wake-up routines. Perhaps a focus on enjoyable, pleasant activities in addition to deep breathing and/or relaxation exercises may help to ameliorate the burden of fatigue throughout the day and before bedtime.

6.19.3 Bright Light Exposure

Daytime bright light exposure is a valuable intervention that will only help strengthen circadian rhythms and augment sleep quality. Patients with fatigue may benefit from natural, bright light exposure, so long as the light exposure is not too close to bedtime. Light exposure upon awakening will regulate the sleep–wake pattern and enhance alertness. This may, in turn, help boost energy levels and decrease the feeling of tiredness or exhaustion.

6.19.4 Increasing Physical, Social, and Pleasant Activity

Helping the patient set small, specific, and realistic goals to increase physical activity during the week (e.g., 10–15 min walk outside twice per week) may help to decrease

fatigue level. As an active coping strategy for lack of energy or motivation, light exercise (e.g., walking, yoga, stretching, pool aerobics) can boost mental clarity and alertness. Incorporating more exercise as part of a daily routine is conducive to achieving better quality sleep. However, increased exercise or physical activity too close to bedtime or during nocturnal awakenings is counterproductive to good quality sleep, as exercise tends to increase core body temperature.

Because irritability, frustration, and mood instability are common among those with fatigue, it may also be useful to recommend an increase in social activity (i.e., scheduling time with friends, day trips with family) or encourage patients to schedule pleasant, enjoyable activities (e.g., painting, knitting, playing an instrument). Incorporating all three areas (i.e., physical, social, and pleasant activity) into the daily schedule encourages patients to become actively involved in their ability to improve their own mood and level of alertness. Partaking in physical and/or social activity while outside (e.g., getting bright light exposure and taking a walk around the neighborhood) is an optimal intervention, which may ultimately decrease overall fatigue level.

6.20 Summary

How Clinically Relevant is it to Differentiate Sleepiness from Fatigue?

Although EDS may be accompanied by physical weariness and mental fatigue, sleepiness is an actual, physical, propensity to fall asleep. In other words, performance may slow or stop entirely with sleepiness while performance may slow/become challenging to complete but will most likely continue with fatigue. Most patients with EDS also report fatigue, but not all patients with fatigue report or experience EDS. Those without a sleep problem should be able to stay awake throughout the daytime (or required period of wakefulness), even in the context of feeling fatigue. Patients may not feel well during the day when impacted by mental and/or physical fatigue, but daily activities are still usually able to be completed without actually falling asleep. Those with true sleepiness will have difficulty staying alert during everyday activities, even when wakefulness is desired and/or required. Thus, it is imperative that this distinction is made, and an appropriate treatment plan is formulated (Table 6.7).

Table 6.7 Subjective and objective measures for EDS and fatigue

Name of test or measure	Subjective vs. objective	Indication
Sleep diaries	Subjective	Sleepiness and fatigue
Epworth sleepiness scale (ESS)	Subjective	Sleepiness and fatigue (can be used to screen for the presence of co-occurring EDS)
Stanford sleepiness scale (SSS)	Subjective	Sleepiness
Pittsburgh sleep quality index (PSQI)	Subjective	Sleepiness
Time of day sleepiness scale (ToDSS)	Subjective	Sleepiness
Morningness–Eveningness questionnaire (MEQ)	Subjective	Circadian preference (may provide insight into etiology of EDS)
Sleepiness–wakefulness inability and fatigue test (SWIFT)	Subjective	Sleepiness and fatigue
Visual analogue scale (VAS)	Subjective	Sleepiness
Karolinska sleepiness scale (KSS)	Subjective	Sleepiness
Multiple sleep latency test (MSLT)	Objective	Sleepiness
Maintenance of wakefulness test (MWT)	Objective	Sleepiness
Polysomnography (PSG)	Objective	Sleepiness and fatigue
Vigilance testing	Objective	Sleepiness and fatigue
Oxford sleepiness resistance (OSleR) test	Objective	Sleepiness
Pupillometry	Objective	Sleepiness
Actigraphy	Objective	Sleepiness and fatigue
Laboratory evaluation/ blood work	Objective	Fatigue
Electroencephalogram (EEG)	Objective	Fatigue
Neuroimaging	Objective	Fatigue
Fatigue questionnaire (FQ)	Subjective	Fatigue
Fatigue severity scale (FSS)	Subjective	Fatigue
Multidimensional assessment of fatigue (MAF)	Subjective	Fatigue
Vitality subscale (energy/ fatigue) of the SF-36	Subjective	Fatigue
Visual analogue scale to evaluate fatigue severity (VAS-F)	Subjective	Fatigue

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Health Economics of Sleep Disorders

7

Babak Mohit, Richard Chang, and Emerson M. Wickwire

Abstract

Economic aspects of health care have never been more important than they are today. In the modern healthcare climate of increasing costs on the one hand and limited resources on the other hand, patients, payers, policymakers, and multiple stakeholders are increasingly attuned to healthcare costs and value derived from healthcare services. The purpose of this chapter is to introduce and briefly review the scientific domain of sleep health economics. First, we present a very brief overview of health economics science. Second, we review several key studies regarding economic aspects of sleep disorders and their treatments. Finally, we suggest future directions for health economic research in sleep medicine.

Keywords

Sleep · Economics · Costs · Utilization · Quality of life · Treatment

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7.1 Introduction to Health Economics

7.1.1 Defining Key Outcomes: Health Economic Perspectives in Sleep Medicine

Economics is a study of the value of limited resources, and from a health economic perspective, value is in the eye of the stakeholder [1]. In sleep medicine, common stakeholders include patients, providers, payers, employers, health systems leaders, and others [2]. Each stakeholder values sleep for different reasons. For example, patients value sleep as a vehicle for enhanced quality of life, greater recreational engagement, and time with family and loved ones [3]. Payers value reduced healthcare spend [4]. Employers value increased workplace productivity [5]. Health systems value increased referrals, revenues, and retention [6]. Table 7.1 presents the perspectives of common stakeholders in sleep medicine.

7.2 Measurement Matters: Costs Framework for Sleep Disorders

7.2.1 Direct and Indirect Costs

In the broadest sense, in addition to morbidity and mortality outcomes, the economic burden of illness [7] is divided into two separate categories of costs [8, 9]. ***Direct costs*** include costs directly associated with medical care for a given disease, such as medical visits, hospitalizations, diagnostic procedures, treatments, and other goods and services [10, 11]. ***Indirect costs***, on the other hand, include additional, non-disease-specific outcomes such as the cost of patient time, the cost of family (or non-family) caretakers, overall healthcare utilization (HCU) (e.g., for comorbid diseases), accident risk, and workplace productivity, to name a few [12, 13]. Notably, each of these indirect costs is measurable in monetary terms and is borne primarily by one stakeholder (e.g., costs associated with workplace productivity are borne by employers).

Table 7.1 Important stakeholders of health care

Stakeholder	Stake
Person/Patient	Personal hygiene; Reduced out of pocket costs; Better quality of life; Increased lifespan
Employer	More productivity; Reduced insurance costs
Healthcare system	Increased referrals; Increased efficiency through economies of scale; Dominant market position
Government	Healthier population; Satisfied population; Increased tax revenue; Lower healthcare costs
Societal	Healthier population; Satisfied population; Increased societal productivity; Lower healthcare costs

7.3 Health-Related Quality of Life (HRQoL) as a Measure of Morbidity

In addition to monetized costs, health-related quality of life (HRQoL) is a key economic outcome that enables payers and policymakers to make evidence-based decisions when allocating scarce health resources. HRQoL is a term that indicates the breadth and diversity of characteristics of life that other traditional measures of "health" do not capture [14, 15]. For example, patients are impacted by factors such as perceived familial and societal roles, freedom of choice (or lack thereof), overall happiness, or perceived disability. Notably, each such component of HRQoL is subjective and rated by the patient [16]. In terms of assessment, HRQoL is typically measured [17] in both general [18] and disease-specific domains [15, 19–21]. For example, the most common general HRQoL instrument used in sleep disorders research is the 36-item Medical Outcomes Study Short-Form 36 (SF-36), which assesses HRQoL in eight domains [22]. Subscale scores range from 0 to 100, based on community norms. Higher scores indicate better HRQoL. Another most common instrument to measure generic health utility scores is the five-dimensional Euro Quality of Life (EQ-5D) developed by the EuroQOL group [23]. The related EQ-5D-5L questionnaire has questions on the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions has five levels, which include no problems, slight problems, moderate problems, severe problems, and extreme problems. Other generic measures that researchers have employed to measure quality of life in sleep disorders have included the Health Utilities Index (HUI) [24], the sickness impact profile scale [25, 26], Nottingham Health Profile [27], functional limitations profile [26], and the WHO Quality of Life-BREF (WHOQOL-BREF) [28]. Complementary, disease-specific measures of HRQoL have been developed for insomnia [15, 16, 19–21, 29–35], obstructive sleep apnea [16, 35–38], and other sleep disorders [35, 39–44].

A standardized HRQoL is often expressed as a utility score, which measures the utility preference weight of time and quality of life on a scale from zero to one [8, 9]. A utility score of one represents the hypothetical "health state" of perfect health [8, 9]. A utility score of zero corresponds with a "health state" equivalent in preference to being dead. HRQoL utility scores between zero and one indicate greater or lesser morbidity, with weights closer to one corresponding to less severe, more preferred "health states," and weights closer to zero corresponding to more severe, less preferred "health states" [8, 9]. The HRQoL measure produces standardized utility scores that are both comparable across "health states," and can also be combined to estimate quality-adjusted survival [8, 9].

7.4 Quality-Adjusted Life Years (QALYs)

Q***uality-adjusted life years (QALYs)*** are a key economic outcome and simply the product of an HRQoL utility score of health state and time (in years) the person spends in that state [8, 9, 45]. Therefore, if a person spends 1 year in the hypothetical

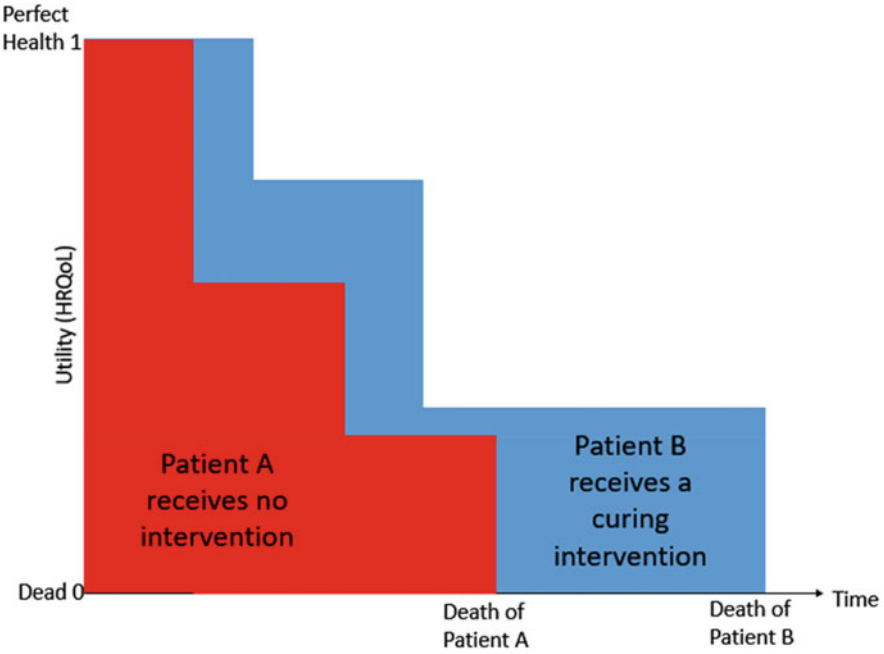

Fig. 7.1 A demonstration of the relation between HRQoL and QALYs

state of perfect health, that person has lived one QALY. If a person spends 6 months (0.5 years) in perfect health, and 6 months in a diseased state with an HRQoL utility score of 0.4, that person has lived $(0.5 \times 1) + (0.5 \times 0.4) = 0.7$ QALY and has lost $(1 - 0.7) = 0.3$ QALYs due to disease. Also, if one patient loses one QALY from sleep apnea and one other patient loses one QALY from insomnia, from a health economics perspective the two losses are equivalent. Similarly, if one health intervention [for example, continuous positive airway pressure (CPAP) for sleep apnea] can help one patient gain one QALY, and another intervention, for example, cognitive-behavioral therapy (CBT) for insomnia, can help another patient gain one QALY, the value of these two interventions is identical from a health economics perspective [45]. These relations are highlighted in Fig. 7.1 where the patient who receives the intervention lives the QALYs indicated by the red and blue areas while the person who did not receive the intervention only lives the QALYs indicated by red area.

7.5 Monetizing QALYs: Cost-Effectiveness

Researchers report the results of a ***cost-effectiveness or cost-utility analysis*** either as a cost-effectiveness ratio (CER) or, more frequently, as an ***incremental cost-effectiveness ratio (ICER)***. A ***cost-effectiveness ratio*** is used to report the results

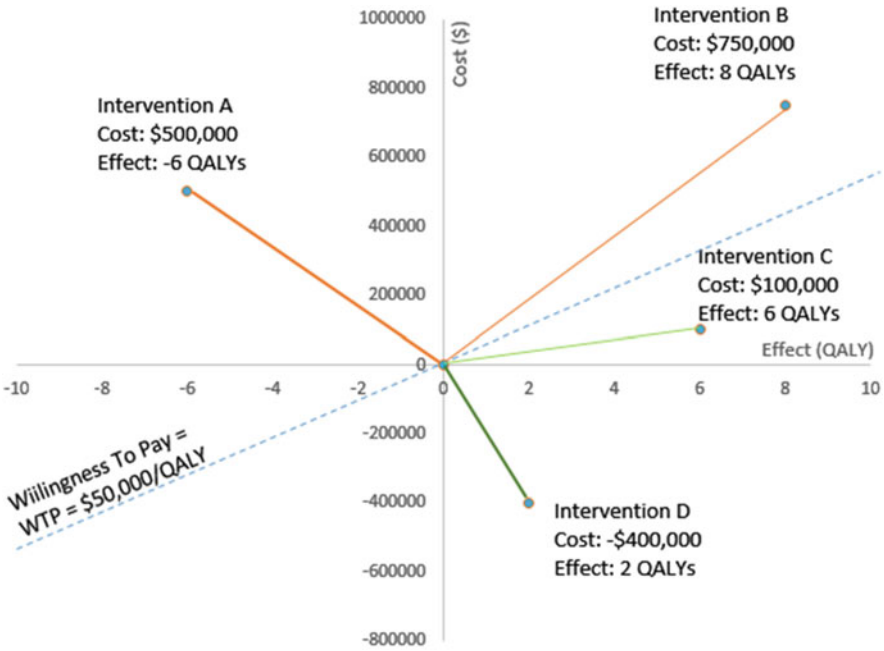

Fig. 7.2 An illustrative guideline to interpreting the incremental cost-effectiveness ratio (ICER). Recreated based on the work by Paulden [48]

of a single intervention, and its unit is dollars per QALY (USD/QALY) [8, 9]. More frequently, the literature reports the results of a cost-utility analyses as an ICER, where the costs and health outcome effects of one intervention are incrementally compared to the costs and health outcome effects of a competing intervention and reported with a USD/QALY unit [8, 9]:

$$\begin{aligned}\text{ICER} &= \frac{\text{Costs of Intervention 2} - \text{Costs of Intervention 1}}{\text{Effect of Intervention 2} - \text{Effect of Intervention 1}} \\ &= \frac{C_2 - C_1}{E_2 - E_1}(\text{USD/QALY}).\end{aligned}$$

When interpreting an ICER, if an intervention costs less than its comparator and produces more QALYs than its comparator, it has higher value and is ***dominant*** to its comparator, suggesting that policymakers should adopt the intervention. If an intervention costs more than its comparator and produces less QALYs than its comparator, it has less value and is ***dominated*** by its comparator and policymakers should not implement the intervention [8, 9]. More frequently, however, interventions either cost less and produce less QALYs or cost more and produce more QALYs. In these cases, the implementation of the intervention will depend on stakeholder's ***willingness-to-pay (WTP)*** [8, 9, 46, 47]. Therefore, in Fig. 7.2, as compared to the point of origin of doing nothing (Cost 0, QALY 0), intervention A is

dominated (Cost 500,000, QALY -6) and should be avoided under all conditions; intervention D is dominant (Cost −400,000, QALY 2) and should be implemented immediately; and intervention C (Cost 100,000, QALY 6) should be implemented if there is a $100,000 startup budget, because it is under the WTP line of $50,000 per QALY. On the other hand, intervention B (Cost 750,000, QALY 8) even though produces the most amount of QALYs, and even if there is a startup budget of $750,000 available, it should be avoided because it falls above the WTP line of $50,000/QALY.

7.6 Economic Aspects of Sleep Disorders and Their Treatments

The economic impact of sleep happens through several mechanisms and pathways. One pathway, which we title as the direct pathway, involves HCU and costs that directly relate to the diagnosis and treatment of sleep disorders such as OSA, insomnia, restless leg syndrome (RLS), excessive daytime sleepiness, and fatigue, as well as circadian conditions such as shift work and jet lag. This is in contrast to what we title the indirect mechanisms, which include the economics of sleep as a comorbidity and the economics of sleep in the workplace. In the workplace, sleep not only impacts absenteeism and presenteeism (being present at work but having less productivity due to insufficient sleep), but also is associated with an increase in accidents and errors, and industrial injuries. Finally, sleep disparities also contribute to socioeconomic disparities, which ultimately impose an indirect cost. The following section of this chapter reviews the literature related to each of these pathways.

7.7 The Direct Pathway

7.7.1 Obstructive Sleep Apnea (OSA)

7.7.1.1 Costs of Untreated OSA

OSA is associated with significant economic costs borne by multiple stakeholders, including patients, payers, employers, and society. A white paper commissioned by the American Academy of Sleep Medicine (AASM) estimated the total societal-level costs of OSA to exceed 150 billion US Dollars (USD) per year in the United States alone, including 30 billion USD due to increased healthcare use [49]. Researchers from New Zealand revealed that the total annual societal costs of OSA for New Zealanders aged 30–60 years were at 40 million USD (range 33–90 million USD) or 419 USD per case, which included 58% direct medical costs [50]. In Denmark, annual costs were estimated at 3860 Euros (EUR) per patient [51]. Researchers from Taiwan report that patients with OSA had significantly more outpatient visits (30.3 vs. 18.6), outpatient costs (1231.2 vs. 764.8 USD), inpatient days (1.8 vs. 1.2), inpatient costs (563.6 vs. 276.7 USD), and total costs (1794.8 vs. 1041.5 USD) than comparison subjects during the 1-year follow-up period [52].

Two separate reports of prospective case–control studies based in Israel reported [53] that OSA patients had 2.2-fold greater utilization as compared to healthy controls. Similarly, this same group [54] reported that the healthcare costs 2 years before diagnosis were over 1.8 times as high for elderly patients with OSA, relative to non-OSA controls. Further, results suggested OSA-related costs increase with age, as they were 1.9 times higher among older adults with OSA than costs among middle-aged adults with OSA.

A series of retrospective studies of the elderly population also report on increased costs of sleep specific to this age group. A study from the United States reported that the total costs for OSA-related hospital admission increased from 22,250 USD per patient in 2002 to 31,527 USD per patient in 2012 [55]. Two recent studies [56, 57] report on the costs of OSA among Medicare beneficiaries. Wickwire and colleagues found that during the year prior to OSA diagnosis and relative to matched non-sleep-disordered controls, patients with OSA demonstrated increased HCU and higher total annual costs across all points of service (19,566 USD), with the greatest marginal increase in inpatient care (15,482 USD), and the lower marginal increase in prescriptions (431 USD) [56]. Similarly, Chhatre also found OSA to be significantly associated with higher costs (OR = 1.60; 95%, CI = 1.58, 1.63) among Medicare beneficiaries [57].

7.7.1.2 Costs Associated with OSA Testing and Treatment

Despite consensus that associates OSA with substantial economic burden, far less is known about the potential economic benefit of OSA treatment. A review by Wickwire et al. [58] focuses on cost-effectiveness and monetized economic impact of OSA treatments and the impact of OSA treatment on monetized health economic outcomes. Most of the studies this review covers report reduced costs. The most straightforward cost of treatment of OSA was estimated in the AASM whitepaper [49]. This paper reports the direct costs that include expenditure associated with testing, appointments, treatment devices, and surgery if necessary. The total expenditure in the United States on diagnosis and treatment of OSA in 2015 was approximately 12.4 billion USD. Physician office visits and testing account for 7% of these costs. Another 50% of the costs are attributable to positive airway pressure (PAP) devices and their accessories, or custom oral appliances. Surgical treatments, which are appropriate for some patients with OSA, account for the remaining 43% of costs. In terms of OSA, surgical costs typically include nasal reconstruction, tonsillectomy, palatoplasty, bariatric surgery, and hypoglossal nerve stimulation. For a typical patient with OSA, these costs average 2105 USD annually. After removing surgical costs, which most patients with OSA do not require, the average cost for a typical OSA patient drops to 1190 USD annually.

Other studies of the costs of OSA treatment include multiple observational studies from Europe, which have evaluated the impact of OSA treatments on HCU and costs [51, 59–65]. The vast majority of these studies report that, compared with no treatment, PAP reduces HCU and costs. However, one study based on a large administrative review in Denmark found that relative to 1 year prior to diagnosis, neither CPAP nor uvulopalatopharyngoplasty (UPPP) was associated with

reductions in HCU volume or cost within 2 years [51]. In addition, three other observational studies evaluated the impact of OSA surgeries on HCU [51, 66, 67]. Two evaluated the economic impact of surgical approaches for OSA among children and adolescents and one among adults. One of the two studies conducted among children involved children with sickle cell disease (SCD), and both studies found that, compared with no treatment, adenotonsillectomy was associated with reductions in total cost, hospitalizations, and Emergency Department (ED) visits, as well as fewer outpatient visits among those with SCD. A third study evaluated UPPP among adults with OSA and found no benefit from UPPP on Healthcare Utilization (HCU) or costs [51]. Finally, a recent study from Canada evaluated the cost-effectiveness of preoperative obstructive sleep apnea screening both perioperatively and during patients' remaining lifespans at four levels [68]. These included (1) no screening, (2) STOP-Bang questionnaire alone, (3) STOP-Bang followed by polysomnography (STOP-Bang + polysomnography), and (4) STOP-Bang followed by portable monitor (STOP-Bang + portable monitor). The results of this study revealed that STOP-Bang + polysomnography was the most effective strategy and was more cost-effective than both STOP-Bang + portable monitor and STOP-Bang alone in both analyses. In perioperative analyses, STOP-Bang + polysomnography was not cost-effective compared to no screening at the $4167/quality-adjusted life month threshold (incremental cost-effectiveness ratio $52,888/quality-adjusted life month). The authors concluded that the cost-effectiveness of preoperative obstructive sleep apnea screening differs depending on time horizon. A recent comprehensive review of economic evaluation of CPAP therapy for obstructive sleep apnea summarizes these findings [69].

7.7.2 Insomnia

7.7.2.1 Cost of Untreated Insomnia

Insomnia is the most common sleep disorder among adults, with a historic prevalence rate ranging between 9 and 12% [70, 71]. Estimates show that up to one of three of the adult population will experience transient insomnia in their lifetime [72, 73]. Insomnia is associated with many adverse health outcomes and diminished quality of life, which place a large economic burden on society. Although study settings, design, and population vary widely, estimates of the total costs of insomnia range from 28.1 billion to 216 billion USD [74, 75].

The literature also shows large variations of direct costs related to Insomnia. Chilcott and Shapiro [76] provide the lowest estimate of annual direct costs of insomnia in the United States to be 2.9 billion USD, whereas Stoller [77] provides estimates for direct costs of insomnia as high as 45.3–51.2 billion USD. Between these two endpoints, another study has estimated the direct annual costs of insomnia at 21.8 billion USD [78]. A study from France aggregated previously published data and estimated the annual direct costs at 3.2 billion USD [11], while a more recent study found annual direct costs in the province of Quebec to be 476.5–509.9 million USD [12].

7.7.2.2 Insomnia Treatment Options and Their Costs

Pharmacotherapy

The first study of insomnia-related treatment costs revealed a per-person 6-month treatment cost of 586.78 USD, which included drug costs, physician visit, and time missed from work for physician visit [79]. A more rigorous study found that relative to no treatment, eszopiclone was associated with a net cost increase of 74 USD per patient (549 vs. 475 USD) over 6 months [80].

Behavioral Treatments

McCrae and colleagues [81] present evidence from a clinical setting, which shows that CBT reduces future healthcare costs for patients with insomnia. They estimated HCU (total costs, outpatient costs, primary care visits, Current Procedural Terminology (CPT) costs, number of office visits, and number of medications), but not indirect costs, in the 6 months before and after treatment. Controlling for baseline costs and relative to non-completers, those who attended at least three treatment encounters demonstrated 196.86 USD lower posttreatment costs. Two recent articles review and summarize these findings [82, 83].

7.7.3 Restless Leg Syndrome

Studies on the economic impact of restless legs syndrome (RLS) have been limited. One study [39] found that decreased workplace productivity loss due to primary RLS was about 5.6 h per 40-h workweek. In this study, the annualized rates of direct healthcare expenditure were estimated at 350 USD (187 USD medical visits, 129 USD medications) for participants with primary RLS, and 490 USD (274 USD medical visits, 171 medications USD) for chronic RLS patients. RLS is common and associated with adverse health consequences among older adults [39, 84]. Another study of elderly RLS patients assessed in an ambulatory care setting in Germany [40] reported that mean annual total costs attributable to RLS were 2090 EUR per patient. This included direct costs (780 EUR, with 300 EUR attributed to drug costs and 354 EUR to hospitalization costs), as well as indirect costs of 1308 EUR based on productivity loss. A second study reported the health burden of RLS in terms of HRQoL but did not present detailed monetary results [42].

7.7.4 Narcolepsy

The first study on the economic impact narcolepsy was from Germany, where the researchers report that the total annual costs of disease were 14,790 EUR per patient. Direct costs were 3180 EUR, which consisted of 1210 EUR in hospital costs, 1020 EUR in drug costs, 90 EUR ambulatory care costs, and 20 EUR ambulatory diagnostics. Over 50% of the drug costs were due to the newer wake-promoting drugs such as modafinil and armodafinil [40]. Furthermore, a study from Denmark

found that the annual total direct and indirect costs were 11,654 EUR for patients with narcolepsy, and 1430 EUR for control subjects, corresponding to an annual mean excess health-related cost of 10,223 EUR for each patient with narcolepsy [85]. A recent US-based study [86] found that narcolepsy patients in comparison to matched controls had significantly higher costs associated emergency department (3667 versus 1543 USD), healthcare professional (22,828 versus 12,667 USD), and hospitalization (27,642 versus 10,998 USD).

7.7.5 Shiftwork

Shift work is an integral part of the economy worldwide and in the United States [87]. Nearly, 17% of the American workforce work in jobs that require them to be on-call, or awake during night hours [88]. This leads to shift worker sleep often conflicting with the patterns of light and darkness in their environment, which in turn leads to circadian misalignment and poor sleep quality [89, 90]. Shift workers often report shorter sleep duration and more drowsiness than workers who do not work overnight [91, 92]. Shift work is also associated with cancer [89, 93, 94], diabetes [95], cardiovascular disease [96, 97], hypertension [93], as well as metabolic syndrome [98]. Sleep disorders are also common in this population such that 36% of shift workers report having OSA [91]. A comprehensive review on the health impacts of shift work [99] highlights disease associated with this condition.

7.7.6 Jetlag

An estimated 4.1 billion passengers chose to travel worldwide by air in 2017 (632 million American travelers—18.6% of all passengers), which represented a 7.3% increase over 2016 [100]. Long-distance air travel often comes along with sleep disruptions, which plays a central role in the clinical manifestations of both travel fatigue and jet lag disorder (JLD). Although the economic consequences of travel fatigue and JLD have not been quantified, several reviews have been published on their health impact [101] as well as their impact on physical [102] and cognitive performance [103].

7.8 The Indirect Pathway

7.8.1 The Economics as Sleep as a Comorbidity

7.8.1.1 OSA

As a comorbidity, OSA contributes a 30 billion USD loss due to increased risk of costly comorbidities such as hypertension, heart disease, diabetes, and depression [49]. OSA also increases costs by worsening outcomes in comorbid conditions. A 2016 study [104] of older patients with end-stage renal disease, along with comorbid

sleep-disordered breathing, revealed that OSA comorbid patients were younger and had more non-Nephrology clinic visits, higher body mass index, and more comorbidity. However, the diagnosis of OSA was associated with lower risks of death, myocardial infarction, and ischemic stroke, highlighting the multifactorial nature and methodological challenges to studying complex disease comorbidities.

7.8.1.2 Insomnia

The association of comorbid insomnia with costs is also well documented. Total medical expenditures are 26% higher among patients with insomnia compared to controls [105–107]. Insomnia has been associated with increased emergency room (ER) visits, hospitalized days, and provider visits [108], and insomnia severity is linearly associated with HCU [109]. Costs of hospitalization of people with insomnia and insomnia-related depression are 36.6 billion USD and 1.5 billion USD per year, respectively [77]. Comorbid insomnia increases both direct and indirect costs of the comorbid disease. For example, relative to patients with depression alone, patients with comorbid insomnia and depression have annual indirect costs which are between 930 USD [10] and 1390 USD [110] higher per year. Insomnia patients also have 4067 USD higher annual all-cause healthcare costs, 557 USD higher annual depression-related healthcare costs, and 1144 USD higher indirect costs for days-out-of-role (short-term disability) at 12 months [111]. Another study reported [107] on older adult patients with hypertension, osteoarthritis, and diabetes. Relative to participants without insomnia symptoms, those patients reporting one or more symptoms of insomnia had greater odds of self-reported hospitalization (adjusted odds ratio [AOR] = 1.28), use of home healthcare services (AOR = 1.29), and any health service use (AOR = 1.28) over a 1-year period. Those reporting two or more insomnia symptoms had even greater odds of hospitalization (AOR = 1.71), use of home healthcare services (AOR = 1.64), and any health service use (AOR = 1.72) over this same period. More recently, Wickwire and colleagues reported the results of two cohort studies examining economic aspects of insomnia [56] and insomnia treatment [112] among older adult Medicare beneficiaries in the United States. Relative to non-sleep-disordered controls, these authors found [56] that beneficiaries with insomnia demonstrated 63,607 USD higher annual all-cause costs. These were driven primarily by inpatient costs of 60,900 USD, as well as elevated Emergency Department costs of 1492 USD and prescription costs of 486 USD [56] . In yet another study Medicare beneficiaries with insomnia, the researchers report [112] increased costs and HCU during the 12 months prior to insomnia diagnosis.

7.8.1.3 Narcolepsy

Comorbid narcolepsy is also costly. Black and colleagues [113] reported that narcolepsy was associated with a wide range of comorbid medical illness claims at significantly higher rates than matched controls. These comorbid conditions include other sleep disorders including sleep apnea, as well as obesity and diabetes. A study using records from the Danish National Patient Registry between 1998 and 2005 calculated the annual direct and indirect health costs of patients with narcolepsy [85]. Relative to non-narcolepsy controls, patients with narcolepsy had significantly

higher rates of HCU and medication use as well as lower levels of income and employment. The annual total costs, including direct and indirect costs, were 11,654 versus 1430 EUR for control subjects. Patients with narcolepsy in Denmark also received more social transfer payments (8107 EUR per year), which includes subsistence allowances, pensions, social security, social assistance, public personal support for education, and other payments versus control subjects (5519 EUR).

7.8.2 The Economics of Sleep in the Workplace Productivity

7.8.2.1 OSA

OSA contributes 86.9 billion USD in lost workplace productivity and absenteeism [49]. Expenses in the workplace from OSA include costs of days missed from work (absenteeism) as well as costs due to lost workplace productivity (presenteeism). Three studies [51, 63, 114] have systematically evaluated the impact of OSA treatment on workplace productivity and days missed from work. The first study [114] found that a year after treatment, CPAP was associated with a significant reductions in days missed from work at 1-year follow-up (7.5 vs. 4.2 days missed). This is while the PAP non-adherers demonstrated a significant increase in days missed from baseline to 1-year follow-up (5.2 vs. 20.8 days). Another study among a self-insured employee population of commercial drivers [63] found that PAP was also associated with fewer days missed from work over 2 years (4.4 fewer days missed in the first year 2.5 fewer days missed in the second year 2). Finally, a study of the Danish national patient registry [51] did not find a significant relation between CPAP and a proxy measure of labor market income.

7.8.2.2 Insomnia

Early investigations found that insomnia is associated with missed days from work [115, 116] and disability [117, 118]. The first study to quantify associated financial costs estimated insomnia-related absenteeism cost to employers at 9670 USD per employee per year [77]. Another study from Europe estimated the cost of insomnia-related absenteeism to be 112 USD per employee per year [119]. A more recent study found that relative to controls absenteeism due to insomnia was associated with 466 USD greater cost over 6 months [13]. Insomnia is reported to be associated with presenteeism as well, where the employee is present at work but less productive [12, 33, 108, 116, 120, 121]. A study that quantified the financial impact of presenteeism reported [122] the annual loss of work performance to be 7.8 days per employee with insomnia (11.3 days when not controlling for comorbid conditions). This resulted in a cost of 2416 USD per employee per year, suggesting a sum cost within the US workforce of 67 billion USD per year.

7.8.2.3 Narcolepsy

When compared to matched controls of the general population, patients with narcolepsy report higher rates of absenteeism (7631 vs. 12,839 USD), and presenteeism (4987 vs. 7013 USD) [113]. Short-term disability for these employees were also

estimated to be 200% higher than matched controls (876 vs. 292 USD) [113]. Patients with narcolepsy in Denmark also received more social transfer payments (8107 EUR per person per year) [85], which includes subsistence allowances, pensions, social security, social assistance, public personal support for education, and other payments versus control subjects (5519 EUR).

7.8.3 The Economic Impact of Sleep on Accidents and Injuries

7.8.3.1 OSA

It is well documented that OSA treatment reduced risk for motor vehicle crashes and other accidents [123]. Three studies [114, 124, 125] have reported on the economic impact of OSA treatments on accident risk, including the risk for motor vehicle crashes (MVC). The first study [114] reported a statistically non-significant reduction in MVC from 1-year pretreatment to 1 year after treatment (2.1 vs. 1.3 MVC). Subgroup analyses among PAP adherers and non-adherers were also not significant. A multicenter Randomized Controlled Trial (RCT) of OSA treatments [125] among older adults also found no differences between patients treated with PAP or best supportive care in home accidents, MVC, or all accidents.

7.8.3.2 Insomnia

Insomnia is associated with accidents [126] and injuries [127], resulting in significant costs. The average costs of insomnia-related accidents or errors are reported to be 10,534 USD higher than other accidents and errors (32,062 vs. 21,914 USD) [128]. Insomnia-related accidents account for 23.7% of the total costs of all accidents and errors and result in estimated annual costs of 32.3 billion USD [128]. Insomnia treatments, particularly older insomnia compounds, can also increase the risk for accidents. A meta-analysis study found sedative hypnotics to be strongly associated with psychomotor accidents such as falls among older adults [129], which in Europe are reported to cost between 1.97 and 2.89 million USD per year [129, 130].

7.8.3.3 Insufficient Sleep and Fatigue

Several studies have sought to quantify the economic impact of insufficient sleep among the "non-ill" general population. In 2014, the Centers for Disease Control and Prevention in the United States has declared insufficient sleep a "public health problem" after finding that more over a third of American adults are not getting enough sleep on a regular basis [131]. In 2016, the RAND corporation released a study [132, 133] in which the authors examined the economic burden of insufficient sleep across five different OECD countries and found that the United States sustains the highest annual economic loss between 280 billion USD and 411 billion USD due to the size of its economy, followed by Japan, which loses between 88 billion and 138 billion USD per year. In another study [134], the total costs of inadequate sleep were found to range from USD 41.38 billion to USD 49.21 billion in Australia in 2017.

7.9 The Impact of Sleep on Health-Related Quality of Life

An extensive scientific literature supports the inverse relationship between sleep quality and health-related quality of life (HRQoL). The number of hours of sleep can influence HRQoL, both when the number of hours is too few or too many. A recent study reports [43] that elderly participants who slept 6 or fewer hours per night had lower EQ-5D scores compared to participants sleeping between 7 and 9 h per night, and participants who slept 10 or more hours per night had a higher mortality rate compared to persons sleeping between 7 and 9 h per night. It also reveals that participants who reported difficulty carrying out certain activities because of being too sleepy or tired had more than a 40% decrease in QALY compared to participants who reported no difficulties (10.6 QALY vs. 17.8 QALY).

7.9.1 OSA

Studies often assess the impact of OSA through comparison of OSA patients with the general population, or through comparison of evidence-based treatments (CPAP) outcomes with supportive care. For example, the earliest study to measure HRQoL in OSA [38] reported the mean utility score and the standard deviation obtained with the standard gamble (the method which today the EuroQOL EQ-5D follows in theory) as 0.87 ± 0.17 on CPAP treatment and 0.63 ± 0.29 pretreatment.

Another study found [36] that the mean baseline of the HRQoL score was statistically and clinically significantly lower in the study patients, especially in the nCPAP group (0.84 compared with 0.91 for general population, respectively). Among the patients, the baseline HRQoL score was worse, but not significantly so, in the nCPAP group (0.84) than in the lifestyle guidance group (0.88). This study also reports that at the 6-month follow-up, the mean 15D score had improved only a little in the lifestyle guidance group (from 0.88 to 0.90) and remained constant in the nCPAP group (from 0.84 to 0.85), and neither of these differences were statistically significant.

7.9.2 Insomnia

The Health Utilities Index (HUI) Mark 3 [24] has been validated for patients with a variety of sleep disorders in a sleep center and has been used to report the mean utility score of insomnia at 0.6 ± 0.35 [117]. Similarly, a more recent study [32] employed the SF-36 and found derived utility scores for those with insomnia to be 0.67 in Japan, 0.57 in France, and 0.63 in the United States.

7.9.3 Other Sleep Disorders

A small number of studies have assessed the HRQoL of other sleep disorders besides OSA and insomnia. One study has commented on the use of utility scores for the treatment of narcolepsy, where the authors report [135] the utility score after 6 months of treatment with sodium oxybate at 0.727, while patients treated with standard treatment of methylphenidate/venlafaxine (placebo) had a utility score of 0.656 after 6 months. Several studies have also measured quality of life measures in RLS patients; however, none report a summary HRQoL utility score [39, 40, 42].

7.10 Sleep and Social Disparities

Not only does sleep have an impact on wealth and the ability to generate wealth, but in turn wealth also impacts sleep. Public health studies associate sleep with socioeconomic status and, in turn, focus on the mediating association of sleep in the spiral down toward poverty [136–145]. One trend among these articles argues that the adverse impact of low socioeconomic status (SES) on health may be partly mediated by the impact of insufficient sleep on the development of chronic conditions, such as obesity, diabetes, and hypertension [136], or infectious illness such as a common cold [142]. This impact was initially found in men [137, 138]; however, later studies found a similar impact among women [139, 141]. The other trend of these studies focuses on the mediating impact of insufficient sleep in the relation between environmental factors, such as living neighborhood characteristics on health [143–145].

7.11 Conclusions and Future Directions

Sleep disorders independently lead to greater utilization of healthcare services, and greater morbidity and mortality. As serious comorbidities, sleep disorders also lead to the exacerbation of other chronic conditions. Collectively, sleep disturbances increase HCU and costs, and evidence suggests that treating common sleep disorders results in economic benefit [56, 58, 112, 113]. Despite these clear general conclusions, much remains unknown. Table 7.2 presents several directions for future research. In the interim, health providers should be strongly encouraged to screen for sleep disorders among their patients. As reviewed in the beginning of this chapter, rational health policy requires the spending of economic and monetary resources to prolong and advance the quality of human life. Targeting sleep disorders (and sleep health more broadly) may also turn out to be cost saving.

Table 7.2 Guidelines and directions for future sleep economic research

Domain	Recommendation
Include health economic end points	Include measures of direct and indirect costs of sleep disorders in all future trials and sleep studies
Advance research on health utility scores for all sleep disorders	Availability of health-related quality of life (HRQoL) utility score measures for all sleep and circadian rhythm disorders included in the International Classification of Diseases (ICD)
Evaluate cost-effectiveness	Include measures of both general and disease-specific measures of health-related quality of life in all future sleep disorder trials
Study-specific populations	Conduct health economic analyses among elderly women, among different ethnic groups, and among patients with varying severities of sleep disorders
Understand comorbid sleep disorders	Study economic impact of insufficient sleep and its treatments in costly and chronic comorbid disease states such as heart failure, type 2 diabetes mellitus, Alzheimer's disease, and depression
Increase adherence	Study economic cost–benefit of interventions designed to increase treatment adherence, including cognitive-behavioral treatment, telehealth and remote monitoring, automated approaches, and other interventions
Adopt employer perspective	Evaluate cost–benefit of insufficient sleep treatments from the perspective of the employers of adults: impact on lost workplace productivity (i.e., absenteeism) and workplace accident and injury risk
Evaluate global impact	Evaluate cost-effectiveness of treating insufficient sleep worldwide in various healthcare delivery systems
Compare economic effectiveness	Compare economic effectiveness between the treatments of insufficient sleep to empower stakeholders to make evidence-based decisions regarding allocation of scare healthcare resources

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Approach to Sleep Complaints

8

Royi Gilad and Colin M. Shapiro

Abstract

Sleep disorders are common across all ages. Patients may present with a variety of complaints representing a variety of sleep disorders. Interestingly for many sleep disorders, complaints may be overlapping. As in the assessments of most patients' complaints, the goal of the physician is to try and find from the information delivered by the patient and thread them in such a way that they start pointing toward a probable diagnosis. In most sleep disorders, the physical examination is expected to be unexceptional, nevertheless, it is important to look for signs that may be suspicious of the existence of a primary sleep disorder such as obstructive sleep apnea (obesity, hypertrophy of nasal or oropharyngeal mucosa, craniofacial abnormalities such as micro/retrognathia). In addition to history and clinical examination, objective measures, for example polysomnography and actigraphy, are useful in diagnosing the presence and severity of a number of sleep disorders. In addition, numerous questionnaires are available that may be used to screen, diagnose, and assess the severity of sleep disorders. This chapter deals with all this information.

Keywords

Sleep complaints · Sleep diary · Questionnaire · Home sleep apnea test · Polysomnography · Multiple sleep latency test · Actigraphy · Dim light melatonin onset test

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Patient's complaints regarding sleep disturbances are of the most frequent complaints, mainly in primary-care and mental health services.

As in the assessments of most patients' complaints, the goal of the physician is to try and find from the information delivered by the patient and thread them in such a way that they start pointing toward a probable diagnosis. It will help the physician to better tune the diagnostic efforts (such as imaging or laboratory tests) in order to find pertinent and necessary aspects of the disorder that will help in proper planning of management.

Assessing sleep complaints is not much different than assessing any other medical complaints. It relies not only on the patient's presenting complaint and medical history, but also on the physical and mental status examination. In the assessment of some complaints regarding sleep quality or daytime sleepiness or fatigue, other diagnostic measures (such as sleep diaries, polysomnography, actigraphy, questionnaires, etc.) might prove helpful as well.

One should bear in mind that the diagnosis of one sleep, or sleep-wake cycle disorder, does not necessarily automatically exclude the possibility of the co-occurrence of other sleep disorders or other mental and medical disorders (e.g., a patient suffering from obstructive sleep apnea (OSA) can not only be suffering from other sleep disorders such as insomnia or delayed phase sleep-wake disorder but can also be suffering from fibromyalgia and chronic pain, major depressive disorder, substance use disorder, etc.).

The co-occurrence of several sleep-related, psychiatric, and other medical disorders can have a profound effect on the laboratory or other diagnostic procedures. For example, a patient who suffers from insomnia and is treated pharmacologically with antidepressant medication might demonstrate prolonged rapid eye movement (REM) latency during the polysomnography that is related to the effect of the antidepressant medication, or a patient who is assessed by a Multiple Sleep Latency Test (MSLT) for excessive daytime sleepiness after a diagnosis of obstructive sleep apnea, who also suffers from alcohol or opioid use disorder, can present with abnormal MSLT results that are heavily affected by the substance use disorder.

Like in most complaints' assessment in medicine, the process of assessing sleep complaints starts with assessing the chief presenting complaint and general medical history.

Presenting Complaints [1–3]

- What is the difficulty in sleep or is that presumed to be related to sleep?
- When did the complaint/symptom first appear?
- Duration of the complaint/symptom
- Effect of the complaint/symptom on the patient and daily life
- Efforts made so far do deal with the complaint/symptom (medication, alcohol, change in lifestyle, etc.)

Cluster of Symptoms

Quality, quantity, and general symptoms –

- Change in sleep time (whether decrease or increase)
- Feeling of "light" or unrefreshed sleep, restless sleep
- Difficulty falling asleep (increased sleep-onset latency)
- Difficulty maintaining sleep (sleep fragmentation), night awakenings incl. activities during the awakenings (micturition, eating, smoking, working, using electronic devices)
- Early morning awakening
- Difficulty waking up

Breathing Related

- Snoring
- Difficulty breathing
- Choking or gasping during sleep
- Waking up perspiring, flushing, or with a headache

Movement Related

- Restless sleep
- Limb "jumps," cramps, or contractions
- Feeling of necessity/compulsion to continuously move in bed
- Teeth grinding or waking up with orofacial pain or headache

Mental and Behavioral

- Disturbing thoughts
- Disturbing or vivid dreams
- Nightmares
- Sensations or visions during falling asleep or awakening
- Walking during sleep
- Injuries that occured during sleep
- Pain or other sensations during sleep initiation, during sleep, or during awakenings

Daytime Complaints/Symptoms

- Daytime sleepiness
- Daytime fatigue
- Difficulty in maintaining daytime alertness
- Changes in mood (depressed, labile, irritable, anger, outbursts)
- Difficulties in memory or attention
- Pain or other sensations/complaints during the day
- Inability to maintain muscular tone during surge of emotions (cataplexy)
- Decrease in occupational, family, or leisure/physical activities

Information from Family or Household Member

- Snoring
- Troubled of disturbed breathing during sleep

- Features of sleep apnea (i.e., reports of witnessed breathing stops during sleep)
- Movement during sleep (including seizures, sleepwalking, or other complex behaviors)
- Talking, shouting, moaning during sleep (Catathrenia), laughing during sleep (Hypnogiggly)
- Sleepiness during daytime
- Decrease in daily functioning
- Change in mood, eating, or behavior
- Prescription or over-the-counter medication use or recreational drug use

Sleep Conditions, Schedule, Habits and Hygiene

- What is the usual bedtime during weekdays and weekends?
- What is the usual wake time?
- Activities around getting to bed and going to sleep (use of electronic and light-emitting devices, smoking, reading, eating)
- Use of prescription or over-the-counter medication, alcohol, nicotine, cannabis, caffeine, or other psychoactive substance during the daytime or prior to sleep
- Food and water consumption before going to sleep
- Physical activity during the day and before going to sleep
- What are the sleeping conditions (in terms of the type of bed, lighting, noise, temperature, airing)?
- Is the bed shared with a partner or other family member?
- Does falling asleep occur in a bed or in other places, such as a living room sofa/couch?
- Does sleeping occur in a bedroom or another room in the house?
- Does the patient wander from the bed during sleep without being fully conscious?
- What are the familial/cultural practices concerning sleep?
- What happens if the patient wakes up during the night?
- What is the morning routine?

Medical History

- Current medical problems/diseases (with emphasis on chronic diseases, hormonal changes, and chronic pain disorders)
- Current menstrual cycle-related symptoms (mainly menopausal symptoms)
- Current treatments (pharmacological and others, with emphasis on recent changes in medications)
- Current disabilities or recent change in daily functioning
- Current stressful life events (familial, marital, parental, or financial difficulties, change in the health status of a family member, relocation and immigration, starting a new job, or academic studies)
- History of medical problems, diseases, and injuries (with emphasis on past sleep complaints/disorders, mental disorders, and concussion or traumatic brain injury)
- Past treatments (mainly those that required pharmaceutical or surgical interventions)

- Past adverse life events/trauma
- Family history of sleep problems and physical or mental problems

Assessment of the mental status: fluctuations in consciousness, fatigue, or lethargy, cognitive impairments, quality of the voice (i.e., gravelly, coarse, or hoarse voice can be a sign of vocal cord dysfunction, a potential cause of obstructive sleep apnea), mood and affect, presence of anxiety, psychomotor activity, signs of substance intoxication, or withdrawal.

8.1 Physical Examination

In most sleep disorders, the physical examination is expected to be unexceptional, nevertheless, it is important to look for signs that may be suspicious of the existence of a primary sleep disorder such as obstructive sleep apnea (obesity, hypertrophy of nasal or oropharyngeal mucosa, craniofacial abnormalities such as micro/retrognathia) or other primary sleep disorders such as bruxism (teeth grinding or erosion, pain over the temporomandibular joint) and signs of another physical condition that may be responsible for the sleep complaints or is a consequence of a sleep disorder (e.g., hypertension, tachycardia or tachypnea, neck swollenness, central or peripheral edema, disturbed breathing or coughing, signs of anemia, belching or signs of gastrointestinal reflux, abdominal tenderness or hyperactive bowel sounds, visual and neurological signs, or signs of thyroid function abnormalities).

8.2 Laboratory Tests [4]

No routine blood tests are mandatory for the diagnosis of sleep disorders, however, if the evaluation of the sleep complaint is the primary medical presentation and blood tests had not recently been done, it would be reasonable to perform a complete blood count, general blood chemistry, and thyroid function test. Other blood tests are warranted only in accordance with clinical suspicion (e.g., iron and ferritin levels in case of suspicion of restless leg syndrome or HbA1C (glycated hemoglobin) levels where suspicion exists for an uncontrolled diabetes mellitus).

No routine urine tests are mandatory for the diagnosis of sleep disorders but when there is a high level of suspicion of substance use disorder and the information from the patient on substance use is doubtful regarding its credibility, it may be warranted to obtain a urine sample for substance residues.

Cerebrospinal fluid (CSF) collection test is only warranted if a specific clinical suspicion emerges (e.g., meningitis or encephalitis, or central nervous system (CNS) lymphoma).

Other tests such as an electroencephalogram (EEG), electrocardiogram (ECG), or an echocardiography are only warranted in regard to the presence of a specific clinical suspicion.

8.3 Imaging Tests [4]

No routine imaging tests are mandatory for the diagnosis of sleep disorders. Neural imaging is only required when there is a suspicion that the sleep complaint is a symptom of a wider neurological manifestation (such as multiple sclerosis, increased intracranial pressure, cerebrovascular disease, dementia, seizures), or in the case of central sleep apnea in children.

Upper airway imaging is not a routine evaluation of sleep complaints. However, recent data suggest that in some patients with craniofacial malformation, cranial radiography might be beneficial in the diagnosis of obstructive sleep apnea. Imaging tests are also warranted for diagnosing patients with obstructive sleep apnea (OSA) who are considered for surgical intervention. In these patients, a combination of magnetic resonance imaging (MRI) and nasopharyngoscopy are the preferred modalities.

8.4 Sleep Diary [5]

A sleep diary is a primary tool for prospective assessment of sleep complaints and conditions. It allows the clinician to evaluate the severity of the sleep complaint on a day-to-day basis, it facilitates identifying possible behaviors that maintain the sleep problem and can help in determining to what extent a component of circadian rhythm disorder is present. It is also useful in gathering data needed to guide future treatment and follow-up.

The use of a sleep diary for 1 or 2 weeks is useful in most patients suffering from a chronic sleep complaint. This is particularly the case in patients who cannot provide an adequate sleep history or who report considerable night-to-night variability. It might be especially important in children and adolescents.

A properly completed sleep diary can provide the clinician with adequate information on the bedtime, wake time, total time in bed, and naps during the day. It can also provide a reasonable estimation of latency to sleep onset, number, and duration of nighttime awakenings and total sleep time. This facilitates a gross estimation of sleep efficiency (total sleep time divided by time in bed multiplied by 100). Though this diagnostic tool is cheap and easy to use, it also relies solely on the subjective report of the patient (or the caregiver in the case of children) and therefore, as in all subjective reports, is liable to the patient's own cognitive biases. It is particularly the case for the estimation of sleep-onset latency (and therefore the total sleep time).

8.5 Questionnaires [5]

The use of retrospective questionnaires can also provide important information on the assessment of sleep complaints. Please refer to Chaps. 6 and 9 for some of these questionnaires. The most commonly used questionnaires in adults are the Pittsburgh Sleep Quality Index (PSQI) for the assessment of insomnia and Epworth Sleepiness

Scale (ESS) for the assessment of excessive daytime sleepiness. In the diagnosis of circadian rhythm disorders, the Morningness-Eveningness Questionnaire (MEQ) can provide important information about the sleep-wake patterns and activities of the patient. In Children, the Sleep Disturbance Scale for Children, the Child Sleep Questionnaire, and the Children's Sleep habits Questionnaire can be used to assess the child's sleep. Questionnaires can provide a relatively quick checklist of the patient's sleep parameters that can assist the clinician in quantifying the sleep complaints for severity assessment and for future follow-up during the initial visit and without the need for prospective active participation from the patient (such as in completing a sleep diary), but are prone to cognitive biases. Both sleep diaries and questionnaires have a modest correlation with objective measurements such as actigraphy.

In patients who are considering receiving treatment such as cognitive-behavioral treatment for chronic insomnia, which could be followed up mainly by subjective measurements, using a sleep diary and questionnaires can be most useful, as they can easily and frequently measure progression over the course of treatment.

8.6 Home Sleep Apnea Test (HSAT)

Home Sleep Apnea Tests are currently prevalent as a main modality for the diagnosis of obstructive sleep apnea and assessment of treatment for sleep apnea (but not for the use of determining the initial level of positive airway pressure therapy). Since mostly used HSAT equipment rarely includes EEG measurement, it cannot provide a definite measurement of sleep onset, and therefore of total sleep time, or awakenings. Therefore, it cannot provide the apnea/hypopnea index (AHI) (which is the number of apneas/hypopneas divided by the total sleep time), or the respiratory effort-related arousals (RERAs) (which measure the arousals related to sleep-disordered breathing events). HSAT can provide only the "respiratory event index" (REI) (which is the divided number of apneas and hypopneas by total recording time and not total sleep time) without RERAs. Recently, a few home polysomnography devices with an ability to measure EEG during sleep have been introduced to the clinical practice. These devices possess almost the same capabilities as an in-laboratory polysomnography (except video surveillance) and can provide the same measurements and indexes. Therefore, they can be used in the assessment of other sleep disorders other than obstructive sleep apnea (e.g., sleep fragmentation, parasomnia, etc.).

HSAT is susceptible to technical difficulties during the test and therefore is considerably dependent on the different technical equipment used and the level of guidance and instruction provided to the patient by the sleep professional. Specific preceding instructions regarding the use of alcohol, caffeine, or medications before the test's night must be carefully kept as in an in-laboratory polysomnography.

8.7 In-Laboratory, Attended Polysomnography (PSG) [6]

In-laboratory, video-synchronized PSG is the gold standard in the diagnosis of most sleep disorders, except circadian rhythm sleep disorders. The test encompasses monitoring the patient during sleep by electroencephalogram (EEG) alongside electrooculogram (EOG) and electromyogram (EMG) that can provide full data on the sleep latency, sleep stages, awakening, parasomnias, seizures, and other disorders during sleep. It also contains full respiratory measurements, oxygen saturation and electrocardiogram (ECG), and therefore, can provide a reliable measurement of the breathing effort and breathing disturbances during sleep, data on oxygen saturation and cardiac rhythm. Video photography (with low light adjustments) during the test enables correlating EEG and EMG findings with actual visible movement on camera. With its many benefits, PSG is an expensive test in both facility, equipment, and the need for skilled professional labor. Furthermore, since it is not performed in the usual sleep environment of the patient it can cause the patient discomfort and distress. There is a well-documented phenomenon call "The first night effect," in which repeated polysomnography tests performed consecutively for several nights demonstrated a difference in the polysomnography results mainly during the first night, possibly due to the difference in the sleep environment and the unfamiliar sensations and anxiety related to sleeping in the laboratory with the mechanical equipment. Subsequently, even though an in-laboratory polysomnography is still the most objective and detailed diagnostic tool in sleep medicine, since in the general clinical practice, the patient will complete only one night polysomnography, the "first night effect" must be taken into account in the clinical interpretation of the polysomnography results while making treatment decisions.

As in HSAT, there are specific preceding instructions regarding the use of alcohol, caffeine, or medications before the polysomnography.

PSG is not routinely required in the assessment of complaints of difficulty falling asleep or other complaints that are pointing toward the diagnosis of insomnia, poor sleep hygiene, or circadian rhythm disorders. Nevertheless, when there is a clinical suspicion that complaints that are mostly pointing to the possibility of insomnia might also be masquerading for possible other sleep disorders (e.g., complaints of frequent awakenings during the night after sleep onset that are caused by breathing disturbances during sleep), PSG might be a vital tool in the diagnosis. PSG can also be efficient in the assessment of different subtypes of insomnia and sleep fragmentation (e.g., frequent awakenings or inability to resume sleep after awakenings vs. increase in arousals during sleep without awakenings). This insomnia subtyping might help the clinician to identify "tailor-made" therapeutic options for the patient (e.g., offering to patients with different insomnia subtypes; Cognitive-Behavioral therapy for insomnia for some, and pharmaceutical therapies for others).

PSG (as opposed to home sleep apnea testing) is particularly important in the diagnostic evaluation of patients suspected of suffering from sleep apnea who have a higher likelihood of central apneas, and in patients suspected of having other comorbid sleep or respiratory disorders and also in the pediatric population.

PSG can assess the efficacy of therapy when there is concern that the patient is not adequately treated with the currently prescribed therapy (whether it is positive airway pressure, oral appliances, or after surgical interventions), or when there has been significant weight change.

PSG is also used to assess and diagnose other forms of sleep-disordered breathing, other than obstructive sleep apnea (OSA), such as Cheyne-Stokes breathing, central apnea, concurrent chronic obstructive pulmonary disease (COPD) and OSA, and hypoventilation.

PSG is also part of the diagnostic evaluation of selected patients with periodic limb movements during sleep, unusual presentation of non-REM parasomnias (i.e., when the age of appearance of symptoms is not typical, or the frequency or disturbance to the quality of life is extreme) and in REM sleep behavior disorder (RBD). Another indication that may warrant PSG test is excessive daytime sleepiness that is suspected to be caused by narcolepsy or idiopathic hypersomnia. When nocturnal seizures are considered as part of the differential diagnosis of abnormal movements or behaviors during sleep, extended electroencephalogram (EEG) monitoring with video surveillance is typically performed during the PSG.

8.8 Multiple Sleep Latency Test (MSLT) [7–9]

The MSLT objectively measures an individual's tendency to fall asleep. It is based on the premise that individuals with a greater degree of sleepiness fall asleep faster than individuals with less sleepiness. The MSLT is considered the standard measurement of sleepiness and has proven to be a sensitive and reproducible test for quantifying sleepiness, regardless of the type of sleep deprivation (partial or complete, acute, or chronic) or the underlying pathologic condition.

Before performing an MSLT, it is important to account for the sleep schedule of the patient by performing a detailed history of his sleep and wakefulness periods, whether by using a sleep diary or actigraphy. It is pertinent to perform a PSG test the night prior to the MSLT, to determine whether the patient's quality and quantity of sleep were satisfying, in order for the results of the MSLT to be well interpreted.

The MSLT begins 1.5–3 h after the PSG is completed. The patient is placed in a sleep-inducing environment and instructed to try to sleep. A sleep-inducing environment refers to a dark and quiet room with the room temperature based on the patient's comfort level. Monitoring includes electroencephalography (EEG), electrooculography (EOG), mental or submental electromyography (EMG), and electrocardiography (ECG).

Each nap session continues for 15 min after sleep onset to detect any occurrence of REM sleep. The sleep latency is documented for each nap session. Sleep onset is defined as the first 30-s epoch in which more than 15 s of the epoch is consistent with any stage of sleep. Sleep latency is defined as the time from lights out of the nap to the first epoch of sleep. If the patient does not fall asleep, the nap session is terminated after 20 min and the sleep latency is documented as being 20 min.

This is repeated at two-hour intervals until the patient has had four or five opportunities to nap. Between nap sessions, the patient should be out of bed and encouraged to stay awake. Smoking should stop at least 30 min prior to each nap session and other stimulating activities should cease at least 15 min prior to each nap session. The five-nap protocol is the recommended protocol. A shorter, four-nap test may be performed, but this is unreliable for the diagnosis of narcolepsy unless two or more sleep-onset REM periods (SOREMPs) have occurred. It should be mentioned that patients suffering from delayed phase sleep-wake disorder might exhibit REM sleep in the first one or two naps (during morning hours) that are not an indication of narcolepsy rather than an indication that at these morning hours these patients are still, chronobiologically, in their third phase of their sleep, and therefore are expected to demonstrate REM appearance in the MSLT. If REM sleep appears only in the first or second nap (or both) of the MSLT, a fifth-nap protocol is vital in order to properly evaluate the possibility of narcolepsy.

The MSLT is part of the routine evaluation of patients who are suspected of having narcolepsy and may also be helpful in the evaluation of patients with suspected idiopathic hypersomnia. While the MSLT may support a diagnosis of narcolepsy or idiopathic hypersomnia, it is insufficient, by itself, to confirm a diagnosis of either.

MSLT is not universally indicated as part of the routine evaluation of patients who are suspected of having excessive sleepiness due to confirmed diagnosis of obstructive sleep apnea, insomnia, circadian rhythm disorders, periodic limb movement disorder, or other medical disorders. In addition, it should not be performed as a sole measurement to assess the effectiveness of therapy or to evaluate the risk for driving, work, or home-related accidents.

8.9 Maintenance of Wakefulness Test (MWT) [7]

The MWT objectively measures the ability of an individual to remain awake for a defined period. It is based on the premise that individuals with a greater degree of sleepiness are less likely to remain awake than individuals with less sleepiness. The main measurement of the test is the mean sleep latency.

Patients should maintain their normal routine prior to the test. Upon arrival, they should be questioned to determine whether their sleep prior to the test was adequate in quality and quantity, and whether they feel alert. The MWT should be delayed if the patient reports suboptimal sleep or not feeling alert. A polysomnogram (PSG) on the prior night is not necessary. Urine drug testing may be indicated to ensure that the result is not influenced by substances other than prescribed medications.

The MWT begins 1.5–3 h after the patient's usual wake-up time. The patient is placed in a room with little or no external light. The only light source should be dim, slightly behind the patient's head, and just out of the patient's field of vision. The room temperature is based on the patient's comfort level. The patient sits upright in bed, with their back and head supported, and is instructed to try to stay awake for as long as possible. Monitoring includes electroencephalography (EEG),

electrooculography (EOG), mental or submental electromyography (EMG), and electrocardiography (ECG).

A session is ended after unequivocal sleep, or after 40 minutes if sleep does not occur. Sleep is considered unequivocal after three consecutive epochs of stage 1 sleep or one epoch of any other stage of sleep. For each session, the sleep latency is recorded. It is documented as being 40 minutes if the patient does not fall asleep. This is repeated every 2 h, until the patient has completed four sessions. Recently, 30-min session MWT showed relatively the same results and validity as the 40-min session MWT.

There is a paucity of data regarding what constitutes a normal mean sleep latency, as measured by the MWT. Among healthy individuals who complete the four session, 40-min protocol described above, the mean sleep latency is approximately 30 min, with greater than 97% of individuals having a mean sleep latency of 8 min or greater.

Since the tendency to fall asleep (which is measured by MSLT) and the tendency to stay alert (which is measured by MWT) are physiologically distinct and could not be compared, the MSLT and MWT cannot be used as an alternative to one another. The MWT may be used to assess an individual's response to therapy. It is the direction of change, not the degree of change, that is meaningful in this situation because the degree of change that is clinically significant has not been established. Currently, the MWT is not a diagnostic tool in any sleep disorder.

8.10 Actigraphy [10–12]

Actigraphy is a diagnostic procedure that utilizes a compact, lightweight, computerized accelerometer-based wristwatch-like device to record and store information regarding body movements over time (minimum of 72 h; typically, 7–14 consecutive days). The data are downloaded and analyzed by a computer in accordance with well-validated algorithms. While actigraphy should not be viewed as a substitute for PSG when an overnight laboratory sleep study is indicated, it can provide evaluation of sleep-wake patterns. It allows for continuous recording for days or weeks in the home sleep environment and, therefore, can record information that is not captured during a night in the sleep laboratory. It is also easier to use, more convenient, and less expensive compared to PSG.

The data collected by the actigraph, in conjunction with a sleep diary, are then analyzed by computer software, using preset activity thresholds to generate a printout of approximate sleep-wake patterns. Software programs for the various available devices allow for a reliable automatic scoring based on established algorithms and yield data reports and clinical summaries. Actigraphy appears to be most useful in delineating sleep patterns and in diagnosing circadian rhythm disorders. Actigraphy may also be used to more accurately document sleep duration, awakenings during the night, and less reliably, sleep-onset latency in patients for whom there appears to be a discrepancy between subjective sleep complaints and daytime consequences (e.g., an adolescent who reports sleeping less than 4 h per

night but has no complaints of daytime sleepiness). Actigraphy can also be helpful in determining sleep time evaluation in families in which the parents are unable to provide adequate information regarding their child's behavior during the night (e.g., the child gets up during the night and uses electronic devices and the parents are unaware of these behaviors). Actigraphy has been validated in a variety of populations and is becoming more common in clinical assessment. Nevertheless, it still has significant limitations. Compared with a gold standard of polysomnography, actigraphy is very accurate for identifying periods of sleep but is less accurate for identifying sleep onset and periods of wakefulness during sleep. Total sleep time and sleep efficiency tend to be overestimated by actigraphy, primarily because the delineation of sleep onset is difficult. This leads to overestimation of sleep time in situations in which patients lie in bed relatively motionless but not asleep. In contrast, actigraphy may underestimate sleep in patients with a movement disorder. Another limitation compared with polysomnography is that actigraphy is not able to identify the different stages of sleep.

Actigraphy is indicated in:

Circadian sleep-wake rhythm disorders—The most common use of actigraphy is in patients with suspected circadian sleep-wake rhythm disorders. In such patients, actigraphy data complement self-reported sleep parameters obtained from a sleep diary and provide a necessary substitute for self-reported sleep parameters in patients who cannot reliably complete a sleep diary.

Insomnia symptoms—Actigraphy is an important tool in the diagnostic evaluation of insomnia symptoms when there is suspicion of a circadian rhythm sleep-wake disorder as an alternative diagnosis to chronic insomnia.

Excessive daytime sleepiness—Actigraphy can be used to verify adequate sleep prior to conducting a Multiple Sleep Latency Test when there are concerns about the reliability of self-reported sleep. Similarly, actigraphy may be used to confirm or rule out insufficient sleep in patients presenting with complaints of excessive daytime sleepiness.

Monitoring response to treatment—Follow-up actigraphy can be a very useful way to objectively measure treatment response and enhance patient education. Follow-up data can be particularly useful for patients undergoing cognitive-behavioral therapy (i.e., as they provide objective feedback on the impact of newly instituted behavioral changes). Patients with a range of sleep habits and sleep disorders can learn to monitor their own sleep and adopt better daily sleep habits by reviewing actigraphy reports with clinicians.

Recently, wearable devices containing accelerometers (just like an actigraph) are introduced to the market. Depending on their validity and reliability, they might substitute, in the future, as a cheaper alternative of actigraphy-like sleep-wake cycle monitors.

8.11 Dim Light Melatonin Onset (DLMO) Secretion Test [13–15]

DLMO secretion test is an immunoassay of saliva sample for the level of melatonin. An alternative test to determine melatonin secretion levels is the melatonin metabolite 6-sulfatoxymelatonin levels in a urine sample. It was studied as an objective assistant tool in the diagnosis of circadian rhythm disorders, mostly delayed sleep-wake phase disorder (DSWPD), and as a measurement for the optimization of administration timing of melatonin or light exposure treatment in patients treated for circadian rhythm disorders. DLMO secretion test was also studied in patients suffering from seasonal affective disorders (SAD). DLMO secretion test has demonstrated capability also to differentiate between patients who will better respond to exogenous melatonin treatment versus those who will have only a minor therapeutic response. Aside from DLMO secretion test, minimum core body temperature (MCBT), and cortisol and thyroid-stimulating hormone secretion were also studied as diagnostic tools in circadian rhythm disorders. Currently, these tests are viewed by some as research tools since normative values have not been established and significant overlap was found in some of the studies between patients suffering from circadian rhythm disorders and healthy controls (Table 8.1).

Table 8.1 Methods of assessment of melatonin [16]

S. No.	Method	Remarks
1.	Urine sampling to assess 6-Sulpftoxymelatonin every 2–8 h over a 24–48 h period	• Can be used in field, clinical and research • No disruption of sleep with 8-h protocol • Morning urine sample can show overnight secretion • Precision less compared to more frequent sampling • Useful among infants as well as among patients suffering from dementia
2.	Salivary sample every 30–60 min under dim light (<30 Lux), starting at least 60 min prior to expected rise	• Can be used in field, clinical and research • Disruption of sleep can influence results
3.	Blood sampling using intravenous catheter which should be placed at least 2 h before start of sampling	• Can be used in field, clinical and research • Value from the plasma sample is nearly three times those of urine and saliva samples providing greater precision • Sleep not disrupted, except in case of pain

8.12 Conclusion

Assessing the patient with sleep complaints requires conducting a thorough interview with emphasis on the patient's entire physical and mental condition, and in some cases, further investigations such as In-Laboratory Polysomnography or Home Sleep Apnea Test, MSLT, or other tests.

Due to the enormous effect that sleep holds on the health and well-being, both physically and mentally, of the patient, it is crucial not to see complaints regarding sleep as an isolated "sleep problem" but as an important element for intervention in an effort to reduce future health complications (e.g., hypertension, major depressive disorder, etc.) and to improve the patient's general health and quality of life.

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Questionnaires for Screening of Sleep Disorders

9

Danielle Penney and Colin M. Shapiro

Abstract

Sleep disorders may present with a number of different symptoms. In a busy sleep clinic or during a population-based assessment of sleep disorders, a face-to-face assessment of all patients may not be feasible. A number of questionnaires have been developed to screen the presence of sleep disorders and to assess the severity of symptoms. These scales provide clinicians with a repertoire of specific, high-yield questions, allowing them to draw upon the extensive experience of their colleagues when attempting to tease apart nuanced problems. However, psychometric properties of each questionnaire determine their usefulness in a given situation. This chapter described questionnaires that may be used in different clinical situations—screening, diagnosis, and severity assessment in addition to their psychometric properties.

Keywords

Sleep questionnaires · Severity rating scales · Psychometric properties

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Many physicians, as well as the general public, often incorrectly view the field of sleep medicine as primarily concerned with the diagnosis and treatment of sleep apnea. In reality, there are far more people who have sleep problems for other reasons—whether it be the vast numbers of people with insomnia, or sleep-related mood problems—than sleep apnea alone [1]. For this reason, it is prudent to consider an initial triage of patients coming for a sleep assessment as to the range of their problems. Even for patients who initially do not report any concerns with their sleep, poor sleep quality has become so normalized in today's society that some patients may not even realize that they have any sleep-related problems, unless explicitly asked [2]. It is therefore of paramount importance that patients be screened with brief sleep questionnaires, both in the primary care setting and in the sleep clinic [3].

Sleep issues can often prove to be a complex clinical problem. The use of scales facilitates an assessment of these problems in a manner that is both quick and accurate. Most physicians can review 10 standard sleep scales in just 3–4 min. In this short time, the clinician can come to a broad but reasonably thorough understanding of the range of sleep-related issues that the patient presents with. For example, a selection of scales may indicate that a patient is sleepy but not fatigued; lacking in alertness with no insomnia; presenting no symptoms of narcolepsy or restless legs syndrome (RLS) but showing clear features of apnea, and exhibiting features of depression. The importance of having a broad range of sleep and alertness questionnaires cannot be overstated. Not only does the use of such scales imply that a clinician is more likely to come to an appropriate diagnosis or diagnoses, but it also prevents clinicians from missing comorbid sleep conditions. For example, a patient with multiple comorbid sleep conditions (one of which being sleep apnea) may have the apnea identified but a whole other aspect of the clinical picture is missed. If this patient is only given treatment for their sleep apnea, and not their other sleep conditions, the patient may not feel any better because their sleep is still poor as a consequence of the other comorbid conditions. Consequentially, patients may reject their sleep apnea treatment because they perceive no benefit and conclude that it was a misdiagnosis, or simply not effective.

Sleep scales are developed by researchers and clinicians who have often spent years in their field investigating, understanding, and precisely honing their preferred methods for assessing various sleep conditions [4]. Thus, scales provide clinicians with a repertoire of specific, high-yield questions, allowing them to draw upon the extensive experience of their colleagues when attempting to tease apart nuanced problems. For the clinician's own knowledge base, reading a scale may provide a deeper appreciation of the sequelae of a condition in a way that is distinctly different—and arguably more practical—than simply reading a chapter in a textbook.

While there is no substitute for a clinical interview and a focused medical examination, these scales can increase the efficiency of a clinical encounter by allowing the clinician to direct the consultation to the issues that the patient perceives as most relevant, and even provide a springboard for explaining the benefits of certain treatment approaches, or the potential outcomes of inaction [5].

Scales can be extremely helpful is when monitoring and contrasting a patient's progress. This is especially true when a clinician is assessing the treatment response

of more qualitative measures, such as alertness, as opposed to something more straightforward, such as triglyceride levels in response to a statin. Scores from questionnaires allow an objective measure to be introduced into the clinical picture that would not otherwise be there. A patient may not always remember, or even be aware of, the difference in their alertness levels on a series of different stimulant medications, for example. The periodic administration of scale assessments over a treatment course may provide an objective record of a given intervention, allowing the clinician to examine and assess the effectiveness of their approach to the patient. Furthermore, assessments with the same rating scale may facilitate compliance with treatment and subsequently increase patient satisfaction, particularly if it provides evidence that the treatment has made a positive change in a patient's symptoms or illness.

Sleep rating scales are also valuable for the enhanced vocabulary that they provide a physician, improving their understanding of each patient. It is important for the physician to precisely pinpoint what the patient feels is the main issue—what aspect of their sleep, if improved, would most enhance their quality of life? For example, for many patients who complain of sleepiness, their objective is not simply to become less sleepy, but to become more wakeful. Conversely, many people can be sleepy, but do not have problems staying awake when they need to. Scales can help a physician distinguish fatigue from sleepiness in a patient, or elucidate the differences between sleepiness and alertness—the latter is not simply the inverse of the former. Thus, it is important that we first distinguish the differences between sleepiness, fatigue, alertness, and wakefulness. Defining these terms allows for a better understanding of exactly what each patient's issues are, and assists in selecting the most appropriate treatment.

Sleepiness is the extreme desire to fall asleep. Simply put, it is the inability to stay awake, even in situations where wakefulness would be required—such as behind the wheel of a car, or while at one's desk at work. Often, sleepiness is relieved by sleep itself.

Fatigue refers to a state of sustained, overwhelming exhaustion, characterized by a decreased capacity for physical and mental work. Low energy, tiredness, and exhaustion are all words that all relate to the concept of fatigue. While people who feel fatigued may feel the urge to rest or nap, often, they will not necessarily be able to (immediately) fall asleep. This is in contrast to people with sleepiness, who will most likely be able to sleep if given the opportunity. In addition, a sense of fatigue felt by an individual is often not relieved by sleep—for example, this is commonly seen in patients with fibromyalgia or multiple sclerosis.

Wakefulness, in the most basic terms, is the state of being awake instead of asleep. It can be best described as a state that is not sleeping and not dreaming, in which an individual is conscious and aware of the world.

Alertness generally has to do with *responsive* wakefulness. Alertness involves the ability to pay close attention to what you should be paying attention to—often, this refers to one's immediate physical environment, but it could also be something like a card game, or any other "arena" in which the individual needs to perform in. A key difference in the distinction of alertness versus wakefulness is responsiveness. When someone is alert, they are not only aware of their immediate physical

environment, but they are able to respond to stimuli in a timely and appropriate fashion; such as a driver who quickly breaks at the sight of a squirrel darting in front of their car. The opposite of state of alertness would be categorized as "groggy," "disoriented," or "fatigued."

In addition to everyday clinical use, the use of scales in the context of research, especially in double-blind crossover trails, is imperative. Even the clinician who is not interested in research will find that assessment scales can become a source of great discovery when auditing their own practice. In this new era where evidence-based medicine reigns supreme, the ability of a clinician to assess their practice in relation to the wider medical community is invaluable. Scales provide standardized measures to compare one's practice with colleagues across cities and countries. This standardization allows increased ease of replicating previous studies and facilitates the rapid synthesis and dissemination of new research in accessible way [4]. It is a symbiotic cycle—scales make this kind of standardization possible, while simultaneously enabling the research efforts that help to formulate these standards. The website sleepontario.com lists six common sleep-related scales in 20 different languages and invites additions to those listed. This can be a helpful addition to clinical practice in increasingly multiethnic societies.

The key to unlocking all the potential advantages that come with the use of sleep scales lies in the selection of appropriate scales. A clinician may want to cover the issues most applicable to their practice, while also inquiring about additional problems or symptoms that could be relevant to a specific patient. For example, a sleep specialist may focus their attention on scales designed to assess specific sleep disorders. However, if a patient is well treated for sleep apnea but still reports low energy and fatigue, it may be extremely useful to know what this patient scores on a depression scale, for example. Information provided by objective questionnaires may assist clinicians in recognizing manifestations of disorders that might fall outside of their specific discipline, allowing for a more holistic treatment approach [4].

With over one hundred questionnaires and scales available, spanning over a wide range of topics, the process of selecting the right scales for one's practice or research project may appear quite daunting. Ultimately, the clinician's particular practice, focus, and patient population will dictate the measures that are needed [6]. The book *STOP, THAT and one hundred other sleep scales* lists over 100 sleep-related scales with key psychometric descriptors of each [6].

While the impulse may be to administer as many scales as possible to patients, the practical challenge is getting a comprehensive enough understanding of a patient's sleep without overwhelming them with too many questionnaires. When selecting a group of questionnaires for routine clinical use, balance is essential: the physician needs enough information to gain a complete enough clinical picture, without overloading the patient with "homework." Anecdotally, most patients appreciate being asked to complete scales and view the process an indicator of the physician's thoroughness (which it is). Patients are often willing to endure more questionnaires than most clinicians are likely to request. Some patient groups that may tend to have difficulty with the task of filling out questionnaires are those not fluent in the

language of the questionnaire, and medical professionals, who tend to view themselves as exempt from the process [6]. In general, however, few patients will refuse to complete a number of high-yield questionnaires.

When it comes to individual questionnaires, there are measures that are of general relevance (such as for fatigue, sleepiness, and alertness) as well as specific ones (such as scales for narcolepsy or sleep apnea). For adults, a set of standard questionnaires that would allow a broad understanding of a patient sleep may include the following:

General
- The Epworth Sleepiness Scale (ESS), a widely used measure of sleepiness
- The Fatigue Severity Scale (FSS), a widely used measure of fatigue
- ZOGIM-A, a scale for measuring the subject's alertness
- Owl-Lark Self-Test, which helps to assess the body clock rhythm
- Nonrestorative Sleep Scale (NRSS), which assesses how restorative patients feel after sleep

Specific
- Athens Insomnia Scale, to quickly assess features of insomnia
- STOP-Bang, easy-to-use inquiry regarding sleep apnea
- The Restless legs questionnaire, for detecting the Restless legs syndrome and the periodic limb movements in sleep (PLMS)
- Cataplexy symptom questionnaire, to screen for narcolepsy disorder

Related
- CES-D (The Center for Epidemiological Studies Depression Scale), a screen for mood problems commonly associated with sleep disorders.
- Zung Anxiety Scale describes anxiety levels.
- Illness Intrusiveness Scale quantifies the impact sleep (or any other conditions) has on a person in the number of domains.

This set of 12 scales, along with their respective references, is attached in the appendix at the end of this chapter. These scales would only take a clinician around 5 min to assess. These scales provide a vast amount of valuable information, compared to the modest amount of time they take to review. Once they have been scored, a physician familiar with these scales would need less than a minute to assemble a reasonably comprehensive sketch of an individual patient. To streamline this process, the set could be emailed out and completed at home prior to a clinical appointment. Other items can be included to meet local regulation requirements. For example, in Ontario it is expected that there is routine evaluation of drug dependence, including over-the-counter medications. A symptom list to screen for panic and/or thyroid problems can be included. This implies local tailoring is available. Often, different sets of questionnaires are used for children and adolescent patients when compared to adults.

Appendix

The Epworth Sleepiness Scale (ESS)

Purpose: The Epworth sleepiness scale is a self-reported questionnaire to assess the daytime sleepiness, by asking subjects to rate how likely they are to fall asleep in 8 different situations on a 4-point scale (0–3). The scale is administered by pen and paper, and takes 2–5 min for completion.

Scoring: The test is scored by adding up the individual scores for each question. A total score of 10 or below is considered within the normal range. A score between 10 and 18 corresponds with an excessive level of daytime sleepiness, with scores of 18 and above denoting a very high level of excessive daytime sleepiness.

Validity: The ESS was found to have a sensitivity of 0.94 and a specificity of 1.00, when compared to two other daytime sleepiness tests.

Reference: John MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*. 1991;14:540–545.

How likely are you to doze off or fall asleep during the following situations, in contrast to just feeling tired? For each of the situations listed below, give yourself a score of 0 to 3, where 0 = Would never doze; 1 = Slight chance; 2 = Moderate chance; 3 = High chance.

Situation	Score
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g., a theater/meeting)	
As a passenger in a car for an hour with no break	
Lying down in the afternoon (when possible)	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
Total	

The Fatigue Severity Scale (FSS)

Purpose: The FSS is a 9-item questionnaire that assesses fatigue by evaluating its interference with certain activities. The scale asks respondents to rate how easily they become fatigued and the degree to which this symptom negatively impacts their life.

Administration: The scale is completed by the patient with pen and paper, requiring approximately 2–3 min for completion.

Scoring: The FSS is scored on a 7-point scale with 1 = strongly disagree and 7 = strongly agree; the individual scores are then added up to get a sum total. The higher

the score, the higher the fatigue severity. A total score of less than 36 is within the normal range; the average total score for a group of healthy adults was found to be 20.7.

Reliability: A score of 36 or higher indicates that the subject is likely experiencing some fatigue. Psychometric evaluation of the FSS found an internal consistency of 0.88 and a test-retest reliability of 0.84.

Reference: Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systematic systemic lupus erythematosis. *Arch Neurol*. 1989;46:1121–1123.

Please circle a number to the right of each of these following nine statements to indicate how much you agree with the statement. "*1*" represents "*strongly disagree*," "*4*" represents "*neither disagree nor agree*," while "*7*" represents "*strongly agree*."

1.	My motivation is lower when I am fatigued	*1*	*2*	*3*	*4*	*5*	*6*	*7*
2.	Exercise brings on my fatigue	*1*	*2*	*3*	*4*	*5*	*6*	*7*
3.	I am easily fatigued	*1*	*2*	*3*	*4*	*5*	*6*	*7*
4.	Fatigue interferes with my physical functioning	*1*	*2*	*3*	*4*	*5*	*6*	*7*
5.	Fatigue causes frequent problems for me	*1*	*2*	*3*	*4*	*5*	*6*	*7*
6.	My fatigue prevents sustained physical functioning	*1*	*2*	*3*	*4*	*5*	*6*	*7*
7.	Fatigue interferes with carrying out certain duties and responsibilities	*1*	*2*	*3*	*4*	*5*	*6*	*7*
8.	Fatigue is among my three most disabling symptoms	*1*	*2*	*3*	*4*	*5*	*6*	*7*
9.	Fatigue interferes with my work, family, or social life	*1*	*2*	*3*	*4*	*5*	*6*	*7*

ZOGIM-A Questionnaire

Purpose: The ZOGIM-A is a scale that assesses respondent's alertness. The scale evaluates respondent's alertness over the course of the day, by assessing the subjective impact of environmental factors (e.g., caffeine), the anticipated benefits of increased energy levels, and the perceived proportion of the day spent at high levels of alertness.

Administration: The ZOGIM-A scale consists of 10 items that are self-administered using paper and pencil, and requires approximately 5 min for completion.

Scoring: ZOGIM-A items are scored using a 5-point Likert-type scale ranging from 1 ("extremely") to 5 ("not at all"). The sum total score provides a global index—lower scores denote impaired alertness, whereas higher scores indicate high alertness.

Reliability: The ZOGIM-A questionnaire has an internal consistency ranging from 0.93 to 0.95 and a test-retest reliability of 0.68. Additionally, scores on the ZOGIM-A differed significantly for patients with narcolepsy.

Reference: Shapiro CM, Auch CH, Reimer M, Kayumov L, Heslegrave R, Hyterer N, Driver H, and Devins GM. A new approach to the construct of alertness. *J Psychosom Res*. 2006;60(6):595–603.

This brief questionnaire deals with your level of alertness. Use the following scale to check one response for each question.

Alertness can be affected by different experiences. How might your alertness be affected by each of the following?	5 Not at all	4 Slightly	3 Moderately	2 Largely	1 Extremely
(a) Losing about 30 min of nighttime sleep					
(b) Doing about 30 min of exercise					
(c) Not drinking coffee or other foods that contain caffeine					
(d) Taking a 1-week vacation					
(e) Forgetting about your worries					
If you were more alert:					
(a) Would you be able to organize your day-to-day activities more effectively?					
(b) Would you be able to complete your tasks more methodically?					
(c) Would new ideas occur to you more readily?					
(d) Would you make fewer careless mistakes?					
(e) What proportion of the day do you feel a high level of alertness?	5 90–100%	4 50–90%	3 10–15%	2 0–15%	1 0%

Morningness-Eveningness Questionnaire (Owl-Lark Self-Test)

Purpose: The Owl-Lark self-test consists of 19 items that function to elucidate circadian rhythm variations. The scale assesses the degree to which respondents are active and alert at certain times, and queries sleep and wake times, as well as subjective "peak" times, where respondents report feeling their best.

Administration: The test is self-administered with pen and paper, requiring between 10 and 15 min for completion.

Scoring: The scale consists of both Likert-type and time scale questions. For the likert questions, the lowest values indicate definite "eveningness". For the time scale questions, each section of the scale is assigned a value of 1 through 5. To obtain a global score, each item is totaled and the sum converted to a 5-point scale:

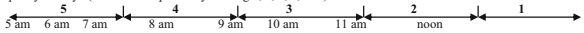
definitively morning type (70–86), moderately morning type (56–69), neither type (42–58), moderately evening type (31–41) and definitely evening type (16–30).

Reliability: An evaluation of the scale's psychometric properties found the internal consistency to be 0.82.

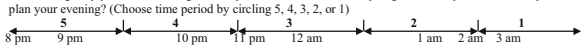
Reference: Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*. 1976;4 (2):97–110.

Select one answer that makes the most sense to you

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day? (Choose time period by circling 5, 4, 3, 2, or 1)



2. Considering only your own "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening? (Choose time period by circling 5, 4, 3, 2, or 1)



3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?
   - *Not at all dependent* **4**
   - *Slightly dependent* **2**
   - *Fairly dependent* **3**
   - *Very dependent* **1**

4. Assuming adequate environmental conditions, how easy do you find getting up in the morning?
   - *Not at all easy* **1**
   - *Not very easy* **2**
   - *Fairly easy* **3**
   - *Very easy* **4**

5. How alert do you feel during the first half hour after having woken in the morning?
   - *Not at all alert* **1**
   - *Slightly alert* **2**
   - *Fairly alert* **3**
   - *Very alert* **4**

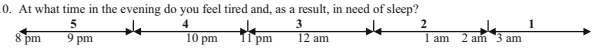
6. How is your appetite during the first half hour after having woken in the morning?
   - *Very poor* **1**
   - *Fairly poor* **2**

7. During the first half hour after having woken in the morning how tired do you feel?
   - *Very tired* **1**
   - *Fairly tired* **2**
   - *Fairly refreshed* **3**
   - *Very refreshed* **4**

8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?
   - *Seldom or never later* **4**
   - *Less than one hour later* **3**
   - *1-2 hours later* **2**
   - *More than two hours later* **1**

9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour, twice a week and the best time for him is between 7:00-8:00 am. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?
   - *Would be in good form* **4**
   - *Would be in reasonable form* **3**
   - *Would find it difficult* **2**
   - *Would find it very difficult* **1**

10. At what time in the evening do you feel tired and, as a result, in need of sleep?



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11. You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering only your own "feeling best" rhythm, which ONE of the four testing times would you choose?
   - *8:00-10:00 am* **6**
   - *11:00 am-1:00 pm* **4**
   - *3:00 pm-5:00 pm* **2**
   - *7:00-9:00 pm* **0**

12. If you went to bed at 11:00 pm, at what level of tiredness would you be?
   - *Not at all tired* **0**
   - *A little tired* **2**
   - *Fairly tired* **3**
   - *Very tired* **5**

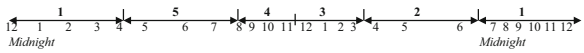
13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?
   - *Will wake up at usual time and will NOT fall asleep again* **4**
   - *Will wake up at usual time and will doze thereafter* **3**
   - *Will wake up at usual time but will fall asleep again* **2**
   - *Will NOT wake up until later than usual* **1**

14. One night you have to remain awake between 4:00-6:00 am in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?
   - *Would NOT go to bed until watch was over* **1**
   - *Would take a nap before and sleep after* **2**
   - *Would take a good sleep before and nap after* **3**
   - *Would take ALL sleep before watch* **4**

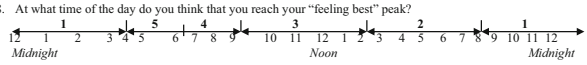
15. You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own "feeling best" rhythm, which ONE of the following times would you choose?
   - *10:00 am* **4**
   - *11:00 am-1:00 pm* **3**
   - *3:00 pm-5:00 pm* **2**
   - *7:00-9:00 pm* **1**

16. You have decided to engage in hard physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 10:00-11:00 pm. Bearing in mind nothing else but your own "feeling best" rhythm, how well do you think you would perform?
   - *Would be in good form* **1**
   - *Would be in reasonable form* **2**
   - *Would find it difficult* **3**
   - *Would find it very difficult* **4**

17. Suppose that you can choose your own work hours. Assume that you worked a FIVE-hour day (with breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you select?



18. At what time of the day do you think that you reach your "feeling best" peak?



19. One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be?
   - *Definitely a "morning" type* **6**
   - *Rather more a "morning" than an "evening" type* **4**
   - *Rather more an "evening" than a "morning" type* **2**
   - *Definitely an "evening" type* **0**

Non-restorative Sleep Scale

Purpose: The Nonrestorative Sleep Scale is used to evaluate nonrestorative sleep. Nonrestorative sleep is defined as the subjective feeling that sleep has been insufficiently refreshing, often despite the appearance of physiologically normal sleep. Nonrestorative sleep has been shown to be associated with a variety of cognitive, affective, and medical complaints.

Administration: The scale is self-administered with pen and pencil, requiring 3–5 min for completion.

Scoring: All items are given a weighted score from 1 to 5 (i.e. for scales items range from 1 to 10, responses 1 and 2 are scored as 1, responses 3 and 4 are scored as 2, etc.). The individual scores for items 4, 5, 6, 7, 11, and 12 must be reversed before scoring. Sum the scores of all the items to find the global score. Global scores range from 12 to 60, where lower scores indicate more severe nonrestorative sleep.

Validity: A cut-off score of **46 or less** is found to maximize sensitivity (0.91) while still providing satisfactory specificity (0.75).

Reference: Wilkinson K, Shapiro C. Development and validation of the Nonrestorative Sleep Scale (NRSS). *J Clin Sleep Med.* 2013;9(9):929–937

Please checkmark the response that best represents your usual experiences over the past month.

How often have you felt really refreshed upon awakening in the morning?

☐ Never ☐ 1 day/week ☐ 2-3 days/week ☐ 4-5 days/week ☐ 6-7 days/week

1. How would you rate the quality of your sleep?

1 2 3 4 5 6 7 8 9 10
Very poor *Very good*

2. Usually, do you think your sleep is restoring or refreshing?

1 2 3 4 5 6 7 8 9 10
Never *Always*

3. Have you felt rested if you've slept for your usual amount of time?

1 2 3 4 5 6 7 8 9 10
Not at all *Absolutely*

4. Have you had physical sensations or unusual feelings in your body that you couldn't identify?

1 2 3 4 5 6 7 8 9 10
Never *Yes, all the time*

5. In the past month, how often have you had one or more of the following: headaches, body pain, numbness or tingling in parts of your body, nausea, racing heart/palpitations, sore throat, frequent cough?

☐ Never ☐ 1 day/week ☐ 2-3 days/week ☐ 4-5 days/week ☐ 6-7 days/week

6. Do you feel that physical or medical problems are dragging you down?

1 2 3 4 5 6 7 8 9 10
Never *Yes, all the time*

7. Do you ever have a sense of panic, or physical symptoms of panic such as heart racing, for no apparent reason?

1 2 3 4 5 6 7 8 9 10
Never *Yes, all the time*

8. How is your memory and concentration during the daytime?

1 2 3 4 5 6 7 8 9 10
Very poor *Very good*

9. What is your usual level of daytime energy?

1 2 3 4 5 6 7 8 9 10
Very low *Very high*

10. Do you usually feel alert during the daytime?

1 2 3 4 5 6 7 8 9 10
Not at all *Very alert*

11. Do you feel depressed or down if you didn't sleep well the night before?

1 2 3 4 5 6 7 8 9 10
Not at all *Very depressed*

12. How often have you felt irritable or gotten the "blahs" if you didn't sleep well the night before?

☐ Never ☐ 1 day/week ☐ 2-3 days/week ☐ 4-5 days/week ☐ 6-7 days/week

Athens Insomnia Scale

Purpose: The AIS is a self-report scale that assesses the severity of insomnia based on the diagnostic criteria set by the International Classification of Diseases (ICD-10). The AIS contains 8 items with 4 responses ranging from 0 ("no problem at all") to 3 ("very serious problem").

Administration: The scale requires 3–5 min for completion.

Scoring: The scale is scored by adding up the individual scores for each question, for a total score ranging from 0 to 24. Higher scores indicate more extensive insomnia symptoms. A cut-off score of 6 in psychiatric patients and a cut-off of 10 for epidemiological studies have been proposed to have optimal specificity and sensitivity.

Reliability: The internal consistency of the AIS-8 and the AIS-5 for primary insomniac patients, psychiatric outpatients, psychiatric inpatients, and healthy controls is 0.89 and 0.87, respectively; test-retest reliability was 0.89 and 0.88, respectively.

Reference:

1. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. J Psychosom Res. 2000;48:555–560.
2. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens Insomnia Scale. J Psychosom Res. 2003; 55:263–267.

This scale is intended to record tour own assessment of any sleep difficulty you might have experienced. Please check the appropriate number in the items below to indicate your estimate of any difficulty, *provided that it occurred at least three times per week* during the past month.

Sleep induction (time it takes you to fall asleep after turning off the lights)	0 No problem	1 Slightly delated	2 Markedly delayed	3 Very delayed or did not sleep at all
Awakenings during the night	0 No problem	1 Minor problem	2 Considerable problem	3 Serious problem or did not sleep at all
Final awakening earlier than desired	0 Not earlier	1 A little earlier	2 Markedly earlier	3 Much earlier or did not sleep at all
Total sleep duration	0 Sufficient	1 Slightly insufficient	2 Markedly insufficient	3 Very insufficient or did not sleep at all
Overall quality of sleep (no matter how long you slept)	0 Satisfactory	1 Slightly unsatisfactory	2 Markedly unsatisfactory	3 Very unsatisfactory or did not sleep at all
Sense of well-being during the day	0 Normal	1 Slightly decreased	2 Markedly decreased	3 Very decreased

(continued)

Functioning (physical and mental) during the day	0 Normal	1 Slightly decreased	2 Markedly decreased	3 Very decreased
Sleepiness during the day	0 none	1 Mild	2 Considerable	3 Intense

STOP-Bang

Purpose: The STOP-Bang questionnaire is designed to screen for symptoms of obstructive sleep apnea (OSA). The scale was originally developed for use in the preoperative setting—as untreated sleep apnea is associated with increased post-operative complications and longer hospital stays. The scale is also extremely beneficially in the clinical setting, as it is short and easy to use.

Administration: The scale consists of 8 questions, and will take a patient approximately 1 min to complete.

Scoring: A score of 1 is given for each 'yes' answer, and 0 is given for 'no'. For the general population, an answer of yes for 0–2 questions indicates a low risk of OSA. A total score of 3 or more corresponds with a 70% chance of OSA, and is considered high risk.

Validity: For patients with moderate-to-severe sleep apnea, the STOP-Bang scale has both a specificity and sensitivity of greater than 90%.

Reference: Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. *Anesthesiology*. 2008;108(5):812-821.

Do you **S**nore?	Yes/No
Do you feel **T**ired, fatigued or sleepy during the day?	Yes/No
Has anyone **O**bserved you stop breathing in your sleep?	Yes/No
Do you have high blood **P**ressure?	Yes/No
BMI greater than 35?	Yes/No
Age older than 50 year old?	Yes/No
Neck circumference greater than 17 inches (if male) or 16 inches (if female)?	Yes/No
Gender- Are you a male?	Yes/No

The Restless legs Questionnaire

Purpose: This 8-item self-report questionnaire is used to evaluate the possibility of periodic limb movements in sleep (PLMS) and/or restless legs syndrome (RLS).

Administration: The scale is administered by pen and paper, and requires approximately 5 min for completion.

Scoring: The first 4 items include 8 questions. If a person answers at least one YES of the first 8 questions, and says YES after question 8, he or she likely has restless legs syndrome. More positive respond (YES) indicates higher possibility of RLS and/or PLMS.

Reference: Allen R, Earley C. Validation of a diagnostic questionnaire for the restless legs syndrome (RLS). *Neurology.* 2001;58(8 Suppl 3), A4

1. Do you experience recurrent unpleasant sensation or tingling in your legs, while sitting or laying down? ❑ Yes ❑ No
   If *Yes*, how would you describe this sensation?
   ❑ a. painful ❑ b. unpleasant ❑ c. both painful and unpleasant

2. Do you repeatedly feel an urge to move your legs while sitting or laying down? ❑ Yes ❑ No
   If *Yes,* do you need to move your whole body not only your legs? ❑ Yes ❑ No
   This feeling that you have to move, is sometimes so pressing that you cannot resist it, or you just simply have to move your arms or legs? ❑ Yes ❑ No

3. Do your legs jump or move a lot, involuntarily, while sitting or laying down? ❑ Yes ❑ No
   If *Yes*, do you think that the sensations I your legs and the movements are connected? ❑ No ❑ Yes

   If *Yes*, how often do these involuntary movements occur? (check only one answer)
   ❑ a. seldom ❑ b. occasionally ❑ c. frequently ❑ d. almost always
   Do these involuntary movements occur only before you fall asleep? ❑ Yes ❑ No

4. Do you have recurrent periods of time where you are so itchy, you can not stay in one place or you have to move your arms or legs? ❑ Yes ❑ No

   Continue to answer the following questions ONLY if you answered "*Yes*" to at least one of the previous questions.

5. When these sensations or movements occur, are they worse while you have a rest (while sitting or laying down) than during physical activities? ❑ Yes ❑ No

6. If these sensations or movements are present and you begin walking, Do they improve or do they disappear while you are walking? ❑ Yes ❑ No ❑ Don't know

   Continue to answer the following questions ONLY if you answered "*Yes*" to at least of the previous questions.

7. If these sensations or movements are present, are they worse in the evening or during the night? ❑ Evening ❑ Night

8. Not NOW, but when these sensations or movements started, were these sensations or movements worse in the evening or during the night? ❑ Evening ❑ Night

Cataplexy Questionnaire

Purpose: The following is a qualitative scale to assess cataplexy symptoms related to narcolepsy disorder. The scale is a self-report, and takes approximately 2–3 min to complete. As cataplexy symptomology can vary greatly between patients, this broad yet comprehensive questionnaire is especially useful for screening patients who may not recognize or identify their symptoms as being cataplexy-related, and is a great tool that allows clinicians to detect potential cataplexy symptoms that could

potentially be missed. This cataplexy questionnaire has yet to be published or psychometrically evaluated. It was developed by Avadel Pharmaceuticals© for research purposes.

1. Have you ever experienced a sudden loss of muscle strength, loss of muscle control, muscle weakness or limp muscles in situations such as feeling very happy, laughing, being surprised? (e.g. unexpectedly encountering a friend, becoming angry, or hearing or telling a joke?
2. If yes, have you experienced one or more of the events listed below? Please checkmark all that apply, regardless of the severity of the cataplexy attacks. Loss of muscle tone can be subtle and partial, only affecting some parts of the body; or complete/generalized, affecting the whole body and lasting from a few seconds to a few minutes. For each of the events, please indicate the most severe frequency, since the frequency may vary widely.

Events	Yes	No	# per week	# per day	Other frequency
Eyelid drooping					
Slackening of the facial muscles, sagging or drooping of the face, spontaneous grimaces					
Head nodding, dropping down, or falling forward					
Slurred or broken speech					
Neck weakness					
Jaw dropping					
Weakness, unlocking, buckling of the knees					
Leg weakness					
Arm weakness, arms dropping to the side					
Complete collapse to the ground with immobility					
Other; please specify					

3. Have you ever avoided emotional situations or doing certain activities (such as attending concerts, sports events, etc.) to avoid an attack? If yes, please describe some of these situations: _____

Center for Epidemiological Studies Depression Scale (CES-D) Questionnaire

Purpose: The CES-D scale is a brief self-report scale designed to measure symptoms associated with depression that have been experienced in the past week. The questionnaire includes twenty items comprising six scales reflecting major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance.

Administration: The scale is a self-report using pen and paper, and takes approximately 5 min to complete.

Scoring: For the majority of questions, an answer of 'Rarely or none of the time' (the first column) receives a score of 0, "some or a little of the time" (second column) receives 1, "occasionally or a moderate amount of time" (third column) receives 2 , and "Most or all of the time" (fourth column) receives 3. However, items 4, 8, 12, and 16 are worded positively, and therefore the scores are reversed to ensure that respondents pay attention to questions and answer honestly. Higher scores represent greater depressive symptoms; a score of 16 or more is suggestive of depression.

Reliability: High internal consistency for the CES-D scale has been reported with Cronbach's alpha coefficients ranging from 0.85 to 0.90 across studies.

Reference: Radloff, LS. The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurements,* 1977;1: 385–401.

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

Zung Self-Rating Anxiety Scale (SAS)

Purpose: The Self-rating Anxiety Scale (SAS) was developed by Zung as a self-reporting instrument for patients being evaluated for anxiety-associated symptoms. The patient answers 20 questions related to the frequency of various symptoms.

Administration: The scale is completed by the patient with pen and paper, requiring approximately 2–3 min for completion.

Scoring: The rating scale is scored from 1 to 4 points. Most answers go in order of 1 (a little of the time) to 4 (most of the time). However, questions 5, 9, 13, 17, and 19 are scored in the opposite order, since they represent positive/non-anxiety statements. The total score is the sum of each item. A cut off score of 45 or higher raises the possibility of anxiety disorder.

- 20–44 → Normal Range
- 45–59 → Mild to Moderate Anxiety Levels
- 60–74 → Marked to Severe Anxiety Levels
- 75–80 → Extreme Anxiety Levels

Reliability: Psychometric testing of the Zung self-rating anxiety score showed an internal consistency reliability coefficient of 0.80.

Reference: Zung WWK. A rating instrument of anxiety disorders. *Psychosomatics*. 1971;12:371–379

For each item below, please check the column which best describes how often you felt or behaved this way during the past several days.

	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel more nervous and anxious than usual				
2. I feel afraid for no reason at all				
3. I get upset easily or feel panicky				
4. I feel like I'm falling apart and going to pieces				
5. I feel that everything is all right and nothing bad will happen				
6. My arms and legs shake and tremble				
7. I am bothered by headaches neck and back pain				
8. I feel weak and get tired easily				
9. I feel calm and can sit still easily				
10. I can feel my heart beating fast				
11. I am bothered by dizzy spells				
12. I have fainting spells or feel like it				
13. I can breathe in and out easily				

(continued)

	A little of the time	Some of the time	Good part of the time	Most of the time
14. I get numbness and tingling in my fingers and toes				
15. I am bothered by stomach aches or indigestion				
16. I have to empty my bladder often				
17. My hands are usually dry and warm				
18. My face gets hot and blushes				
19. I fall asleep easily and get a good night's rest				
20. I have nightmares				

Illness Intrusiveness Scale

Purpose: Illness intrusiveness was introduced to represent illness-induced disruptions to lifestyles, activities, and interests that compromise quality of life. Illness intrusiveness is measured using the Illness Intrusiveness Rating Scale (IIRS), which assesses the extent to which one's "illness and/or its treatment interfere" with 13 life domains central to quality of life.

Administration: The scale is a self-report using pen and paper, and requires 2–3 min to complete.

Scoring: The higher the sum score, the greater the illness intrusiveness and presumable more impaired the quality of life. A testing of 606 subjects with chronic disease has found that the observed range of the IIRS was 13–91, with a mean of 44.2 and standard deviation 18.3.

Reference: Devins GM, Flanigan M, Fleming JAE, Morehouse R, Moscovitch A, Plamondon J, Reinish L, Shapiro CM. Differential illness intruciveness associated with sleep-promoting medications. *Eur Psychiatry*. 1995;10(973):153–159.

Please circle the one number (scale 1–7) that best describes your current life situation. If an item is not applicable, please circle the lowest number (1) to indicate that this aspect of your life is not affected very much.

How much does your sleep problem and/or its treatment interfere with your:

	Not very much ⟶ Very much						
Health	1	2	3	4	5	6	7
Diet	1	2	3	4	5	6	7
Work	1	2	3	4	5	6	7
Active Recreation (e.g., sports)	1	2	3	4	5	6	7
Passive Recreation (e.g., reading, listening to music)	1	2	3	4	5	6	7
Financial Situation	1	2	3	4	5	6	7
Relationship With Your Spouse (girlfriend or boyfriend, if not married)	1	2	3	4	5	6	7
Sex Life	1	2	3	4	5	6	7
Family Relations	1	2	3	4	5	6	7
Other Social Relations	1	2	3	4	5	6	7
Self-Expression/Self-Improvement	1	2	3	4	5	6	7
Religious Expression	1	2	3	4	5	6	7
Community and Civic Involvement	1	2	3	4	5	6	7

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Methods of Evaluation of Sleep Disorders

10

Meenakshi Gupta, Mohaddeseh Gholizaded, and Colin M. Shapiro

Abstract

There are a number of sleep disorders that may mimic each other, at least superficially. These disorders may be differentiated from each other by a careful clinical history and physical examination. Questionnaires and scales also help in screening and assessing the severity of certain sleep disorders. However, at times, certain investigations like actigraphy and polysomnography provide invaluable information regarding diagnosis as well as management. These methods may also be important during follow-up to assess the compliance to and progress after treatment. This chapter discusses these issues.

Keywords

Sleep disorders · Questionnaires · Actigraphy · Polysomnography

There are over 80 different sleep disorders (International Classification of Sleep Disorders) and in the current DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5), "sleep" is the second largest section. However, most doctors, dentists, psychologists, and nurses have little or no formal training in sleep [1]. The disorders are diverse including insomnia, sleep apnea, narcolepsy, phase delay, parasomnia, and mood disorder but to assess any of them, the assessment is similar and should be systematic. While many sleep clinics today focus on the respiratory sleep disorders,

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it is true to say that all sleep disorders will increase mental health disorders such as anxiety and depression by approximately fivefold [2]. If one sleep disorder is remedied but another is not, it is likely that the patient will not perceive the benefit of the therapy (that of continuous positive airway pressure for example Therefore, the patient will not be compliant in using this lifesaving treatment because the health worker was too cavalier to look beyond the most obvious of sleep disorders.

10.1 Common Diagnoses

10.1.1 Obstructive Sleep Apnea (OSA)

It is defined as a sleep disorder that involves the cessation or a significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals from sleep.

10.1.2 Narcolepsy

It is characterized by the classic tetrad of excessive daytime sleepiness (EDS), cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis.

10.1.3 Circadian Rhythm Disorder

This can be categorized into two main groups: transient disorders (e.g., jet lag or a changed sleep schedule due to work, social responsibilities, or illness) and chronic disorders (e.g., delayed sleep-phase syndrome [DSPS], advanced sleep-phase syndrome [ASPS], and irregular sleep-wake cycle).

10.1.4 Mood Disorder

Sleep markers of depression, PTSD (posttraumatic stress disorder), and anxiety can help detect mood disorders.

10.1.5 Insomnia

It is defined as difficulty with sleep initiation or maintenance, waking too early, or sleep that is nonrestorative, despite ample opportunity to sleep. It should be accompanied by at least one manifestation of daytime impairment (such as fatigue, mood disturbance, headaches, or gastrointestinal symptoms in response to sleep

loss), or impaired memory, concentration, or performance. To be considered clinically significant, the frequency of symptoms should be 3 or more nights a week.

10.1.6 Parasomnia/Non-rapid Eye Movement (NREM) Sleep Arousal Disorder

This disorder is described as being characterized by abnormal complex movements occurring during NREM sleep or rapid eye movement (REM) sleep. Common disorders occurring during NREM are somnambulism (sleep talking, sleepwalking), sleep terrors, and confusional arousals. REM (rapid eye movement) sleep behavior disorder is important, as it is associated with other neuropsychiatric problems.

Identifying and diagnosing sleep disorders could at times be difficult because of the overwhelming number of patients with sleep problems relative to the scarce resources of relatively few sleep specialists. That creates an artificial barrier to a patient from having formal sleep assessment. This may also lead sleep clinicians to deal with only part of the sleep problem and not the whole sleep problem. Furthermore, this results in poor management of the patient. For example, a patient diagnosed with sleep apnea who also happens to have delayed sleep-wake phase disorder and continues to go to bed at 3 am is not going to feel better without some management of his associated body clock problem and is very unlikely to use the treatment suggested for his sleep apnea, especially if he is frustrated by a very long sleep onset. We have known of examples where very competent respiratory-oriented sleep physicians who were questioned by a postdoc fellow trained abroad, the response was "we don't deal with that." The fellow's interpretation was that the clinician was practicing "apnea medicine" and not "sleep medicine" and subsequent contact showed that the patient did not use continuous positive airway pressure (CPAP) as needed. Recently, Keenan, Pack, and their colleagues [3] have described different phenotypes of sleep apnea, which includes patients with sleep apnea presenting with comorbid insomnia (COMISA) or just insomnia complaints. There is a general mantra that patients with insomnia do not need a sleep evaluation, and underlying or comorbid sleep apnea challenges that presumption. Similarly, Zalai et al. [4] have shown in a large study of patients with postconcussion insomnia, a sizable number of patients had other sleep disorders which needed formal diagnosis to facilitate the recovery from insomnia. In this population, this is of particular importance because insomnia is a predictor for recovery from postconcussion. The other unrecognized disorders included: delayed sleep-wake phase disorder; sleep apnea and periodic limb movements of sleep (PLMS).

10.1.7 Sleep History

The first step in diagnosing a sleep-related disorder (as is the case for any disorder) is by taking a detailed history.

This may appear to be inanely basic and banal but there has emerged in sleep circles in some jurisdictions an approach of doing a sleep study first and then asking the patient why they came for a sleep assessment. This may be a good business model but it will almost certainly narrow the focus of inquiry and almost certainly produce a lower yield of useful information. At its simplest, if a patient is not asked if they have symptoms of narcolepsy they are unlikely to be best sent for an MSLT (Multiple Sleep Latency Test) (see below) and the diagnosis will be missed. If the clinical interview suggests symptoms of temporal lobe epilepsy, then a full-montage electroencephalography (EEG) should be carried out. Conversely, the results of the sleep study may suggest further inquiry; for example, a patient with periodic leg movements should have their iron levels checked, as low iron can be a cause of PLMS. We have had patients where this was done and the iron and hemoglobin were low. Further testing showed blood in stool. Further investigation revealed early colon cancer which was the cause. Early intervention was fortuitously achieved with good long-term outcome in both patients (seen by C. M. Shapiro, Sleep medicine specialist).

The history in a sleep disorder does not only include asking the questions of the patient but also the bed partner or a family member or even a roommate, as they may have a different insight into the patient's behavior during sleep or about their mood which may profoundly impact their sleep [5].

A uniform approach to the sleep history facilitates a thorough medical decision-making process. Some of the pertinent questions involved in diagnosis include those given in Table 10.1:

Specific questionnaires are described in Chap. 10 of this book and two books dealing specifically with questionnaires and processes of measurement in patients can be referred to; "STOP, THAT and one hundred other sleep scales" [6] and "Measuring human problems" [7].

Various questionnaires have been implemented to be used while taking a sleep history. These questionnaires correlate strongly with a diagnosis. For example, the **snoring, tiredness/fatigue/sleepiness, observed apnea, high BP (blood pressure), BMI (body mass index), age, neck circumference, and male gender (STOP BANG)** questionnaire can be used to determine the probability of having sleep apnea. For the general population, an answer of yes for 0–2 questions indicates a low risk of OSA. A total score of 3 or more (out of 8) corresponds with a 70% likelihood of an apnea diagnosis [8]. Other questionnaires that are widely used and helped include the **Epworth Sleepiness Scale (ESS)**, which is an 8-item self-report questionnaire on which a score of 10 or higher is indicative of daytime sleepiness (range 0–24); the **Fatigue Severity Scale (FSS)** where a score of more than 3.3 indicates fatigue (range 1–7); **Centre for Epidemiologic Studies-Depression Scale (CES-D)** which is a 20-item self-report questionnaire in which a score of 16 or more is suggestive of depression; **Screen for Child Anxiety Related Disorders (SCARED)**, where if the sum $\geq$30 is more specific for anxiety; **Toronto Hospital Alertness Test (THAT)**, a test designed to measure alertness and a score of $\leq$20 indicates reduced alertness; **Zung Anxiety**, where if the sum $\geq$40 is more specific for anxiety. The **Owl-Lark Self-Test** consists of 19 items that function to elucidate circadian rhythm variations. The scale consists of both Likert-type and timescale

Table 10.1 History questions

(a) History of presenting complaint
• Onset of sleep disorder • Course of sleep disorder (worsening gradually or rapidly) • Duration • Aggravating factors • Relieving factors • Frequency—how often does the sleep problem happen? • Severity—does it affect quality of life? • Precipitating factors such as fever, stress, or trauma
(b) Daytime functioning
• Daytime sleepiness • Time it takes to fall asleep during naps • Sleeping while driving, eating • Episodes of cataplexy • Hypnagogic hallucinations—Vivid dreamlike experiences that seem real and occur while falling asleep • Hypnopompic hallucinations—Vivid dreamlike experiences that seem real and occur while waking up • Sleep paralysis
(c) Sleep schedule
• Activities done prior to going to bed (bedtime routine) • Bedtime • Time it takes to fall asleep once in bed • Number of times one wakes up during the night • Description of activities during nocturnal awakening • Time it takes to go back to sleep at night • Wake-up time
(d) Other symptoms
• Periodic leg movements/restless leg syndrome • Decreased alertness while driving • Impaired interpersonal relationships • Decreased concentration or memory
(e) Past medical history
• History of hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), iron deficiency, thyroid disease, renal disorders, arrhythmia
(f) Drug (medical and recreational drug) history
• Alcohol use • Cannabis use • Smoking
(g) Use of sleep aids and stimulants
• Over-the-counter (including herbal) agent • Prescription medication • Caffeine • Energy drinks
(h) Family history
• Relatives with history of sleep disorders, parasomnias, or mood disorders
(i) Nocturnal sleep-related breathing problem
• Snoring • Episodes of choking or breathing cessation

(continued)

Table 10.1 (continued)

• Not feeling refreshed upon awakening • Excessive fatigue throughout the day • Taking naps during the day • Dry mouth • Mouth breathing • Morning headaches • Nasal congestion • Erectile dysfunction • Urinary frequency
(j) Nocturnal behaviors
• Sleepwalking • Sleep talking • Sexsomnia • Sleep eating • Bruxism • Acting out dreams • Time of the night when these activities occur
(k) Mood-related questions
• Symptoms of depression • History of PTSD • Stress or anxiety states

questions. For the Likert questions, the lowest values indicate definite "eveningness." To obtain a global score, each item is totaled and the sum converted to a 5-point scale: definitively morning type (70–86), moderately morning type (56–69), neither type (42–58), moderately evening type (31–41), and definitely evening type (16–30) (for further details, see Chap. 10).

Sleepiness is thought to result from neurobiological processes that regulate circadian rhythms and the drive to sleep, and some individuals will clearly articulate sleepiness as a tendency to doze unintentionally [9]. Fatigue is defined as "reversible, motor, and cognitive impairment with reduced motivation and desire to rest," and is postulated to represent a process that is distinct from sleepiness. However, patients often interchangeably use the terms "tiredness," "sleepiness," and "fatigue."

Daytime sleepiness is a very critical issue to evaluate. If an individual can sleep while talking, driving, eating, or working, it may result in danger to both the individual and others surrounding the individual. Daytime sleepiness that impairs a patient's functional capabilities can threaten job security and have a negative impact on interpersonal relationships. The context of a patient's daytime sleepiness highlights its severity and impact. There are both questionnaire approaches and objective approaches, for example, the Multiple Sleep Latency Test (MSLT) for sleepiness and the Maintenance of Wakefulness Test (MWT) for wakefulness; as well as, for example, using a driving simulator [10].

Leg discomfort associated with an urge to move that worsens at night and improves with leg movement may indicate restless legs syndrome (RLS) and may contribute to the patient's poor sleep quality and impair daytime functioning. It can

also be caused by iron deficiency, thus ferritin levels should be checked in patients presenting with this. Other common causes/associations are SSRI (selective serotonin reuptake inhibitor) medications, renal disease, and Parkinson's disease.

Obstructive sleep apnea usually presents with a history of snoring, or episodes of choking with a nonrefreshed sensation in the morning, despite the patient feeling that they slept the whole night.

10.2 Physical Examination

A physical examination is the next step in coming to a diagnosis. The weight, height, BMI, neck circumference, and blood pressure help to estimate the likelihood of sleep apnea diagnosis such as obstructive sleep apnea where an increase in any of those indices (except height) is more suggestive of its presence. The patient's facial morphology should be assessed for features of elongated midface, small jaw/retrognathia, nasal septal deviation, nasal atrophy, and tonsil size.

10.3 Mental Status Examination and Neurological Examination

These should be done in any patient with excessive daytime sleepiness, mood disorder, or memory loss. Thyroid examination can also help to rule out medical causes of extreme fatigue. Sleep-related disorders, especially OSA, can lead to complications in almost every system of the body, for example, it can increase the risk of or cause memory disturbance, stroke, hypertension, cardiac arrhythmia, myocardial infarction, glaucoma, bowel disturbance, diabetes mellitus, and metabolic syndrome [11]. Making patient aware of these comorbidities is a powerful weapon in the battle for compliance with treatment.

10.4 Investigations

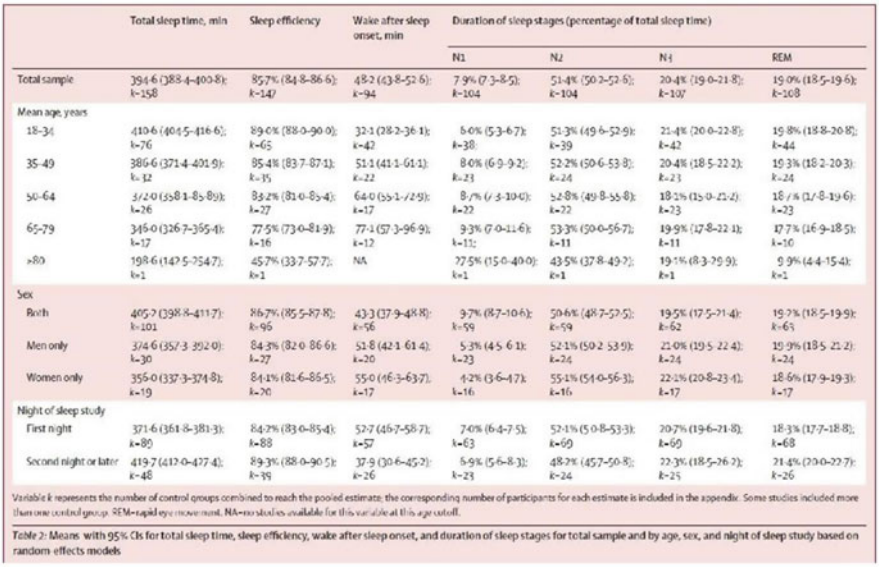
10.4.1 Polysomnography (PSG)

This is the most common investigation done to assess sleep-related disorders. PSG consists of a simultaneous recording of multiple physiologic parameters related to sleep and wakefulness. Electrodes are placed on the scalp to monitor the different sleep stages by observing the wave patterns. In addition, electrodes are placed on the chin in relation to the eyes (to detect eye movements that help to differentiate between awake and REM sleep), the chest, and the legs. Respiration is monitored with a nasal cannula/pressure transducer system, mouth thermistor, chest and abdominal bands, and pulse oximeter. Bruxism is monitored by the chin electrodes. The chin electrodes are also helpful in electromyography (EMG) recording and help to differentiate REM when the muscle tone is relaxed from other sleep stages. Leg movements are assessed with surface EMG electrodes typically placed on the right and left anterior tibialis muscles. Sleep stages, microarousals, periodic limb

movements of sleep (PLMS), and respiratory events are manually scored according to standard criteria [12]. Video may or may not be recorded as well depending on the indications for the study such as parasomnias. Drugs that may interfere with sleep latency or REM latency should be noted. There are two schools of thought concerning the use of drugs during the PSG. On the one hand, some clinicians believe that they should stop the medications prior to a sleep study (e.g., SSRIs that suppress REM sleep should not be used 2 weeks before an MSLT—other than fluoxetine which has a half-life of 6 weeks). This aids in getting a cleaner (unaltered result) with no effect of the drug on the sleep observed. However, on the other hand, the impact of most drugs on sleep architecture is well known [13]. Thus, if a patient is already taking, for example, Zopiclone, it would be clinically prudent to record sleep with the medications, as doing a study without it and then detecting, for example, and then recommending that the patient take Zopiclone sleep fragmentation would make the individual feel that the physician is a fool and nothing has been achieved by the exercise. For this reason, many clinicians would take the stance that patients should be taken "as they are" and then sleep evaluated to see what improvements can be made.

The same line of thought is involved in the use of alcohol prior to a sleep study. If a person uses alcohol, giving an instruction not to take it prior to doing the PSG means that one is not examining the "real" patient. Alcohol is known to increase the chances of having sleep apnea and parasomnias, thus it is essential that the patient be evaluated in their "natural/usual state." The caveat to this is that clear instructions should be provided to the patient that they should not drink and then drive to the sleep laboratory. Thus, they should arrive early at the sleep laboratory and then consume the alcohol.

The "first night effect" (FNE) is the alteration of sleep architecture observed on the first night of the PSG [14]. There was a point in time when all patients coming to a certain sleep lab would have two nights of sleep study to overcome "The first night effect." This was a carrying forward of a research approach into the clinical domain. However, not surprisingly the financial implications put a stop to this practice. At that time, a review of the last 500 patients who had two consecutive diagnostic nights in the sleep laboratory was assessed with the help of blind raters. The exercise was to find if the final diagnosis would have been established from a single night in the sleep laboratory. A disillusioning 16% of patients would not have received the ultimate diagnosis, if the first night only was taken into account. This leads to the conclusion that in a clinic day, with 12 patients being provided with feedback of a single sleep study, two patients are likely to receive erroneous information. The implications of this observation are that the treating physician needs to retain his/her clinical suspicion about a potential diagnosis, even in the face of a supposedly objective evidence that points to a contradictory conclusion. Recently, one of us (C. M. Shapiro, Sleep medicine specialist) had a patient who presented with an account that sounded very much like sleep apnea. He scored positively on five of eight items on STOP BANG and the clinical assessment was that he had a likelihood of sleep apnea of 85%. The results of the sleep study showed an AHI (apnea/hypopnea index) of 5.8. As a treating clinician, one was surprised and



	Total sleep time, min	Sleep efficiency	Wake after sleep onset, min	Duration of sleep stages (percentage of total sleep time)			
				N1	N2	N3	REM
Total sample	394·6 (388·4–400·8); k=158	85·7% (84·8–86·6); k=147	48·2 (43·8–52·6); k=94	7·9% (7·3–8·5); k=104	51·4% (50·2–52·6); k=104	20·4% (19·0–21·8); k=107	19·0% (18·5–19·6); k=108
Mean age, years							
18–34	410·6 (404·5–416·6); k=76	89·0% (88·0–90·0); k=65	32·1 (28·2–36·1); k=42	6·0% (5·3–6·7); k=38	51·3% (49·6–52·9); k=39	21·4% (20·0–22·8); k=42	19·8% (18·8–20·8); k=44
35–49	386·6 (371·4–401·9); k=32	85·4% (83·7–87·1); k=35	51·1 (41·1–61·1); k=22	8·0% (6·9–9·2); k=23	52·2% (50·6–53·8); k=24	20·4% (18·5–22·2); k=23	19·3% (18·2–20·3); k=24
50–64	372·0 (358·1–85·89); k=26	83·2% (81·0–85·4); k=27	64·0 (55·1–72·9); k=17	8·7% (7·3–10·0); k=22	52·8% (49·8–55·8); k=22	18·2% (15·0–21·2); k=23	18·7% (17·8–19·6); k=23
65–79	346·0 (326·7–365·4); k=17	77·5% (73·0–81·9); k=16	77·1 (57·3–96·9); k=12	9·3% (7·0–11·6); k=11;	53·3% (50·0–56·7); k=11	19·9% (17·8–22·1); k=11	17·7% (16·9–18·5); k=10
>80	198·6 (142·5–254·7); k=1	45·7% (33·7–57·7); k=1	NA	7·5% (5·0–40·0); k=1	43·5% (37·8–49·2); k=1	19·1% (8·3–29·9); k=1	9·9% (4·4–15·4); k=1
Sex							
Both	405·7 (398·8–411·7); k=101	86·7% (85·5–87·8); k=96	43·3 (37·9–48·8); k=56	9·7% (8·7–10·6); k=59	50·6% (48·7–52·5); k=59	19·5% (17·5–21·4); k=62	19·2% (18·5–19·9); k=63
Men only	374·6 (357·3–392·0); k=30	84·3% (82·0–86·6); k=27	51·8 (42·1–61·4); k=20	5·3% (4·5–6·1); k=23	52·1% (50·2–53·9); k=24	21·0% (19·5–22·4); k=24	19·9% (18·5–21·2); k=24
Women only	356·0 (337·3–374·8); k=19	84·1% (81·6–86·5); k=20	55·0 (46·3–63·7); k=17	4·2% (3·6–4·7); k=16	55·1% (54·0–56·3); k=16	22·1% (20·8–23·4); k=17	18·6% (17·9–19·3); k=17
Night of sleep study							
First night	371·6 (361·8–381·3); k=80	84·2% (83·0–85·4); k=88	52·7 (46·7–58·7); k=57	7·0% (6·4–7·5); k=63	52·1% (50·8–53·3); k=69	20·7% (19·6–21·8); k=69	18·3% (17·7–18·8); k=68
Second night or later	419·7 (412·0–427·4); k=48	89·3% (88·0–90·5); k=39	37·9 (30·6–45·2); k=26	5·9% (5·6–8·3); k=23	48·2% (45·7–50·8); k=24	22·3% (18·5–26·2); k=24	21·4% (20·0–22·7); k=26

Variable k represents the number of control groups combined to reach the pooled estimate; the corresponding number of participants for each estimate is included in the appendix. Some studies included more than one control group. REM=rapid eye movement. NA=no studies available for this variable at this age cutoff.

Table 2: Means with 95% CIs for total sleep time, sleep efficiency, wake after sleep onset, and duration of sleep stages for total sample and by age, sex, and night of sleep study based on random effects models

Fig. 10.1 With permission from lancet neurology

discombobulated as to the treatment approach that should be taken. The decision was taken to do a home study that incorporated full EEG (Neurozone Inc.). There is evidence that the home study is not subject to the first night effect phenomenon [15] as would be the case with a repeat in-laboratory study (the location is novel after 7–10 days away from the place of the original study). The repeat study at home showed an AHI of 17.1 and the patient was placed on CPAP with positive effect (other features, for example, sleep onset and distribution of sleep stages were more "normal" at home) (Fig. 10.1).

The sleep stages and their duration are noted in the Table 10.2:

Some of the features on PSG and what they imply have been illustrated in the table below:

10.4.2 Home Study

An in-lab PSG may not reveal the true sleep disorder, as patients may experience what is known as the First Night Effect (see above). This arises as a result of a patient being in a new environment compared to his/her usual sleep place pattern and may give false positive or negative results. In such cases, if the in-lab PSG does not correlate with the clinical symptoms and signs, a home study may be performed where a patient takes the portable device and attaches it at home. The patient may use it whenever he is ready to use it and feels that that will be a good night and returns the device the next day to upload the study. In this study, electrodes are only attached behind the ear, on the forehead, on both sides of the eye, below the chin, the chest,

Table 10.2 Characteristics on PSG (polysomnography) and related differentials

Characteristics on PSG (polysomnography) and differentials to be considered
• **Delayed sleep onset latency:** Insomnia; study has been initiated well before usual bedtime, delayed sleep-wake phase disorder • **Abrupt sleep onset latency:** Narcolepsy; OSA (obstructive sleep apnea); study has been initiated later than usual bedtime, advanced sleep-wake phase disorder
• **Reduced sleep maintenance efficiency:** Depression; OSA; periodic limb movements, central sleep apnea, narcolepsy, parasomnia, insomnia, sleep-related hypermotor epilepsy (SHE)
• **Increased arousals from SWS (slow-wave sleep):** Sleep fragmentation; parasomnias; OSA
• **Long REM (rapid eye movement) onset latency:** PTSD (posttraumatic stress disorder); drugs • **Reduced REM (rapid eye movement) onset latency:** Depression; sleep deprivation; narcolepsy
• **Increased apnea-hypopnea index (AHI):** OSA; central sleep apnea
• **Decreased REM proportion:** PTSD • **Increased REM proportion:** Depression; narcolepsy
• **Increased amount of SWS:** Narcolepsy; CPAP (continuous positive airway pressure); medications; idiopathic hypersomnia; sleep deprivation • **Decreased amount of SWS:** Depression; head injury; epilepsy; anorexia; insomnia
• **Increased periodic/isolated leg movements:** OSA; PLMS (periodic limb movements of sleep); RLS (restless legs syndrome)
• **Increased chin/jaw movements:** Bruxism
• **Nocturnal movements:** PLMS; sexsomnia; parasomnia; sleep-related hypermotor epilepsy
• **Abnormal cardiac rhythm:** OSA; cardiac arrhythmia
• **Decreased oxygen saturation:** OSA; sleep-related hypoventilation
• **No thoracic and abdominal effort:** Central apnea
• **Dream enactment:** Parasomnia
• **Seizure activity: Sleep-related hypermotor** epilepsy

and the legs as compared to the standard PSG but produces the results that are comparable to those of an overnight in-lab study [16].

Abumuamar et al. [17] carried out a study in a series of 100 patients who were being followed up by cardiologists with the tentative diagnosis of arrhythmia. These patients had two nights of home sleep study and one night in the laboratory. The two nights at home were identical, indicating that the long-held view that first night effect was a cavitation of location and wires attached is probably wrong and it is all about location. The paper that was published had the provocative title "One night at home, two nights in the lab."

Home sleep study has also been seen to be less expensive with less clinician resources and expenses as well as being convenient. It can be used in patients in whom in-lab PSG is not feasible. However, its efficiency is noted more in patients with a high probability of moderate-to-severe OSA and is not recommended for persons with significant comorbid conditions or other suspected sleep disorders [18].

10.4.3 DLMO (Dim Light Melatonin Onset) Test

Melatonin is the hormone responsible for preservation of the circadian rhythm. Patients with a circadian rhythm problem may have discrepancy in melatonin production. The DLMO test is a test done from 8 p.m. to about 3 a.m., in which the patients are placed in a dark room and their melatonin is measured via their saliva every hour. In a normal individual, melatonin starts to rise around 8 p.m. and peaks in the middle of the night, after which it falls down. However, patients with a phase delay may not produce melatonin until early morning. DLMO is useful for determining whether an individual is entrained (synchronized) to a 24-h light/dark (LD) cycle or is in a free-running state. DLMO is also useful for assessing phase delays or advances of rhythms in entrained individuals. Additionally, it has become an important tool for psychiatric diagnosis, its use being recommended for phase typing in patients suffering from sleep and mood disorders. More recently, DLMO has also been used to assess the chronobiological features of seasonal affective disorder (SAD) [19]. The DLMO marker is also useful for identifying optimal application times for therapies such as bright light or exogenous melatonin treatment [19].

10.4.4 MSLT (Multiple Sleep Latency Test)

The MSLT is a validated tool that is considered the de facto standard for objective assessment of excessive daytime sleepiness [20]. The recommended protocol involves four to five 20-min nap opportunities held at 2-h intervals throughout the day. If sleep is observed, the patient is allowed to sleep for at least 15 min. The sleep latency for each nap is measured as the time from the start of the nap trial to the first epoch of sleep. A sleep latency of 20 min is assigned to nap trials during which no sleep is observed. The mean sleep latency, calculated as the average sleep latency across all nap trials, is the final result. The presence and number of sleep onset REM periods (SOREMPs) are also determined, as this information can help to establish a diagnosis of narcolepsy without cataplexy or to confirm narcolepsy with cataplexy. The MSLT should be started 1.5–3.0 h following completion of a nocturnal polysomnogram, which should record at least 6 h of sleep in order for determination of the mean sleep latency to be valid.

The second edition of the International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD-2) requires the presence of a mean sleep latency of less than 8 min and two or more SOREMPs as part of the diagnostic criteria for narcolepsy without cataplexy. However, the ICSD-2 also notes that a mean sleep latency of less than 8 min may occur in up to 30% of the general population. Therefore, while the MSLT is a helpful and widely used tool, it remains an imperfect gold standard in the assessment of daytime sleepiness. This necessitates that the evaluation of daytime sleepiness does not rest on the MSLT results alone but assimilates the clinical history, subjective complaints, diagnostic study results, and other pertinent medical information [20].

10.4.5 MWT (Maintenance of Wakefulness Test)

The MWT provides an objective measure of a patient's ability to remain awake, rather than the tendency to fall asleep, during the day, that is, it assesses daytime alertness. The key difference between the MWT and the MSLT is that in the former, the patient is asked to try to stay awake under circumstances conducive to sleep, rather than to fall asleep. The MWT provides an objective, validated assessment of the ability to remain awake for a defined length of time [20]. The recommended protocol includes four 40-min trials that begin at 2-h intervals, with the first trial to start 1.5–3.0 h after the patient's wake-up time. A nocturnal polysomnogram on the preceding night is not required. However, the patient should obtain a sufficient amount of sleep during the night before the MWT. Each trial is terminated after 40 min if no sleep occurs, or after unequivocal sleep onset (defined as three continuous epochs of stage N1 sleep or one epoch of any other stage of sleep) has occurred. One indication for the MWT is to assess an individual's ability to remain awake when his or her inability to remain awake constitutes a public or personal safety issue. This can become a pressing issue for individuals employed in the transportation, construction, or health care industries. The MWT may be indicated to assess the treatment response in patients with known excessive daytime sleepiness.

Doghramji et al. [21] arbitrarily chose a 40-min test, which was enough time for people to fall asleep. Recently, Thomas Roth, Sleep medicine specialist, has suggested (through personal communication) that patients often lose attention, for example seen in clinical trials of narcolepsy where they are required to do repeated MWTs over time. For this reason, the pendulum is swinging toward a 30-min test. A 30-min test has been used to allow the time before the next MWT for the execution of a performance test such as a driving simulator test which takes 10 min. This provides a different perspective of the alertness being assessed. Mitler et al. [22] showed that the 30-min and 40-min tests provide very similar results. On these bases, the authors felt that the 30-min and 40-min tests were of equal value but then the 30-min test was less "onerous" on the patient.

10.4.6 Actigraphy

This is used in the clinical evaluation of patients with sleep disorders, particularly circadian rhythm sleep disorders. An actigraph is a watch-like device that is worn on the wrist for an extended period, usually in the range of weeks. The actigraphy records movement and uses an algorithm to estimate the amounts of sleep and wake time during the recording period. It is often used in conjunction with a sleep diary to help score sleep onset and awakening. Analysis software uses movement to estimate when sleep and wakefulness have occurred. Review of the data can provide objective insight into the patient's sleep pattern, including timing and duration of major sleep disruptions. Actigraphy is indicated as part of the evaluation of patients with advanced sleep-phase syndrome, delayed sleep-phase syndrome, and shift work

disorder and may be indicated in the evaluation of jet lag disorder and non-24-h sleep-wake syndrome, including that associated with blindness. It can also serve as a measure of treatment response in patients with insomnia and circadian rhythm sleep disorders. There is high concordance in total sleep time between actigraphy and PSG. It may also detect periodic limb movements in sleep, if placed on the ankle or great toe however it gives less reliable estimates of sleep onset latency than PSG and cannot be used to stage sleep or to determine sleep-related breathing disorders [20].

For populations in which traditional sleep monitoring may be challenging, such as pediatric or older adult patients (when the sundowning may be a problem), actigraphy may provide valuable information about the patient's sleep pattern or response to treatment.

10.5 Sleep Diary

A sleep diary is a record of an individual's sleeping and waking times with related information, usually over a period of several weeks. It is self-reported or can be recorded by a caregiver. It helps to gather information about sleep patterns: sleep onset latency, wakefulness after initial sleep onset, total sleep time, total time spent in bed, sleep efficiency, and sleep quality or satisfaction. It is a useful resource in the diagnosis and treatment of especially circadian rhythm sleep disorders, and in monitoring whether treatment of those and other sleep disorders is successful. Sleep diaries may be used in conjunction with actigraphy. In addition to being a useful tool for medical professionals in the diagnosis of sleep problems, a sleep diary can help to make individuals more aware of the parameters affecting their sleep. These data alone can help people self-diagnose what helps them get a good sleep.

10.6 Other Assessment Modalities

Laboratory evaluation and neuroimaging with either computed tomography (CT) or magnetic resonance imaging (MRI) may be considered on an individual basis, as indicated by the clinical history. Complete blood count (CBC), serum chemistries, glycated hemoglobin, or measures of thyroid function may be obtained, if an underlying medical disorder is thought to contribute to the patient's sleep symptoms. For instance, these laboratory studies may be considered when daytime fatigue is a predominant symptom. Serum iron studies, including ferritin level, should be checked in patients with restless legs syndrome. Neuroimaging should be considered in patients with antecedent trauma, or for any sleep disorder patient with an abnormal neurologic examination, to evaluate for a structural etiology of the patient's symptoms. Bright light therapy (can be used in patients with suspected seasonal affective disorder or sleep disorders such as circadian rhythm sleep disorder) involves sitting in front of a light source that has an intensity of 5000–10,000 lux.

The duration used has varied in different protocols. It should be within 1 h of arising in the morning.

10.7 Summary

There are multiple ways of approaching measurements of sleep. The understanding of limitations and advantages of various sleep-specific evaluation methods is important, as there is a wide spectrum of options. It is essential to choose the right combination in a particular patient to pursue diagnostic testing in such a way that the resources will come in to the issue. The one which gives the best results should be the one to be used.

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Part II

Behavioral Presentations of Sleep Disorders

Behavioral Presentations of Insomnia

11

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Abstract

Insomnia is a common disorder that results in short sleep at night along with daytime symptoms, for example, fatigue, lethargy, poor concentration, cognitive problems, and mood alteration to name a few. These symptoms may, at times, be so severe that they can be mistaken for a number of psychiatric disorders, for example, depression and somatic symptoms disorders. Moreover, insomnia also increases the risk for cognitive impairment and dementia. Fibromyalgia and chronic fatigue syndrome are other common presentations of chronic insomnia. Many patients with chronic insomnia try to self-medicate using addictive substances, for example, alcohol that may culminate in alcohol use disorder. A number of patients continue hypnotic medications beyond the prescription period and a proportion of them increase the dose, thus clinically presenting with benzodiazepine use disorder, according to the present classification system. A careful assessment of these patients may unmask the underlying chronic insomnia. Optimal treatment of insomnia using behavioral and pharmacological measures can improve the prognosis.

Keywords

Chronic insomnia · Depression · Anxiety · Fatigue · Cognitive behavior therapy

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11.1 Daytime Sequelae of Insomnia

Individuals of all ages, races, and cultures report symptoms of insomnia. Insomnia symptoms with distress or impairment occur in 10–15% of the population [1]. Researchers have suggested that global sleep dissatisfaction [2], difficulty falling asleep after an awakening [3], and polysomnography-determined amount of wake time after sleep onset [4] may impact daytime functioning [5]. Individuals who suffer from insomnia are prompted to seek treatment for symptoms that are associated with daytime functioning [6]. Data have suggested that irritability and fatigue may cause interpersonal difficulties for insomnia patients. In some cases, interpersonal difficulties may exacerbate insomnia problems, leading to restriction of daytime activities, including social events, exercise, or work [6]. Lack of regular daytime activities and exercise may, in turn, contribute to insomnia [1]. Individuals with insomnia have reported poorer mental health-related quality of life (Refer Chap. 11) as well as elevated symptoms of anxiety and depression [6].

A study with participants representative of a national sample found that those who reported non-refreshing sleep, difficulty falling asleep with sleep latency longer than 35 minutes, and problems with sleep maintenance experienced daytime impairment, such as irritability and concentration difficulties [5]. Other studies have corroborated these findings, indicating that daytime symptoms in individuals with insomnia include fatigue and mood disturbances (e.g., difficulty handling minor irritations, reduced interest and decreased satisfaction in leisure activities and relationships) [6, 7]. Additional daytime symptoms consist of excessive daytime sleepiness, tendency to fall asleep during the day, decreased alertness, inability to nap, tension, hyperarousal, impaired memory functioning, mental inefficiency, difficulty with complex mental tasks, decreased ability to concentrate, social aversion, anergia, disturbed cognitions about sleep, and difficulty in work and social life [1]. Interestingly, many of the aforementioned symptoms overlap with symptoms of depression; thus, patients with chronic insomnia have increased risk for depression.

11.2 Cognitive Effects of Insomnia

Insomnia has been associated with mild to moderate impairments on specific cognitive functions [6, 7]. Data showed that individuals with insomnia performed worse than normal sleepers on tasks assessing working memory, which includes retention and manipulation, episodic memory, and problem-solving [7]. Those who present with insomnia also complained of memory and concentration problems. They reported difficulty with making decisions and made frequent work-related mistakes. These individuals exhibited a mild to moderate impairment for several attentional processes, such as choice reaction time, information processing, and selective attention [7].

Shekleton et al. [6] found that patients with insomnia disorder and no other medical or psychiatric conditions showed significant performance impairments on

tasks of switching attention. However, those with insomnia did not significantly differ from normal sleepers on tasks that measured sustained attention. Individuals with insomnia also performed similarly to normal sleepers on tasks that measured alertness, divided attention, sustained attention and vigilance, perceptual and psychomotor processes, and verbal functions [7]. Performance on procedural memory, some aspects of executive functioning (verbal fluency and flexibility), and general cognitive functioning was comparable to the control group. Fortier-Brochu et al. [7] indicated that daytime deficits may be related to increased errors or accidents and decreased work productivity. Poorer performance on those tasks may also be associated with a number of factors including sleep loss, fatigue, and mood disturbances. In addition, over time, chronic symptoms of insomnia were found to be a significant risk factor for cognitive decline [7]. It should be noted that the increased risk was not due to incidental poor sleep. Data showed that individuals with incident insomnia were not at increased risk for cognitive decline [8].

Cognitive impairments as well as disrupted sleep, which includes sleep fragmentation, daytime napping, and nighttime arousals, are typically experienced by individuals with Alzheimer's disease [9–11]. Research has also found that sleep disturbance, which include insomnia, contribute to the etiology and progression of Alzheimer's disease [11–14]. Moreover, studies suggest that individuals with insomnia are at a higher risk for developing Alzheimer's disease than those who do not experience sleep disturbance [14]. Liguori [10] has indicated that orexin, which is a neurotransmitter that produces wakefulness, may impact the sleep-wake cycle in Alzheimer's disease. Furthermore, research has shown that the orexinergic system interacts with the cerebrospinal fluid biomarkers (e.g., beta-amyloid and tau proteins) of Alzheimer's disease [10]. In addition, patients with impaired cognition or increased beta-amyloid deposits tend to exhibit decreased sleep [12]. Moreover, sleep-wake disturbance has also been linked with increased levels of central nervous system oxidative stress and weakens blood-brain barrier functioning, which are conditions that have been associated with the development and progression of Alzheimer's disease [12]. Researchers advise that identifying patients with sleep disturbance, such as insomnia, and treating disrupted sleep may prevent or postpone the onset of Alzheimer's disease [11, 13–15].

11.3 Differential Diagnosis

When diagnosing insomnia, Morin [16] has suggested that it is important to consider the severity, frequency, and duration of nocturnal and daytime symptoms. Individuals with insomnia may complain of difficulty initiating sleep, maintaining sleep, or both. In order to fit the criteria for sleep-onset insomnia, latency to sleep onset, or the time it takes one to fall asleep, should be greater than 20 min after turning off the lights. In some cases, individuals may fall asleep fairly quickly; however, they may report that they awaken frequently throughout the night. These individuals are experiencing sleep maintenance insomnia, which is characterized by frequent or extended nocturnal awakenings totaling more than 30 min of

wakefulness after sleep onset or premature awakening in the morning with less than 6.5 h of sleep. Some individuals may present with both sleep onset and sleep maintenance insomnia. They are experiencing mixed sleep onset and sleep maintenance insomnia, which involves a combination of difficulties with initiating and sustaining sleep [16].

Although short sleep duration may suggest insomnia, it is important to note that some people are short sleepers and manage with 4–5 h of sleep. These individuals do not present with daytime symptoms of insomnia, such as mood disturbance, fatigue, or cognitive or behavioral impairments [16, 17]. Therefore to diagnose chronic insomnia disorder, the American Academy of Sleep Medicine [18] has indicated that the following criteria need to be met: individuals or their caretakers need to (1) report experiences of non-restorative sleep (e.g., difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance to going to bed on appropriate schedule, difficulty sleeping without parent or caregiver intervention); (2) have sleep disturbances be accompanied by daytime impairments, such as fatigue/malaise, impaired attention, concentration or memory, impaired social, family, occupational, or academic performance, mood disturbance/irritability, daytime sleepiness, behavioral problems (e.g., hyperactivity, impulsivity, aggression), reduced motivation/energy/initiative, proneness for errors/accidents, or concerns about or dissatisfaction with sleep; (3) have adequate opportunity and circumstances to sleep; (4) experience difficulty with sleep at least three times a week; (5) have duration of insomnia be at least 3 months; and (6) the sleep/wake difficulty is not explained by another sleep disorder [18].

The American Academy of Sleep Medicine [18] has combined insomnia subtypes such as primary insomnia (e.g., psychophysiologic, idiopathic, and paradoxical) and secondary insomnia (e.g., insomnia that is associated with psychiatric and medical conditions) under a single, chronic insomnia disorder [18–20]. Experts have indicated that combining various insomnia subtypes under one disorder should not suggest that there are no differences between them. Researchers have recognized that currently, the field is not able to reliably distinguish between these subtypes or customize specific therapeutic interventions for each subtype [21]. The ICSD-3 insomnia category has changed to chronic insomnia disorder, short-term insomnia disorder, and other insomnia disorder [18]. Diagnosis of chronic insomnia disorder should be used only when the insomnia is prominent or unexpectedly prolonged and is the focus of clinical evaluation and treatment [21].

11.3.1 Chronic Insomnia Disorder

Patients who are diagnosed with chronic insomnia disorder may present with various insomnia subtypes [17, 19]. In some cases, insomnia may be associated with a learned and conditioned cognitive and physiological arousal response related to the bedroom environment [20]. Insomnia commonly develops as a response to a stressful life event, and can be precipitated by concerns of sleep loss as well as fear of losing control over the sleep process [16]. Some patients may complain of

poor quality sleep but have polysomnography data showing a sleep efficiency that is within normal limits [17]. One hypothesis suggests that current EEG systems are not sensitive enough to differentiate between subtle shifts between sleep and wake brainwaves, masking sleep fragmentation [16]. Patients may also complain of insomnia that starts in childhood and is characterized by a lifelong inability to obtain adequate sleep [17]. It is believed that this type of insomnia is associated with a defect in the neurological mechanism of the sleep-wake system [16]. Others may present with insomnia that developed as a result of habits that are not conducive to sleep, such as having an irregular sleep-wake schedule, consuming alcohol or caffeine close to bedtime, or participating in emotionally or physically stimulating evening activities [20].

Furthermore, patients with various medical and psychiatric conditions may experience insomnia [17]. In some cases, those who experience sleep-onset or sleep-maintenance difficulties and daytime symptoms of insomnia, such as difficulty concentrating, fatigue, irritability, memory problems, tension, hyperarousal, impairment of cognitive and behavioral performance, and tendency to fall asleep during the day, may be afflicted with other sleep disorders (e.g., sleep apnea, sleep-related movement disorders, disorders of sleep-wake schedule, and parasomnias), medical conditions (e.g., central nervous system disorders, congestive heart failure, chronic pulmonary, endocrine, gastrointestinal, fibromyalgia, and renal diseases), or psychiatric illnesses (e.g., anxiety and affective disorder) [16]. In such cases, insomnia is likely to be comorbid with a medical or psychiatric condition [17]. For example, people with fibromyalgia may present with symptoms, such as trouble sleeping, morning stiffness, headaches, and cognitive problems and memory impairment [21]. Typically, patients with fibromyalgia report non-restorative sleep as the third symptom experienced after stiffness and fatigue [22]. Consistent with this finding, unrefreshing sleep is one of the most common complaints for patients with fibromyalgia in addition to widespread pain, cognitive symptoms, fatigue, and a number of somatic symptoms [23].

In addition, insomnia can often be a direct side effect of medication that is used to treat the above-mentioned medical and psychiatric conditions [16]. Insomnia may also be associated with alcohol and drug dependency [17]. In cases where insomnia is associated with substance or alcohol dependency, individuals rely on alcohol, cannabis, over-the-counter sleep aids, and/or hypnotics to fall asleep. Without the use of these substances, patients experience difficulty initiating sleep. It should be noted that individuals who have insomnia associated with substance dependency differ from those who present with drug or alcohol addiction. Those with insomnia associated with substance dependency use hypnotics close to bedtime. Substances can have a significant impact on sleep quality [16]. For example, alcohol can increase arousals and cause sleep fragmentation during the second half of the night [24]. In some cases, dependency is psychological rather than physical and sleep may improve after a period of abstinence from substance use [16]. It should be noted that poor sleep may exacerbate the symptomatology of comorbid conditions and contribute to the onset of mood disorders [1].

11.3.2 Short-term Insomnia Disorder and Other Insomnia Disorder

The American Academy of Sleep Medicine [18] has indicated that short-term insomnia disorder is diagnosed when complaints of sleep initiation or maintenance and daytime sequelae are present despite adequate opportunity to sleep for less than 3 months. This insomnia presentation is likely to be associated with a daily stressor, including a change in work or school schedule, stressful events, marriage difficulties, or financial hardship. Although short-term insomnia is a common ailment, it is usually corrected with a resolution of stressors [17]. Other insomnia disorders include patients who complain of insomnia features, such as persistent difficulty with sleep initiation or maintenance while having adequate sleep opportunity and associated daytime dysfunction, but do not meet the full criteria for either chronic insomnia disorder or short-term insomnia disorder [17].

11.4 Assessment

A.A. is a 39-year-old male who presented to the sleep specialist partly due to encouragement from his supervisor at a hedge fund where he works. The patient informed his provider that prior to coming to this appointment, he has not slept for 3 days. He reported irritable mood and problems concentrating. He told the provider that he does not want to go to sleep and denies fatigue. A.A. proceeded to tell the sleep specialist that he has accomplished much more than his peers due to his exceptional cognitive abilities. A.A. was unusually talkative during the clinical interview and presented with pressured speech as well as difficulty staying on the topic of conversation. He insisted on telling the provider that he recently purchased a collection of luxury watches. The sleep specialist had to redirect him several times during the interview.

Given the tendency of insomnia to present with similar daytime sequelae as some psychiatric and medical disorders, it is recommended that clinicians carefully assess patients for insomnia [16, 17]. The first step in clinical assessment is the interview. During a clinical interview, the clinician collects a detailed history of the patient's sleep problem, including onset, course, duration, and nature of the sleep-wake problem [16]. In addition, the clinician collects information about the current sleep-wake schedule, use of sleep aids, bedroom environment, eating habits, exercise routine, substance use habits, bedtime routine, and other factors that may impact sleep quality (Table 11.1). The clinician also inquires about symptoms of other sleep disorders (e.g., narcolepsy, restless legs, periodic limb movements, sleep apnea, gastro-esophageal reflux, and sleep-wake schedule disorder), medical and psychiatric history, medication use, and history of psychiatric treatment [16]. Nowell et al. [25] have suggested that sleep hygiene and negative conditioning which are not listed in the diagnostic criterion for insomnia are a way to identify whether insomnia is related to mental or psychiatric disorders. The presence of significant sleepiness should prompt a search for other potential sleep disorders. The number, duration,

Table 11.1 Key points in assessment of a patient with insomnia

History of sleep problem	Examples
List of non-sleep activities in bed	Watching TV, eating, reading, etc.
Sleep environment	Room temperature, noise, etc.
R/o medical conditions	(including but not limited to) hyperthyroidism, sleep apnea, cancer
Medication	Alerting
Substances	Alcohol, illicit drugs

Table 11.2 Information obtained from a sleep diary

Assessment tool	Information included	Instructions
Sleep log/sleep diary	Bedtime, periods of sleep, wake time, estimated sleep latency, estimated sleep time, daytime naps, and daytime fatigue/sleepiness, hypnotic medication, alcohol usage	Patients complete at least 1 week of sleep logs (2 weeks preferred) each morning upon wakening

and timing of naps should be thoroughly scrutinized, as both a consequence of insomnia and a potential contributing factor [25].

An essential component of assessment for insomnia is a subjective sleep diary [16] (Table 11.2). The clinician asks the patient to complete a daily sleep log and report bedtime, arising time, sleep-onset latency, number and duration of awakenings, time of the last awakening, naps, medication intake, and an indication of sleep quality. The patient records sleep information in the sleep diary for at least 2 weeks before starting treatment. The patient is encouraged to continue entering sleep data throughout the duration of the intervention. The clinician reviews the diary at each visit and provides corrective information [16]. After a week of collecting sleep information, a Sleep Efficiency ratio is calculated by obtaining total sleep time (total wake time − time in bed), dividing total sleep time by time in bed, and multiplying the quotient by 100. Sleep Efficiency continues to be calculated throughout treatment. Total sleep time and Sleep Efficiency are significant for sleep restriction, which is one of the components of behavioral treatment for insomnia that will be discussed in the treatment section [16].

Additional tools for assessment of insomnia are sleep questionnaires (e.g., Sleep Impairment Index [16] and The Beliefs and Attitudes about Sleep Scale [26], nocturnal polysomnography, and behavioral assessment devices (e.g., wrist actigraph and sleep assessment device)). These instruments aid in assessing insomnia and can be used in conjunction with a clinical interview and sleep diaries. If after a thorough assessment, the clinician believes that a patient's insomnia is secondary to a psychiatric or medical illness, those conditions should become the primary focus of treatment. In cases where a patient presents with mixed features of psychiatric or medical illness and insomnia, the clinician should use his/her clinical judgment when designing a treatment plan.

A.A.'s provider recognized that although the patient presented with irritable mood, difficulty concentrating, and inability to sleep for the past 3 days, A.A. denied wanting to sleep. After a thorough clinical interview, in which the sleep specialist identified symptoms (e.g., not wanting to sleep, pressured speech, and grandiosity) that were indicative of a manic episode rather than insomnia, A.A. was referred to a psychiatrist for stabilization.

11.5 3P Model of Insomnia

Clinicians use the 3P model of insomnia to understand its course and treatment. The 3P model explains that predisposing, precipitating, and perpetuating factors keep an individual from having adequate sleep [27]. Predisposing characteristics evolve from genetic composition and personality traits that may make an individual more prone to having a low threshold for anxiety and excessive arousals. Some individuals may be more likely to have hyperarousal, which is a driving force of insomnia and increases the risk of developing the disorder [28]. Difficulties sleeping may be further exacerbated by precipitating factors such as daily life pressures, health concerns, and emotional stress [29]. The perpetuating habits, including staying in bed longer than needed and spending a majority of that time on the internet, watching television, and eating and/or consuming alcohol close to bedtime, may contribute to the development of chronic insomnia [30].

11.6 Treatment

The American Academy of Sleep Medicine has recommended that psychological and behavioral interventions are effective in the treatment of chronic insomnia [31]. Research has shown that cognitive behavioral therapy for insomnia (CBT-I) successfully reduces symptoms of insomnia, including shorter sleep-onset latency, reduction in wake after sleep onset, and increases in sleep efficiency [26–32]. Cognitive therapy aimed at changing negative believes associated with sleep in conjunction with corrective strategies intended to improve cognitive performance may be helpful to individuals with chronic insomnia [7]. Typically, CBT-I is comprised of education regarding dysfunctional beliefs about sleep, restricting time in bed, stimulus control instructions, and relaxation techniques. It should be noted that research indicates that behavioral treatments for insomnia (BT-I) that include two main interventional strategies, sleep restriction (SR) and stimulus control (SC), have been shown to be effective for insomnia, even if delivered as stand-alone treatments [33].

11.6.1 Stimulus Control

This treatment has been around since the 1970s and its efficacy has been supported by numerous research studies [32, 34, 35]. Stimulus Control includes five simple steps: (1) do not get into bed unless you are sleepy; (2) do not use the bedroom for anything except sleep and sex; (3) if you cannot fall asleep within 10–20 min of getting into bed or upon awakening from sleep, get up and go to another room; (4) get up at the same time each morning; (5) do not take naps during the day.

Stimulus control therapy aims to teach the patient to associate the bedroom with sleep and nighttime rituals with rapid sleep onset [36]. It is conceptualized as a learning theory; when an individual lies in bed and worries about the inability to sleep and daytime impairment every night, he/she will begin associating the bed and sleep with frustration and sleepless nights. The bedroom will then start arousing negative thoughts and emotions and serve as a negative stimulus for sleep. Thus, stimulus control therapy re-teaches the patient to break the endless cycle and build new associations with the bedroom and sleep. Some insomnia patients report sleeping better when away from home and even in the sleep laboratory with numerous invasive sensors on their body. Because the negative stimuli are absent from the new environment, the learned associations are not triggered, and sleep is facilitated [32, 34–36].

11.6.2 Sleep Restriction Therapy

Sleep restriction restructures sleeping conditions and fosters an environment that facilitates sleep at bedtime. This technique was developed in the 1980s [27] and concentrates on restricting the time a patient spends in bed. If a patient is unable to go to sleep after an awakening, he is instructed to get out of bed, go to a different room, and engage in an activity that is likely to promote sleepiness, such as reading. Furthermore, reducing time in bed is likely to lead to a degree of sleep deprivation, which will accelerate sleep onset as well as foster deep and sustained sleep. A critical part of sleep restriction therapy is the sleep log. This treatment lasts between 6 and 8 weeks. For 2 weeks, the patient is instructed to document their sleep patterns. Eventually, the notes from the sleep log allow the clinician to set a sleep/wake schedule. The necessary sleep time is calculated according to the sleep log and prescribed to the patient as the time needed to stay in bed. For example, if a patient's average sleep time was determined to be 6 h, he/she will be instructed to stay in bed for 6 h. The lowest amount of time allowed for sleeping is 5 h and naps are not permitted. During this therapy, the patient has to wake up with an alarm clock 7 days per week, at the time he/she usually gets up during the week. Bedtime and wake time may vary depending on the restricted schedule and the person's morning awakening time. For example, if an individual wakes up at 6:30 a.m. on weekdays and 9:30 a.m. on weekends, he/she will go to sleep at 12:30 a.m. and wake up at 6:30 a.m. every day. Sleep is a biological function regulated by the circadian rhythm and homeostatic sleep drive. Therefore, establishing a regular sleep and wake pattern improves sleep.

At the beginning of treatment, patients are informed that they will feel tired and that their daytime performance may be impeded. Fatigue and impaired daytime functioning are associated with sleep loss [27].

Throughout this treatment, patients continue to record sleep in the sleep log. Morin [16] suggested that patients with insomnia have a sleep efficiency that is less than 85%. When sleep efficiency reaches 90% and the patient still feels sleepy during the day, he/she is rewarded with an additional 15 min in bed. However, if sleep efficiency is lower than 85%, 10 min are subtracted. Sleep efficiency between 85 and 90% does not warrant any changes in the time allocated to sleep. The criteria for sleep efficiency in older individuals changes to 85% for an additional 15 min and 80% for decreasing the time in bed. Furthermore, when allocating the necessary bedtime, it is important to pay attention to mood, subjective view of sleep quality, and the level of alertness as well as the ability to function during the day. Patients find this treatment challenging for the first few weeks, but sleep quality usually improves rapidly. Sleep restriction therapy provides patients with a tool that can help them gain control over their sleep difficulty [16].

11.6.3 Cognitive Therapy

Cognitive therapy aims to restructure negative beliefs about sleep. A person may stay awake in bed and worry about the effect of sleep deprivation on his/her long-term health and daytime performance. These thoughts feed emotional arousal and produce anxiety at bedtime. Dysfunctional beliefs associated with sleep can influence insomnia severity as well as the daytime functioning and medication use [37]. Cognitive therapy was developed by practitioners of psychodynamic therapy, who became dissatisfied with the inability of the psychodynamic approach to reduce cognitive errors [38]. These scholars formulated a therapy that directly targets the thought process that underlies psychological disorders. The first step in treating insomnia with cognitive therapy is to identify the patients' maladaptive believes about sleep. Morin [16] created a Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS), which has 30 self-reported questions about sleep attitudes and categorizes faulty beliefs as:

1. Attribution of transient sleep difficulties as a chronic problem
2. Beliefs that most daytime problems are the result of poor sleep
3. Unrealistic expectations regarding sleep need
4. General cognitive errors, including overgeneralization, rumination, and magnification
5. High anxiety regarding sleep that often emerges with the start of bedtime activities

Once anxiety-provoking thoughts are identified, the clinician uses reassurance techniques to educate the patient and challenge the patients' irrational beliefs. Sleep is likely to improve following the amelioration of anxiety. During treatment

sessions, a patient may indicate that he/she cannot function because of insomnia. The clinician will advise the patient to collect information about his/her daily performance to help him/her understand that it is not solely based on sleep quality. Harvey et al. [39] showed that treating patients with cognitive therapy alone improved symptoms of insomnia. Therefore, cognitive therapy is one of the multivariate components of CBT-I.

11.6.4 Sleep Hygiene

This therapy established specific rules to improve sleep quality [40]. Most often these rules include:

Consistent sleep and wake times. Generally, going to bed and awakening at the same time every day establishes a schedule for the patient and synchronizes the patient's sleep and biological clock.

Limit time in bed. This instruction is similar to "Sleep Restriction Therapy."

1. No napping. Because sleeping during the day may cause difficulties falling asleep at bedtime, napping is generally discouraged. However, it is allowed for individuals who experience daily impairment from sleep deprivation, such as the elderly who have difficulty maintaining sleep at night and shift workers.
2. Remove the clock from the bedroom. Because watching the clock is counterproductive to sleep, regardless of the patients' need for time awareness, it should be obstructed from view.
3. Avoid caffeine. This stimulant is often associated with sleep disturbance.
4. Avoid alcohol. Although many individuals may view alcohol as a sedative, it actually leads to sleep fragmentation later in the night. Patients can resume reasonable alcohol consumption once their insomnia symptoms are resolved.

It should be noted that the American Academy of Sleep Medicine indicated that there is not enough evidence that this intervention is an effective single treatment for insomnia [31].

11.6.5 Relaxation

Relaxation training can be an effective therapy when treating chronic insomnia [31]. Any relaxation technique that the patient finds effective can be used to limit cognitive arousal and reduce muscular tension to facilitate sleep. Specific techniques that may be used include meditation, mindfulness, progressive muscle relaxation, guided imagery, and breathing techniques. Researchers found that hospitalized older adults who practiced progressive muscle relaxation and deep breathing exercises showed significant reduction of anxiety and psychological distress as well as improvement in the quality of sleep [41]. Other studies found that relaxation techniques including guided imagery, deep breathing, and progressive muscle

relaxation were effective in decreasing insomnia symptoms in a sample of patients who were 16–88 years old [42], older adults [43], and menopausal woman [44]. It should also be noted that researchers also found that progressive muscle relaxation has been shown to increase anxiety in individuals with insomnia who do not experience tension in their muscles [45].

11.6.6 CBT-I and Improvement in Daytime Symptoms

Data have indicated that patients with chronic insomnia who were treated with CBT-I have shown significant improvement in daytime symptoms, including cognitive performance [46], mood, depressive symptoms, fatigue [47], daily functioning, and psychological well-being [48]. A study compared online and face-to-face delivery of CBT-I, which included the following modules of standard multicomponent treatment for insomnia: (1) psychoeducation; (2) progressive muscle relaxation; (3) sleep hygiene; (4) sleep restriction (i.e., restricting time in bed to actual sleeping time, the sleep restriction parameters); and (5) cognitive exercises (i.e., challenging the misconceptions about sleep). Data from sleep diaries and a self-report measure of insomnia symptom severity showed improvement in the participants' ability to function at work, fatigue, concentration, memory, and mood [49]. Ballesio et al. [33] found that patients with insomnia who participated in CBT-I trials that included at least a sleep restriction component showed a reduction in depressive symptoms and fatigue. Another study showed that patients with chronic pharmacotherapy treatment-resistant insomnia reported significant improvement in subjective daytime dysfunction including mood, functioning as well as depressive symptoms with CBT-I [50].

Additionally, studies have suggested that CBT-I has been shown to improve areas of cognitive functioning [46]. Researchers found that CBT-I reduced insomnia severity as well as improved inhibition, verbal memory, and performance recall in both patients with and without mild cognitive impairment [46]. Although this study reported improvement in several cognitive areas, a meta-analysis comprised of 18 studies, which included 923 individuals with insomnia symptoms, reviewed cognitive performance as an outcome of CBT-I, using either self-report questionnaires or cognitive tests, and found that there is a paucity of studies on the impact of CBT-I on objective cognitive performance. The researchers also suggested that participants reported improvement on subjective measures of cognitive functioning [51]. According to the findings, more studies that use objective measures, such as cognitive performance tests, are needed to further understand the impact on CBT-I on cognitive functioning.

Researchers also indicated that individuals with chronic insomnia and comorbid medical and psychiatric symptoms who received CBT-I treatment showed improvement in daytime symptoms of insomnia [52, 53]. A study found that patients with fibromyalgia and insomnia reported improvement in sleep, daily functioning, and psychological well-being [48]. Furthermore, CBT-I intervention has been effective in treating symptoms of comorbid diagnoses, such as chronic pain, cancer,

depression, PTSD, bipolar disorder, and alcohol dependence [54]. These results were corroborated by a meta-analysis that examined the efficacy of CBT-I across 37 randomized clinical trials that included 2189 patients with insomnia comorbid with psychiatric (e.g., depression, alcohol dependency, and PTSD) and medical conditions (e.g., cancer, fibromyalgia, chronic pain, renal disease, COPD, osteoarthritis, coronary artery disease, pulmonary disease, Parkinson's disease, and multiple medical conditions). Researchers reported a reduction in daytime insomnia symptoms, including improvements in daytime functioning and mood. Data also indicated that participants maintained the benefits of CBT-I for 3–12 months after completing treatment. In addition, patients with comorbid psychiatric disorders showed more significant changes in mood and functioning than those with a medical comorbidity [53].

Jansson-Fröjmark and Norell-Clarke [55] reviewed studies investigating the efficacy of CBT-I in patients with depression, bipolar disorder, psychotic disorders, and PTSD. Their findings indicated that although patients with psychiatric disorders who received CBT-I showed improvement in their insomnia symptoms compared to patients in control conditions, some studies did not exhibit improvement in participants' sleep diaries. Moreover, data on the impact of CBT-I treatment on psychiatric symptoms suggested mixed findings. Specifically, while several studies indicated improvement in psychiatric symptoms, the majority did not show significant changes in psychiatric symptoms when compared to control conditions. Researchers have suggested that the relationship between insomnia and psychiatric disorders is complex and that studies have used generic CBT-I treatment as well as modified versions of the intervention, which may have impacted their conclusions about the effect of CBT-I treatment on comorbid psychiatric disorders. Jansson-Fröjmark and Norell-Clarke [55] have recommended that future researchers provide descriptions of ways that CBT-I interventions have been modified for populations with psychiatric disorders.

11.7 Conclusion

Daytime symptoms of insomnia are likely to prompt patients to seek treatment for this disorder. Individuals may present with mood disturbances, fatigue, excessive daytime sleepiness, decreased alertness, impaired memory functioning, decreased ability to concentrate, and difficulty in work and social life [1]. It is important to note that these symptoms may or may not be comorbid or due to medical or psychiatric conditions. It is recommended that the clinician makes a thorough assessment of patients' symptoms, ruling out other causes of sleep dysfunction. Once chronic insomnia disorder, short-term insomnia disorder, or other insomnia disorder has been diagnosed, it is recommended that the clinician use CBT-I as treatment, as it has been shown to improve daytime sequelae [46–48].

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Behavioral Presentations of Sleep-Related Breathing Disorders

12

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Abstract

Obstructive sleep apnea (OSA) is a breathing-related sleep disorder that is associated with substantial morbidity and disturbed quality of life. It is a systemic disorder that is associated with a wide range of comorbid abnormal behavioral symptomatology. OSA usually presents with snoring, daytime sleepiness, and choking attacks during sleep. However, the disorder may present with unusual presentations such as behavioral, psychiatric, and neurocognitive abnormalities, or abnormal movements disorders during sleep. Additionally, OSA may worsen comorbid psychiatric and behavioral disorders. Therefore, it is imperative for healthcare providers to have the knowledge and clinical skills to recognize the unusual presentation of OSA, particularly, changes in behavior, and to recognize the interaction between OSA and its comorbidities, which may affect behavior. This chapter discusses the association between OSA and psychiatric and behavioral disorders, which may influence the presentation of OSA.

Keywords

Obstructive sleep apnea · Depression · Dementia · Panic disorder · PAP therapy

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12.1 Introduction

Obstructive sleep apnea (OSA) is a prevalent breathing-related sleep disorder (BRSD). OSA syndrome prevalence is around 3–18% in men and around 2–17% in women among the middle-aged population. Its prevalence increases with age, and it is estimated that around 28–67% older men and 20–54% older women have OSA [1–3].

OSA is characterized by recurrent episodes of partial (hypopnea) or complete (apnea) upper airway obstruction during sleep. These obstructive events are usually followed by arousals. The two major pathophysiological consequences of sleep apnea are sleep fragmentation and blood oxygen desaturation [4]. OSA is associated with adverse health outcomes, including decreased quality of life, psychological symptoms, insulin resistance, and increased risk for cardiovascular disease and mortality [5]. Excessive daytime sleepiness (EDS) is a major consequence of OSA that often constitutes a risk factor for motor vehicle crashes [6]. The repetitive episodes of blood oxygen desaturation followed by rapid re-oxygenation lead to oxidative stress [7], which is observed in almost every organ, further confirming that OSA is a systemic disorder. The disorder has numerous other consequences, including cardiovascular diseases and an increased risk of cardiovascular events such as myocardial infarction [8, 9], hypertension [10], stroke [9], atrial fibrillation [11], diabetes [12], increased cancer incidences [13], cognitive impairment [14], and increased mortality [8].

There is a bidirectional relationship between OSA and psychiatric disorders. Both OSA and some psychiatric disorders share common features such as similar risk factors, symptoms, illness course, and outcomes [15, 16]. Shared risk factors include obesity, metabolic syndrome, and inflammation [17].

Several factors put patients with psychiatric disorders at risk for OSA. Substance use can be a significant risk factor for OSA, especially when sedating substances such as alcohol and narcotics are used [18]. Alcohol use has been found to be a significant risk factor for OSA. It is theorized that alcohol increases the risk for OSA by decreasing the breathing drive and relaxing the muscles of the upper airway, which in turn causes more obstructive episodes [19]. Similarly, sedatives, such as opiate pain killers and opioid street drugs, can increase the frequency of obstructive events through the same mechanism and may also increase the risk of developing central sleep apnea and ataxic breathing [20]. Patients on psychotropic medications with sedating side effects, metabolic side effects, or weight gain profile may be at higher risk for developing OSA compared with patients not taking psychotropic medications [21]. Given the significant overlap between many psychiatric symptoms (daytime fatigue, reduced energy level, decreased motivation, reduced concentration and cognitive function, decreased libido, and frequent awakenings at night) and OSA, OSA should be carefully explored in patients with psychiatric disorders and vice versa [22].

The bidirectional relationship between OSA and psychiatric conditions complicates the process of OSA diagnosis and consequently affects the management plan of both disorders. This chapter reviews the behavioral presentations of OSA,

taking into consideration the clinical features, diagnosis, and appropriate management of OSA in relation to its behavioral presentations. Initially, this chapter gives a brief overview of OSA and then discusses the association between OSA and psychiatric and behavioral disorders, which may influence the presentation of OSA.

12.2 Assessment of OSA

Proper assessment of OSA usually involves a clinical interview, physical examination, and the use of diagnostic testing such as polysomnography (PSG). PSG performed in a sleep laboratory (type I attended) has been the gold standard method to diagnose OSA; however, it requires specialized facilities, is expensive, and requires patients to spend the night under observation outside the patient's house. In addition to PSG, portable unattended sleep studies (types II and III) can be used to diagnose OSA, although the measured apnea hypopnea index (AHI) score can differ substantially from that measured with PSG [23]. Clinical interviewing usually involves the patient and additional information from the bed partner who may observe the patient during sleep. History taking should cover common symptoms of OSA, such as snoring, including witnessed apneas, gasping/choking episodes, nocturia, excessive daytime sleepiness (EDS), morning headaches, sleep fragmentation/sleep maintenance insomnia, and decreased concentration and memory. The assessment should also include evaluation of the risk factors and common presenting symptoms for OSA. OSA symptoms may be reported during the evaluation of other complaints or detected during health maintenance screening. Additional history taking should include medical conditions that are commonly associated with OSA, such as psychiatric symptoms, hypertension, cardiovascular diseases, diabetes, EDS, and history of motor vehicle crashes.

EDS may be evaluated using the Epworth Sleepiness Scale (ESS). However, it is essential to consider the overlap between EDS in OSA and EDS in other conditions such as depression [16].

12.3 Management of OSA

OSA management usually involves a multidisciplinary approach. Goals of OSA management include improving sleep quality, alleviating symptoms, managing comorbidities and normalizing AHI, and oxygen saturation level.

Positive airway pressure (PAP) therapy is the first-line treatment for OSA [24]. Other treatment modalities may be considered based on the severity of OSA, including oral appliances, upper airway surgery, hypoglossal nerve stimulation or upper airway stimulation, and pharmacological treatments [25].

Patients should be educated on the risk factors, natural history, and consequences of OSA. A warning should be given to all patients on the increased risk of motor vehicle accidents associated with untreated OSA and the consequences associated

with driving while sleepy [6]. Counseling should also be given to patients to avoid activities that require alertness and vigilance, especially if they complain of EDS.

12.4 OSA and Emotional Regulation

Human behavior and emotions are under control of the amygdala, locus coeruleus, and the prefrontal cortex [26]. Sleep, and specifically REM sleep, supports a process of brain homeostasis, which prepares for optimal social and emotional functioning [27]. A large body of evidence supports the notion that sleep is critical for the formation of emotionally valenced information throughout all the stages of emotional regulation; negative memories seem to be more resistant to the effect of sleep loss during the encoding phase, probably because such memories are more salient for individuals even in the presence of the neural dysregulation imposed by sleep fragmentation [26]. During the consolidation phase, although sleep could preferentially consolidate unpleasant stimuli, an important effect of sleep loss could be a next-day enhancement of negative affective tone, leading to a propensity of sleep-deprived individuals to assess stimuli as more negative [28].

Thus, sleep is vital for the regulation of emotions [26], and hence sleep disturbances seen in patients with OSA, such as slow wave sleep (SWS) and REM sleep disturbances, may predispose to neurological and psychiatric disorders.

12.5 OSA and Depression

There is a bidirectional relationship between OSA and depression. The symptoms of OSA and depression may overlap to cause the association (Fig. 12.1). According to ICD-10 [29], depression is a symptom complex of persistent low mood and other somatic complaints, not attributed to the abuse of psychoactive substances or to an organic mental disorder, lasting for more than 2 weeks. There is considerable overlap between the somatic complaints of depression and OSA. Several studies investigated the correlation between OSA and depression. Ohayon et al. [30] investigated approximately 20,000 randomly selected adults aged 15–100 years old, representing the general population of the United Kingdom, Germany, Italy, Portugal, and Spain. The results of this study showed that 18% of individuals with a major depressive disorder diagnosis also had a DSM-IV breathing-related sleep disorders diagnosis, and 17.6% of subjects with a DSM-IV breathing-related sleep disorders diagnosis had a major depressive disorder diagnosis.

Most studies assessing the prevalence of depression among patients with OSA could not determine the temporal relationship between them (i.e., if OSA preceded depression or vice versa) [16]. The prevalence of depression among OSA patients was assessed in both clinical settings and in community samples. Previous studies aiming to assess depression among OSA patients used clinician assessments, patients' self-reported symptoms, or clinical questionnaires intending to diagnose depression. Among the clinical questionnaires used are the Beck Depression

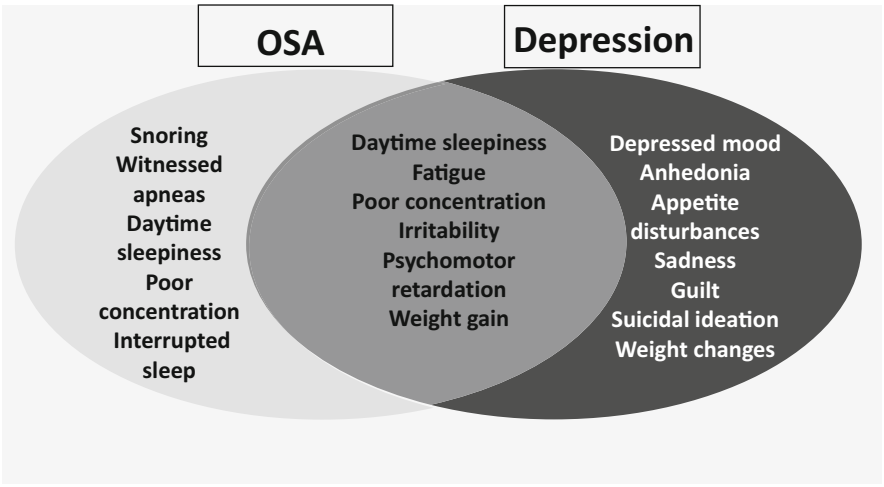

Fig. 12.1 Overlapping symptoms of obstructive sleep apnea and depressive disorders

Inventory (BDI) [31], the Center for Epidemiological Studies Depression Scale (CES-D) [32], the Minnesota Multiphasic Personality Inventory (MMPI) [33], the Profile of Mood States (POMS), the Hospital Anxiety and Depression Scale (HADS) [34], the Patient Health Questionnaire (PHQ-9) [35], the Hamilton Rating Scale for Depression (HRSD) [36], the Structured Interview Guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder Version-Self-Rating Version (SIGH-SAD-SR), the Symptom Checklist 90 (SCL-90) [37], the Mini International Neuropsychiatric Interview 6.0 (MINI) [38], and the Zung Self-Rating Depression Scale (SDS) [39]. Among these questionnaires used, only the CES-D and the MINI were specifically designed to diagnose depression; the other remaining scales are designed to assess the severity of depression, usually aiming to assess depression over a longitudinal period, and are meant to be used after the clinical diagnosis of depression.

Several theories have tried to explain the possible mechanism of the comorbidity between OSA and depression. One theory proposed that sleep fragmentation and hypoxia during sleep cause disruption of sleep-related restorative effects on the prefrontal cortex [40]. This, in turn, may result in "executive dysfunction," which refers to the abilities crucial for organization and planning, and might predispose to mood disturbances.

Some researchers have also linked OSA to suicidal behaviors [41, 42] across all countries, where 60% of transitions from suicidal ideation to plan and attempt occurred within the first year after ideation onset [43]. This may be very risky, especially for people with undiagnosed and untreated OSA. Sleep disorders, including OSA, are rarely assessed regularly in patients suffering from psychological distress or depression. OSA patients with depressive symptoms or fatigue may suffer from psychomotor retardation and, consequently, may have a weak motivation to

visit the hospital, get a diagnosis, and receive appropriate OSA treatment [42]. It might be beneficial to detect suicidal behaviors in patients with OSA for better prevention and management strategies.

12.6 Effect of OSA Management on Mood Symptoms

Few studies investigated the effects of OSA management on depressive symptoms in OSA patients. The majority of observational studies showed a reduction in depressive symptoms in OSA patients on CPAP therapy. However, in a Cochrane meta-analysis in 2006, a comparison between CPAP and placebo was done, and a secondary outcome considered in this study was the effect of CPAP therapy on depression among OSA patients using the HADS [44]. The pooled fixed effect for depression significantly favored CPAP therapy. Nevertheless, random effects modeling was applied due to the high level of statistical heterogeneity in the studies considered, and the subsequent result showed no significant effect of CPAP therapy. In addition, a randomized controlled trial that used the Geriatric Depression Scale (GDS) reported no significant difference in the change in depression between the control and CPAP therapy arms [45]. Two subsequent short-term (2 weeks of CPAP therapy) randomized controlled trials reported no mood improvement associated with CPAP [46] [47].

Most of the studies mentioned above assessed the outcome of CPAP treatment on depressive symptoms after only a few weeks (2–4 weeks) of CPAP use. A more recent study of 17 adult patients with treatment-resistant depression and OSA showed that 2 months of CPAP treatment resulted in a significant reduction in depression scores in BDI and HRSD scales [48]. In addition, another recent multicenter, prospective cohort study evaluated 300 adult patients with OSA for the prevalence and correlates of persistent depressive symptoms after long-term CPAP therapy [49]. The study revealed a significant improvement in depression scores on the QD2A scale (measured by the 13-item, self-rated Pichot depression scale ≥ 7) after CPAP therapy over an average of 529 days. However, the study showed that 125 subjects (41.7%) continued to have persistent depressive symptoms despite CPAP treatment for at least 1 year [49]. The persistence in depressive symptoms in this study was associated with persistent EDS, comorbid cardiovascular disease, and female sex; these findings supported the findings of previous research demonstrating the association between EDS and persistent depressive symptoms in OSA patients treated with CPAP [48, 50].

12.7 OSA and Panic Disorder

There have been few studies addressing the relationship between OSA and panic disorder; most were case reports [51]. Sleep apnea has been identified as a potential risk factor for panic disorder. The association between sleep apnea and panic disorder could be supported in several ways. Sleep fragmentation, awakening with

feelings of choking or suffocation, and excessive daytime sleepiness have been suggested as mechanisms of anxiety in OSA. Additionally, the recurrent obstructive events resulting in intermittent hypoxemia (and possibly hypercapnia) may enhance oxidative stress-related functional deterioration and central nervous system injury, thus enhancing the risk of panic disorder. Functional and structural neuroimaging studies show that OSA alters brain structure with time, leading to a decrease in gray matter in the hippocampus, frontal lobe, and the anterior cingulate cortex [52]. Damage to similar regions is also seen in patients with panic disorders. Moreover, hypercapnia may contribute to the development of a panic attack as it has been reported that a panic attack can be provoked by inhalation of carbon dioxide [52].

12.8 OSA and Post-traumatic Stress Disorder

Disturbed sleep is a common manifestation in patients with post-traumatic stress disorder (PTSD). OSA, in particular, is common in PTSD, reaching up to 72.7% in a cross-sectional study of veterans with PTSD [53]. Several studies showed greater impairments in the quality of life and daytime functioning in PTSD patients with comorbid OSA [54–57]. In a case-controlled observational cohort study of 200 patients who have PTSD, patients with PTSD and comorbid OSA had worse disease severity and sleep-related symptoms [58]. The quality of life in PTSD patients with comorbid OSA was worse in comparison to those with either condition alone and healthy individuals [58]. Additionally, patients with PTSD and OSA in the study had a poorer response to positive airway pressure (PAP) therapy and were less likely to have symptom resolution. It is important to note that patients with PTSD and comorbid OSA have poor adherence to PAP therapy [59, 60]. The complexities of managing PTSD and comorbid OSA is probably due to the possible contribution of hyperarousal and high levels of sympathetic activation in PTSD that can cause sleep fragmentation and increased upper airway collapsibility and OSA in patients with PTSD. Gupta suggested mood stabilizers to improve sleep and potentially decrease the apnea-hypopnea index [61]. This therapeutic strategy could be useful in OSA patients with the low arousal threshold phenotype, which is similar to the profile of patients with PTSD. Although adjunctive pharmacotherapy may be beneficial, the use of additional psychoactive medications should be approached with some caution in PTSD population, as drugs commonly used in this population have the potential to alter sleep architecture, potentially worsen sleep disturbances, and unfavorably affect daytime function. A better comprehension of how widely used psychoactive medications in this population affect sleep quality and sleep-disordered breathing would offer another avenue to improve care in this high-risk population [62].

On the other hand, several studies reported improvement in PTSD symptoms with CPAP therapy for comorbid OSA [63–66]. A recent controlled study of 59 patients with PTSD showed that the mean total PCL (the military version of the PTSD Checklist) decreased significantly after 6 months of CPAP treatment [66]. Another prospective study of Veterans with confirmed PTSD and a new diagnosis of OSA

revealed a significant reduction in PTSD symptoms, measured by PCL after 6 months of CPAP therapy. Additionally, the improvement was documented in measures of sleepiness, sleep quality, daytime functioning, and quality of life [65]. Nevertheless, adherence to CPAP therapy remains a major problem in this group of patients [64]. A new study showed that mandibular advancement devices are effective in reducing PTSD symptoms in patients with comorbid OSA [63].

12.9 OSA and Nightmares

Previous studies have shown that OSA patients with a higher AHI report a significantly lower frequency of nightmares [67, 68]. Because nightmares are a REM-related parasomnia [69], they are likely to occur during REM sleep, which is usually suppressed in patients with severe OSA. Nevertheless, nightmares have been reported in patients with REM-predominant OSA [70]. Pagel and Kwiatkowski proposed that the suppression of REM sleep in patients with severe OSA can explain the reduction in nightmares in patients with an increased AHI [67]. Carrasco et al. have speculated that respiratory events during REM sleep might result in hyperactivation of the limbic system, which could lead to dreams with high emotive contents [71]. A study of 99 patients who had been diagnosed with OSA with nightmares (excluded patients with psychiatric disorders) revealed that patients with nightmares had a significantly higher AHI during REM compared with the patients without nightmares, and logistic regression analysis identified REM-AHI and interrupted sleep at night as the independent predictors of nightmares in the OSA patients [70]. Interestingly, nightmares disappeared in 91% of the patients who adhered to CPAP therapy compared with 36% of patients who refused to use CPAP ($p < 0.001$) [70].

12.10 OSA and Parasomnias

Fragmentation of sleep caused by recurrent episodes of upper airway obstruction and episodic desaturations in patients with OSA may provoke parasomnias [72, 73]. If OSA is suspected in patients with arousals parasomnias, PSG should be performed before starting treatment with clonazepam. More research is needed to elucidate the relation between OSA and parasomnias and the efficacy of CPAP therapy in patients with parasomnia and comorbid OSA.

12.11 OSA and Cognition

Cognitive function encompasses the broad domains of attention, memory, executive function (higher order cognitive skills such as planning, problem-solving, and mental flexibility), visuospatial/constructional abilities, processing speed (the speed of cognition), and language (both expressive and receptive) [74]. To date,

the literature on cognitive deficits in OSA seems contradictory. This is because domains of cognition have been assessed using tests that monitor different components of a domain (facets); using different tests leads to differing conclusions. However, when cognitive outcomes are categorized into theoretical facets, instead of across an entire domain, more consistent patterns of impairment and preservation have been revealed [74]. Systematic and meta-analytic reviews provide robust evidence that OSA influences attention and vigilance, long-term (episodic) verbal and visual memory [75], and visuospatial or constructional abilities [76]. In addition, all aspects of executive functioning are influenced by OSA, including the ability to shift between tasks or mental sets, to inhibit dominant responses, to update and monitor working memory representations, to efficiently access semantic (knowledge or long-term memory) stores (i.e., in generativity), and in problem-solving [77].

Several studies have shown consistently that recurrence of apnea, daytime sleepiness, nocturnal hypoxemia, and sleep fragmentation does lead to reduced cognitive function in OSA patients [78–81]. The specific effects of OSA on cognition are in vigilance, memory, attention, executive function, and psychomotor performance [82–84]. Nevertheless, the presence and extent of cognitive changes in OSA subjects remain a subject of debate, and the cognitive impairment may worsen over time with disease severity but not linearly [85, 86]. A review by Lim et al. [87] stressed that though hypoxemia and sleepiness may trigger neuropsychological deficits in OSA patients, the comorbidities observed in OSA patients affect neurocognitive functions much more than the sleep apnea itself. The comorbidities named here include physical inactivity, obesity, and cardiovascular diseases. It should be taken into consideration that there is large heterogeneity in the neuropsychological tests used in OSA patients thus making it difficult to compare the results of different studies [88].

Possible mechanisms of cognitive impairment in OSA patient have been investigated in previous studies. One theoretical model argues that cognitive difficulties are the short-term, reversible consequences of poor nighttime sleep that adversely affect cognition either by producing daytime sleepiness or by producing daytime difficulties with attention. It also proposed that the higher level memory and executive problems in OSA as secondary to sleepiness, or to attention deficits [89]. The second theoretical model proposes that OSA leads to long-term changes in the brain, characterized by vascular changes, neural damage, and cell death, which, in turn, lead to cognitive dysfunction [90]. One such mechanism proposes that increased reactive oxygen species and oxidative stress, as a result of chronic intermittent hypoxia, lead to cortical cell death and, thus, cognitive dysfunction [90]. A third mechanism emphasizes the importance of blood-gas abnormalities and cerebral homeostatic changes due to sleep fragmentation and cyclical changes in blood gases on the health of the frontal and hippocampal regions, leading to memory and, particularly, executive function deficits [2, 74].

With these limitations in mind, high interest in recent years has been focused on impairments of cognitive functions that refer to the ability to sustain a flexible approach and goal-directed approach to problem cases and to allow people to make use of their adaptive skills in a changing external environment. Examination of this domain may be done by tests demanding organization, problem-solving,

planning, and mental flexibility [91]. Results from studies on cognitive function in OSA have a heterogeneous nature, with some studies suggesting attention impairment [92] or executive dysfunction [85, 93].

It was recently documented that obstructive OSA is frequent in patients affected by subjective cognitive impairment, thus inducing Alzheimer disease (AD) biomarkers [94]. Accordingly, OSA altering sleep quality and continuity, and producing intermittent nighttime hypoxia, promotes AD neurodegenerative changes. Since OSA increases in midlife to older-age populations, it could be responsible for the relationship between prolonged sleep and neurodegeneration [94]. OSA is intrinsically associated with disruptions of sleep architecture, intermittent hypoxia, and oxidative stress, intrathoracic and hemodynamic changes, as well as cardiovascular comorbidities. All of these could increase the risk for AD, rendering OSA as a potentially modifiable target for AD prevention. Furthermore, OSA has been found to disturb B-amyloid metabolism in the brain and enhance amyloid plaque production. This finding confirms the relationship between OSA and AD [95].

CPAP treatment is moderately effective in reducing neurocognitive impairment in OSA patients with EDS; however, there is no evidence that it improves these impairments in OSA patients without EDS [96, 97]. Moreover, CPAP treatment has been shown to induce positive changes in brain morphology and functionality [96].

12.12 Neuroimaging and Behavioral Changes in OSA

Neuroimaging investigational studies provided important contributions toward understanding the relationships between OSA and its behavioral and functional presentations. Neuroimaging performed usually include functional MRI, structural MRI, and magnetic resonance spectroscopy. Neuroimaging studies aim to determine whether or not OSA has any negative impact on the brain.

A review of neuroimaging studies in OSA patients revealed mixed results regarding structural brain abnormalities [98]. While some studies reported no differences in periventricular hyperintensities, white matter, or gray matter in OSA patients compared to healthy patients, other studies have reported detectable changes. Reports from these studies suggest that OSA causes a decrease in the hippocampal gray matter, cerebellum, temporal lobes, parietal lobes, and the frontal lobes. Additionally, other studies have revealed a reduction in brain activation in the frontal, cingulate, and parietal regions while the subject performs sustained attention tasks compared to control subjects [98, 99].

Several studies revealed that OSA is associated with a decrease in hippocampal volume; the hippocampus plays a vital role in memory consolidation [100]. In addition, OSA patients may have compromised blood-brain-barrier function, and that may introduce neural damage contributing to abnormal brain functions observed in OSA patients [101].

Recent understanding of the neurocognitive impairment in OSA highlights the role of distorted connectivity among fundamental structures for executive and

memory processes such as frontoparietal regions, hippocampus, thalamus, and cerebellum [102]. This proposal is supported by recent neuroimaging studies, which have demonstrated abnormal activity in the right anterior insula, a central node of the salience network associated with high-level cognitive control and attentional processes in OSA patients [103].

12.13 OSA and Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neurocognitive behavioral developmental disorder. Its major characteristics include impulsiveness, hyperactivity, and impairment in social, occupational, and academic functioning, short attention span, and onset of symptoms before the age of seven [104]; however, ADHD may continue into adulthood [105]. A review of six studies that examined the effect of OSA treatment on ADHD concluded that up to 95% of OSA patients might suffer from attention deficits similar to that in ADHD, and 20–30% of ADHD patients may suffer from OSA [106]. In addition, treating OSA in ADHD patients resulted in improvements in behavior, inattention, and the overall management of ADHD.

12.14 OSA and Personality Type

Several studies have used personality type indicator measures to investigate individuals with varying degrees of OSA [107]. According to several studies, type D personality appears to be a prevalent personality in 30% of the OSA patients [108]. Type D personality is characterized by two traits: (1) negative affectivity, which is the tendency to experience negative emotions; and (2) social inhibition, which reflects the hindering of emotional and behavioral expression for fear of rejection or disapproval by others [109]. Type D personality has been linked to specific negative behaviors like an unhealthy lifestyle, reluctance to consult or follow medical advice, and poor treatment outcomes, which adversely affect the clinical course of the medical problem and the adherence to treatment [110]. Type D personalities are more likely to have medical comorbidities, a decreased personal view of their health, decreased physical functioning, and poor psychosocial functioning [111]. Their subjective perception of the problem does not always adequately reflect the actual severity of the condition, and they report the side effects of CPAP more frequently. The decreased adherence to CPAP in type D personality may be related to the decreased perceived effects of the treatment and low self-efficacy [112].

12.15 OSA and Behavioral Presentations in Children

Symptoms of OSA may be difficult to detect in children, as children usually fail to report EDS adequately. There has been growing interest among scientists on sleep-disordered breathing in children. A study by Perfect et al. reported that children who have OSA had higher rates of behavioral problems such as communication problems, aggressiveness, hyperactivity, and difficulty paying attention [113]. Such children are more likely to have learning problems and to have lower academic performance compared to those without OSA. A systematic review and meta-analysis of 20 studies found that children who had OSA showed more signs of hyperactivity, difficulty interacting with peers, issues with self-conduct, and an inability to obey rules and regulations [114]. The effects of OSA and other sleep disorders were observed in children as young as 6 months of age. Previous studies that examined the behavioral and neuropsychological functions of children with OSA reported conflicting results. In a recent systematic review of studies that evaluated cognition, behavior, or academic achievement of children meeting clinical criteria for OSA revealed that intellectual abilities of children with OSA might be impaired but remain within the normal range [115]. The specific cognitive ability that drives the impairment is not known until now.

In children, OSA has been shown to result in acute brain changes in areas that regulate autonomic, cognitive, and mood functions, and chronic changes in frontal cortices essential for behavioral control [116]. Additionally, cortical thinning was detected in several regions such as the superior frontal, ventral medial prefrontal, superior parietal cortices, bilateral precentral gyrus, mid-to-posterior insular cortices, and left central gyrus, as well as the right anterior insular cortex [116]. These cortical changes may disrupt neural developmental processes, including maturational patterns of cortical volume increases and synaptic pruning. Both the thinning and thickening associated with OSA in children may contribute to the cognitive and behavioral dysfunction frequently found in the condition [117].

Furthermore, nocturnal enuresis is a common presentation of OSA in children. Increased intra-abdominal pressure caused by forceful inspiratory efforts against a closed upper airway has been proposed as a possible cause of enuresis [118]. In addition, it was shown that the fractional urinary excretion of sodium increases in parallel with the severity of OSA and diastolic blood pressure in children with snoring [118]. The repetitive increases in systemic blood pressure that occur at the termination of nocturnal obstructive events may lead to pressure-induced natriuresis. Moreover, upper airway obstruction is accompanied by significant negative intra-thoracic pressure swings, increased systemic venous return, and preload to the right ventricle together with increased left cardiac ventricle after load. Acute overload of the cardiac ventricles could stimulate the release of brain natriuretic peptide from ventricular myocytes, which induces vasodilation and natriuresis.

Screening for OSA is essential in children with hyperactive behavior and those with behavioral problems. Unfortunately, the link between OSA and behavioral changes in children is under-recognized. A cross-sectional survey study conducted by members of the American Academy of Pediatrics investigated sleep-screening

Table 12.1 A summary of the neuropsychiatric manifestations in OSA

Neuropsychiatric manifestations in OSA			
Depression	**Panic disorder**	**PTSD**	**Nightmares**
• Bidirectional relationship • 18% of MDD patients have OSA • 17.6% of BRSD patients have MDD • OSA management reduces depressive symptoms	• OSA may be a risk factor for panic disorder • Hypercapnia in OSA may provoke panic attacks	• Up to 72.7% of patients with PTSD suffer from OSA • OSA impairs quality of life in PTSD patients • OSA worsens PTSD severity • PTSD patients have poor adherence to CPAP therapy • OSA management may improve PTSD symptoms	• Higher AHI may reduce REM and associated nightmares • Conversely, patients with nightmares have high REM AHI • CPAP may eliminate nightmares in OSA
Cognition	**ADHD**	**Personality type**	**Presentations in children**
• OSA may impair multiple cognitive domains: – Attention and vigilance – Verbal and visual memory – Visuospatial abilities – Executive functions • CPAP moderately reduces neurocognitive impairment in OSA patients with EDS	• Up to 95% of OSA patients have attention deficits • 20–30% of ADHD patients have OSA	• 30% of OSA patients have type D personality traits • Type D personality is related to decreased CPAP adherence	• OSA in under-recognized in children • OSA in children may present with: – Hyperactivity – Difficulty in peer-interaction – Conduct issues – Impaired intellectual abilities within normal range – Nocturnal enuresis – OSA is associated with brain changes that affect neural developmental processes

practices among pediatricians and reported that less than 20% had ever received formal training on sleep disorders. Pediatricians who had received training about sleep disorders had significantly higher knowledge scores on sleep problems and reported significantly higher confidence scores regarding counseling patients/guardians on sleep problems [119] (Table 12.1).

12.16 Conclusion

Recent scientific advances allowed for greater understanding of sleep physiology and sleep disorders pathophysiology. Sleep is vital for emotional regulation, and there is a bidirectional relationship between OSA and mental health. However, patients and physicians pay little attention to sleep problems. OSA is closely related to many psychiatric disorders, such as MDD, panic disorder, PTSD, and ADHD. Additionally, OSA is under-recognized in children, which may have an impact on the child's behavior and neurodevelopmental process. The treatment of OSA may reduce symptomatology in patients with concurrent psychiatric disorders, improve their quality of life, and have an impact on their healthcare costs. There is a need for appropriate screening of comorbid conditions in OSA, especially behavioral presentations, as the proper treatment of OSA may improve the quality of life of patients and have an impact on their healthcare costs.

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Behavioral Presentations of Central Disorders of Hypersomnolence

13

Samir Kumar Praharaj

Abstract

Central disorders of hypersomnolence include narcolepsy, idiopathic hypersomnia, Kleine-Levine syndrome, and other conditions. Behavioral symptoms are commonly associated with these syndromes and include mood changes, apathy, motor symptoms, changes in appetite and libido, hallucinations, and cognitive symptoms. Differentiating these behavioral presentations from common psychiatry disorders is necessary for proper management of these conditions.

Keywords

Atypical depression · Apathy · Hyperphagia · Hypersexuality · Hallucination · Cognitive symptom

The central disorders of hypersomnolence are characterized by excessive daytime sleepiness or periods of irresistible sleep during the day. The speed with which a person falls asleep during daytime, that is, hypersomnolence, is the hallmark of these disorders. Hypersomnia, which refers to increased sleep duration, may not be a feature of all disorders. The disorders that are included under central disorders of hypersomnolence are listed in Table 13.1. Behavioral symptoms are common among these patients.

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Table 13.1 Central disorders of hypersomnolence (ICSD 3)

	Disorders	Description
1	Narcolepsy type I	Narcolepsy with cataplexy. Lower hypocretin-1 levels in CSF (<110 pg/mL) or chronic sleepiness with mean sleep latency ≤8 min and ≥2 SOREMPs. Obesity common
2	Narcolepsy type II	Narcolepsy without cataplexy. Chronic sleepiness with mean sleep latency ≤8 min and ≥2 SOREMPs. Hypocretin levels normal
3	Idiopathic hypersomnia	Sleep drunkenness, excessive daytime sleep, non-refreshing sleep or naps, with or without prolonged nighttime sleep (10 or more hours)
4	Kleine-Levine syndrome	Recurrent periods of hypersomnia, hyperphagia, hypersexuality, apathy, confusion. Background slowing in EEG
5	Hypersomnia due to a medical disorder	Excessive daytime sleepiness associated with endocrine or neurological condition (e.g., tumor, stroke, demyelination, sarcoidosis, paraneoplastic disorder)
6	Hypersomnia due to a medication or substance	Excessive daytime sleepiness associated with use of sedating medications or stimulant withdrawal
7	Hypersomnia associated with a psychiatric disorder	Excessive daytime sleepiness associated with psychiatric disorders (e.g., depression)
8	Insufficient sleep syndrome	Excessive sleepiness associated with restricted sleep or irregular sleep-wake cycle

SOREMP sleep-onset REM periods

13.1 Narcolepsy

Narcolepsy was initially termed by Gelineau in 1880, and hence is also known as *Gelineau syndrome*. The *classic tetrad* of narcolepsy is excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnogogic or hypnopompic hallucinations. In this condition, daytime sleep attacks occur despite sufficient nighttime sleep. However, nighttime sleep is fragmented in many patients and could possibly be counted as a core symptom of narcolepsy, making it a *pentad*. Cataplexy is pathognomonic of narcolepsy, and is seen in 65–75% of patients. It is present only in type I narcolepsy and is absent in type II variety. Presence of cataplexy correlates with severe orexin deficiency. Rarely, genetic syndromes such as Niemann–Pick disease type C, Norrie disease, Prader–Willi syndrome, Angelman syndrome, Moebius syndrome, and Coffin–Lowry syndrome may present with cataplexy-like episodes [1]. Typical cataplexy has been reported to occur in another rare genetic disorder, autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) [1]. Delay in diagnosis of narcolepsy is common, specifically in the absence of the characteristic symptom, cataplexy.

Excessive daytime sleepiness typically occurs during periods of relative inactivity or while engaged in monotonous situations. There is an irresistible desire to sleep that occurs almost daily and sometimes several times in a day. Patients may nod or

doze in relaxed and sedentary situations. The sleep attacks increase in frequency and intensity, which peak in afternoon, and during evening hours they feel fresh. The naps taken during daytime are short and refreshing for most individuals, and many recall dreams after waking from naps. This is in contrast to persons with sleepiness associated with obstructive sleep apnea, who have non-refreshing sleep. Occasionally, automatic activities are associated with such naps (e.g., saying something out of context during a conversation). The sleepiness can be severe and may lead to inability to focus or stay awake at school or work, or during periods of less activity such as watching a movie. Rarely, sleepiness can occur during periods of driving that can result in accidents. Sometimes, the sleepiness comes to clinical attention only after serious consequences such as falling grades in school, poor work performance, or motor vehicle accident. Sometimes, patients may report of "feeling tired" or "fatigued" instead of sleepiness. Patients may be described as "lazy" by the family members.

Cataplexy is sudden loss of muscle tone, typically in response to a strong emotion, with preserved consciousness. It can affect all skeletal muscles, but some muscle groups are preferentially involved. A common presentation is sudden fall while laughing or telling a joke. The symptoms usually begin in the neck or facial muscles, causing slurred speech and a jerky irregular tremor of the head with facial twitching. At the onset of cataplexy, there may be intermittent loss of tone, resembling asterixis. Most commonly the cataplectic episodes are *partial* but can also be *complete* involving the whole body. The weakness may spread *cephalo-caudally* over a few seconds leading to sagging of the knees and collapse to the ground. The mouth may hang open and the eyes are shut. It is always *bilateral*, though some asymmetry may be present occasionally. These episodes last for less than 10 s; however, there may be incomplete recovery and the weakness may appear to wax and wane for several minutes. The patient is fully *conscious* and *aware* during the whole episode. Sometimes, if it is prolonged, there can be dream-like experiences or sense of detachment. When prolonged and awareness is altered, it raises erroneous suspicion of an epileptic seizure. It is uncommon to witness cataplexy in doctor's office, and the diagnosis rests solely based on history. Most patients will have a combination of partial and complete attacks. The frequency of episodes varies widely from less than once in a month to several times in a day.

Minor episodes are common and can be difficult to recognize. This can include slight drooping of the head, slurred speech, or dropping an item from the hand, making it virtually undetectable by family members. Another uncommon presentation is unilateral limb weakness that may be confused as a transient ischemic attack. These phenomena also need to be distinguished from related phenomena such as drop attacks and psychogenic symptoms. Cataplexy mimics are summarized in Table 13.2 [1, 2]. Slurred speech, related to muscle weakness, with preserved hearing of auditory stimuli, helps differentiating from conditions such as syncope, seizures, and other conditions involving loss of consciousness. Syncope can be differentiated by presence of prodromal symptoms such as feeling of fainting, changes in vision, typically a black curtain falling in front of eyes, in a precipitating situation, and almost invariably in standing position. Loss of consciousness is the

Table 13.2 Cataplexy mimics

	Condition	Description	Comments
1	Leg weakness while laughing	Mild sagging of knees during laughter	Normal physiological response
2	Pseudocataplexy	Sudden collapse during negative emotions related to stress. All episodes are complete, duration longer (minutes to hours)	No progression of weakness, no positive motor phenomena, favored by negative emotions
3	Syncope	Loss of consciousness with loss of muscle tone and rapid recovery	No awareness of episodes is differentiating feature
4	Gelastic syncope	Laughter produces collapse with pallor and unawareness	Rare episodes, not precipitated by other stimuli
5	Cardiac arrhythmia	Emotional stress is known to trigger cardiac events in long QT syndrome type 2	Typical triggers are negative symptoms and stress
6	Gelastic seizure	Stereotyped laughter without mirth, occasionally with collapse	Loss of awareness, speech arrest
7	Atonic seizure	Sudden loss of muscle tone with fall	Seen in symptomatic epilepsies
8	Hyperekplexia	Exaggerated startle with stiffness following sudden acoustic stimuli	Increased tone and posturing
9	Episodic ataxia	Cataplexy like attacks during exercise, emotional stress, or during illness	Difficulty extending legs, head tremor, dysmetria, and tremulous voice on examination
10	Drop attacks	Sudden falls without loss of consciousness in elderly	Transient impairment of posture and balance
11	Periodic paralysis	Episodic limb weakness associated with hypokalemia or hyperkalemia	May be associated with muscle stiffness

distinguishing feature in syncope but can be challenging in children who are unable to describe whether were conscious during the episodes.

The relationship to *emotional stimuli* distinguishes this phenomenon from others. Positive emotions such as humor and pleasant surprise precipitate episodes readily, though occasionally frustration or mild anger may be related. In one study of emotional triggers of cataplexy, laughter was found to be most likely trigger, followed by other related positive emotional states such as hearing a joke, feeling excited, feeling elated, remembering a happy moment, or experiencing an unspecified emotional event [3]. Some patients have reported episodes that were triggered by unexpectedly meeting an old friend, suggesting that surprise can be a factor. It is not only the actual emotion, but the anticipation of the effect which can trigger such episodes. However, strong negative emotions rarely provoke attacks. In contrast, *pseudocataplexy* episodes are precipitated by strong negative stimuli, associated with low mood, weakness is variable and the duration is variable, lasting for minutes to hours [1, 4] (Table 13.3). Also, the pattern of weakness is global in pseudocataplexy, in contrast to partial forms seen in cataplexy. In a pseudocataplexy attack, deep tendon reflexes are preserved on examination during the episode,

Table 13.3 Comparison of cataplexy and pseudocataplexy

	Feature	Cataplexy	Pseudocataplexy
1	Emotional trigger	Positive emotions	Negative emotions
2	Pattern of weakness	Partial or global	Global
3	Duration	Short	Longer
4	Deep tendon reflexes	Abolished	Preserved
5	Frequency	Variable	Variable
6	Associated features	Narcolepsy symptoms	Depression symptoms

whereas they are abolished in true cataplexy [4]. However, episodes of pseudocataplexy may coexist with true cataplexy in patients with narcolepsy, thus leading to diagnostic challenge. A formal interview to uncover depressive symptoms may be useful in such situations. Sometimes, video recording of the episodes may be helpful. Hypotonia in craniocervical region may abruptly interrupt smiling or other facial expressions, very characteristic of true cataplexy [5].

Injury during a cataplexy episode is uncommon, even with complete forms with falls. Even during a severe attack, most patients are able to find support and prevent oneself from falling or may be able to sit down at the onset of the attack. Cataplexy can be one of the most disabling aspects of narcolepsy, specifically in a subset of patients with recurrent episodes. Sometimes, cataplectic episodes occur repeatedly for hours or days continuously, that is, *status cataplecticus*. These episodes are characterized by impairment of motor control of upper part of the body, almost continuous head nodding, speech difficulties, and dropping objects. If it involves whole body, there is difficulty maintaining posture and walking, leading to falls. The weakness evolves slowly, and patients usually do not injure themselves during the fall. Patients often "learn" to avoid provoking situations. Also, they may avoid social situations because of fear of unpredictable attacks, which may be mistaken as social phobia. However, in social phobia, the underlying cognition is the fear of negative evaluation in social situations. Some patients learn "tricks" to avoid or interrupt a cataplectic attack.

Children with cataplexy have presentations different from adults. Specifically, facial muscles are affected more than limb and trunk muscles, leading to repeated grimacing, sometimes with tongue protrusion. There may be associated ptosis and slackened jaw with slurred speech. This has been described as *cataplectic facies* that is seen during the onset of narcolepsy [6, 7]. Hypotonia with typical facial features are sometimes accompanied by choreic movements, leading to confusion in diagnosis in children [8]. The episodes tend to be prolonged and unrelated to emotional stimuli. Also, irritability, poor attention, and hyperactivity are characteristic features rather than somnolence, which makes it difficult to distinguish from attention deficit hyperactivity disorder. These symptoms evolve to the adult presentation over a period of time, frequently resulting in a delay in diagnosis.

Hallucinations occur during falling asleep (*hypnogogic*) or while waking (*hypnopompic*). Most common are visual hallucinations and threatening. They can vary from simple geometric patterns to images involving people, animals, faces, and

scenes. Less frequently, auditory phenomena such as voices (words, names, people talking) and other sounds (phone, doorbell, music) can occur. Somatic experiences such as body distortions, feeling of heaviness or weightlessness, flying sensation, or falling sensations can also occur. Hallucinations can be very prominent symptoms and sometimes may lead to a mistaken diagnosis of psychosis. However, their strict relationship to sleep and presence of insight helps to differentiate from hallucinations seen in psychosis. Furthermore, auditory hallucinations are frequently associated with visual hallucinations in patients with schizophrenia, and secondary delusions are common. Nevertheless, assessment of psychotic symptoms can be challenging in patients with narcolepsy owing to presence of hypnogogic and hypnopompic hallucinations which can occasionally be *multimodal* and complex. Some patients with narcolepsy may experience hallucinations during wakefulness, making differentiation from schizophrenia difficult. These *"psychotic" forms* of narcolepsy have good insight into hallucinations and do not manifest any other symptoms of schizophrenia [9]. Over time, the hallucinations can become less frightening, as is seen in other forms of psychosis. In children, it may be difficult to distinguish hallucinations from dreams as they may be afraid to report these symptoms.

Sleep paralysis, though not specific, is commonly associated with narcolepsy. Typically, patients wake up and report an inability to move their limbs for few seconds to minutes (*hypnogogic paralysis*), which can be frightening. Episodes of sleep paralysis may result in panic attacks immediately on waking. However, spontaneous panic attacks are absent, and these episodes are not related to any other situation. Sleep paralysis is also more common in patients with trauma, and disturbed sleep associated with posttraumatic panic may induce sleep paralysis. Sometimes, sleep paralysis occurs immediately prior to falling asleep (*hypnagogic paralysis*).

Nighttime sleep is *disturbed* in 75% of patients with narcolepsy. Typically, they report awakenings during night, which are usually of shorter duration, but can be for hours. *Nightmares* with vivid dreams are common and reported by one-third of the patients [10]. Aggressive dreams are frequent in patients with narcolepsy including sexual themes, such as incest and raping. Several researchers have found the dreams to be repetitive, terrifying, and have a negative tone. Patients have higher recall of their dreams, and content can be frequently bizarre and of longer duration. Occasionally, dreams can have positive experiences too. *Lucid dreaming*, the experience of being aware of dreaming while asleep and continuing to dream, is common in narcolepsy patients [11]. Many patients confuse dream with reality and may develop delusional belief that dreamed events have actually occurred, that is, *dream delusions* [12]. These dream delusions are memory source confusion possibly related to misattribution of the origin of memory. Dreaming is also common during the short, daytime naps.

In a large population-based study in the USA, high rates of psychiatric comorbidity were found in those diagnosed with narcolepsy [13]. Specifically, higher rates of depressive disorders (35.8% vs 13.0%; OR = 3.9; 95% CI, 3.7–4.1), and anxiety disorders (25.1% vs 11.9%; OR = 2.5; 95% CI, 2.4–2.7) were found in narcolepsy as compared to general population. Panic attacks and social phobia is seen in

one-fifth of patients with narcolepsy. Also, anxiety disorder patients may have higher rates of cataplexy, possibly suggestive of association with a subclinical form of narcolepsy, specifically with panic disorder and generalized anxiety disorder [14]. Sleep paralysis in the absence of narcolepsy is not uncommon and is associated with anxiety and mood symptoms. In one-third of individuals with sleep paralysis, panic attacks were reported. Sleep paralysis also correlated strongly with history of trauma [15].

Major depressive disorder is a major confounder in the diagnosis of narcolepsy, specifically type II in which cataplexy is absent. The studies suggest increased rates of depression in patients with narcolepsy. However, subjective measures of depression using self-rated instruments could be unreliable because of potential overlap of symptoms. Specifically, decreased nighttime sleep, poor attention, changes in body weight, psychomotor retardation, and fatigue are common to both the conditions, and hence, may confound the diagnosis. However, anhedonia and pathological guilt are unlikely to be a part of narcolepsy, and presence of these symptoms could suggest depression. Subsyndromal depression is more common than syndromal depression in patients with narcolepsy.

Another phenomenon associated with narcolepsy is *binge eating episodes* during nocturnal arousals. In these patients there can be intense *carbohydrate craving*. In one study, 23% of patients with type I narcolepsy fulfilled diagnostic criteria for an eating disorder, and most had an incomplete form of binge eating disorder [16]. Symptoms of hyperphagia and hypersomnia along with other depressive symptoms can lead to mistaken diagnosis of atypical depression, which is characterized by reverse vegetative signs.

REM sleep behavior disorder, in which there are intrusions of wake behaviors in REM sleep, is not uncommon with narcolepsy, which is characterized by intrusions of REM sleep into wake behaviors [17]. Furthermore, REM sleep behavior disorder is much more common in patients with frequent cataplexy (68%), in contrast to 14% in those with infrequent cataplexy. Although uncommon, REM sleep behavior disorder can be an initial presentation of narcolepsy, specifically in the young [18, 19]. It is prudent to screen for narcolepsy when REM sleep behavior disorder is found in a child or young adult.

Symptoms of attention deficit hyperactivity disorder are common in pediatric narcolepsy patients, and presence of these symptoms was associated with increased levels of sleepiness, fatigue, and insomnia [20].

13.2 Idiopathic Hypersomnia

The concept of idiopathic hypersomnia originated with the description of "sleep drunkenness," a major difficulty in awakening, by Roth. The hallmark of this condition, as for other disorders of hypersomnolence, is *excessive daytime sleepiness*. However, the hypersomnolence is considered less irresistible than type I narcolepsy. Also, the *sleep duration is usually prolonged*, typically more than 10 h, in at least one-third of the patients. They report of non-restorative sleep, despite

adequate sleep duration. Although insomnia is a characteristic feature of depression, occasionally hypersomnia can be associated, specifically in bipolar depression, and may make the diagnosis of idiopathic hypersomnia difficult. In such patients with depression, atypical features are prominent, that is, mood reactivity, leaden paralysis, carbohydrate craving with weight gain, and interpersonal rejection sensitivity, in addition to hypersomnia. Roth had described two forms of idiopathic hypersomnia, a *monosymptomatic form* characterized by excessive daytime sleepiness alone and a *polysymptomatic form* which has prolonged nocturnal sleep and difficulty in awakening, in addition to excessive daytime sleepiness.

A characteristic feature of idiopathic hypersomnia is *sleep drunkenness* or *sleep inertia*, that is, a prolonged and marked difficulty in waking up from sleep, and the person is confused for a variable period of time. This can help in differentiating this condition from depression and other central disorders of hypersomnolence. There can be *long daytime naps*, lasting for several hours, which is *non-refreshing*. Awakening can be difficult in the morning or from naps and is accompanied by disorientation, confusion, poor motor coordination, and repeatedly going back to sleep. On efforts to rouse the patients, they can be irritable and frankly abusive. *Sleep inertia* is the transitional state between sleep and wakefulness, which is characterized by impaired performance, reduced vigilance, and a desire to return to sleep. This is a normal phenomenon that is present for minutes to several hours. Sometimes, a transitional period similar to a very pronounced sleep inertia is present in disease conditions and is known as *sleep drunkenness*, which is the hallmark of idiopathic hypersomnia. This sleep drunkenness is much more severe than physiologic sleep inertia seen in normal individuals and may require assistance of another person for waking. During the period of sleep drunkenness, patients have been shown to have ataxia, orthostatic changes, and hyporeflexia. However, this characteristic symptom of sleep drunkenness is seen in only half of the patients with idiopathic hypersomnia.

As patients with sleep inertia require extended sleep periods that may not be fulfilled leading to *functional sleep deprivation*, which could potentially worsen sleep inertia. Also, patients with idiopathic hypersomnia could have delayed sleep phase, which could exacerbate sleep inertia. Patients with idiopathic hypersomnia avoid daytime naps, which are non-refreshing and could potentially lead to episodes of sleep drunkenness; in contrast, naps are refreshing for narcolepsy patients (Table 13.4).

Cognitive symptoms such as memory complaints and attention problems are reported by more than half of subjects with idiopathic hypersomnia. Sometimes, symptoms are prominent and may meet the criteria for attention-deficit disorder [21]. Other subjective symptoms include being more alert in the evening than in the morning, difficulty focusing for more than an hour, and mental fatiguability. Sometimes, *autonomic symptoms* such as orthostatic hypotension, syncope, headache, and Raynaud's phenomenon are associated with idiopathic hypersomnia [22].

It is important to remember that idiopathic hypersomnia can also present with depressive symptoms related to impairment in function. A good history of the onset and evolution of the symptoms may aid in differentiating which one is primary. Sometimes, a therapeutic trial of antidepressants may be necessary. Also, "difficulty

Table 13.4 Comparison of narcolepsy and idiopathic hypersomnia

	Feature	Narcolepsy	Idiopathic hypersomnia
1	Age of onset	Adolescence	Adolescence
2	Familial	Rare	Rare
3	EDS	Yes	Yes
4	Cataplexy	Yes (70%)	No
5	Sleep paralysis	Common	Uncommon
6	Hypnogogic hallucinations	Common	Uncommon
7	Total sleep time	Normal	Increased
8	Nighttime sleep	Fragmented	Normal
9	Sleep onset REM	Common	No
10	Naps	Short, refreshing	Longer, non-refreshing

EDS Excessive daytime sleepiness

in getting out of bed" is commonly reported in almost three-fourth patients with depression, in addition to other sleep problems such as difficulty falling asleep, difficulty staying asleep, and feeling sleepy. Also, individuals with bipolar disorder report difficulty in getting out of bed. The sleep inertia in mood disorders is presumably related to their mood and decreased motivation, rather than a primary sleep disorder. Typically, depressed patients reporting difficulty getting out of bed also endorse wishing not to awaken from sleep and also dread about starting the day.

The complications seen in idiopathic hypersomnia include decline in school and work performance, sleeping during recreational activities, and higher chances of car accidents. The diagnosis once established is stable, though fluctuations are not uncommon. There can be spontaneous recovery in almost half of the individuals.

13.3 Kleine-Levin Syndrome

This is a rare relapsing-remitting disorder of young, characterized by periods of recurrent hypersomnia along with hyperphagia, hypersexuality, apathy, confusion, and derealization, lasting several days to months. The *classic triad* was described by Crichtley, which consists of recurrent hypersomnia, hyperphagia, and abnormal behavior. However, there has been a suggestion that the *tetrad* consisting of hypersomnia, confusion, apathy, and derealization is more suggestive of KLS and was seen in all subjects in a large series, as compared to only 45% having the classic triad [23]. Almost half of the patients report a flu-like illness prior to the clinical presentation of KLS. Behavioral disturbances and other psychiatric symptoms are reported to occur during episodes in more than half of the patients.

Hypersomnia is an essential symptom of KLS, at least during the initial part of illness. The total sleep duration is often more than 18 h per day during those periods. Despite sufficient sleep, patients feel tired and irritable. Most of the patients have a long nighttime sleep which continues till midday and a long nap in the afternoon. A window of "wakeful period" when they are alert is seen in the evening at 6 p.m. They

may wake up spontaneously to void and eat and go back to sleep immediately. If they are aroused from sleep or prevented to go back to sleep, they may become irritable and aggressive. The need for sleep can be intense and patients may sleep in unusual places or situations. Many patients report prodromal symptoms prior to onset of hypersomnia, which include sudden, overwhelming tiredness and reluctance to get out of bed in the morning.

Cognitive symptoms are common during the episodes. This includes *mental confusion* and *slowed thinking* which are manifested as decreased spontaneous speech, increased reaction time, and very brief responses during conversation. They may answer questions as "yes" or "no" or even with moaning sounds. Patients may report difficulty in understanding the questions. Sometimes, they may not recall or partially recall of events during the episode suggestive of *amnesia*. *Abnormalities in speech* have been reported to occur during the episodes. These may include being mute, monosyllabic speech or short sentences, verbal stereotypy, and echo phenomena. Sometimes, speech may be slurred or muddled and child-like which can be incoherent and difficult to comprehend. Disorientation to time is sometimes observed; however, disorientation to place is not common. Some subjects reportedly had academic decline with recurrent episodes, and in them mild cognitive dysfunction persisted beyond the episodes. They usually have problems in multitasking during these episodes. The neurological examination is normal in most of the patients.

Hyperphagia (or megaphagia) is seen in two-third of patients with KLS. It is typically described as compulsive with bouts of "binge eating," that is, eating large amount of food. There may be a preference for sweets and carbohydrates. Sometimes, patients may lose their inhibition and eat whatever is available. Specifically, they cannot refrain from eating food within their reach, in a compulsive fashion. The frequency of eating may also increase, and some patients may eat 6-8 meals a day, resulting in significant weight gain. Some patients can eat food that they have refused in the past or were aversive to them. Increased drinking may also be associated, but is not usually observed in the absence of hyperphagia. Occasionally, hyperorality has been described in KLS, which includes compulsive mouthing of objects [24]. Very few patients may have variable presentation of eating behavior and can have aversion to food in some episodes and hyperphagia in other episodes; however, such presentation is less than 5%. Hyperphagia can be distinguished from bulimia as there is no associated compensatory behavior such as vomiting for weight control and the cognition related to weight is absent.

Apathy during the episode is observed in almost all subjects with KLS. They stop going out with friends and stop using smartphones or social media, and grooming becomes poor. Most of the time they spend lying on the bed. On observation they appear totally exhausted, sleepy with eyes closed, and unconcerned. Apathy may be a result of affective or motivational deficit in which the goals have less affective value for the patient, or it may be related to cognitive impairment in which there is difficulty in planning a complex action.

Another symptom that is fairly common in KLS patients is *derealization*. They typically report that the surroundings appear unreal or that everything is part of a

dream. They may perceive the objects being far off or the voices coming from distant places. Some report of their own voices appearing strange to themselves or other changes in themselves suggestive of *depersonalization*. It is the "as if" quality of these phenomena that distinguishes these from the delusional beliefs. The sensations may feel wrong and unpleasant, and sometimes, patients test their environment by spraying water on their face or counting their fingers to reassure themselves that everything is normal.

Hypersexuality is also seen in two-third of patients which present with frequent masturbation, demanding more sex from sexual partners, inappropriate sexual behavior including exposing and touching themselves in front of others, and sexual advances to others. Inappropriate sexual advances may include assault on nursing staff, visitors, or relatives. Sometimes, patients swear profanities or make inappropriate proposals. Overt hypersexuality is more commonly seen in males but rarely reported to occur in females. Sometimes, *repetitive behaviors* such as pacing, tapping, snapping, etc. are observed. Compulsive behaviors during the episodes can also include inappropriate singing, body rocking, chewing lips, writing on walls and stripping down wallpaper, and fire-setting. Sometimes, regressive, child-like behavior has been reported including child-like speech.

Depressive symptoms are common during the episodes and are seen in almost half of all the patients, particularly in females [25]. Suicidal thoughts are reported to occur in 15% of individuals, though attempted suicide is uncommon. Depressive symptoms usually resolve toward the end of KLS episodes, though it may persist longer in a few. Occasionally, brief periods of hypomania have been reported to occur at the end of KLS episodes which are characterized by feeling of relief, elation, logorrhea, and insomnia lasting 1 or 2 days. *Anxiety* is reported in 70% of patients that includes fear of being left alone or going outside and meeting people. Some may become rude and aggressive and may actually hit others on slightest provocation.

Hallucinations are reported in several patients during KLS episodes. Most commonly, hallucinations occur in visual modality, in contrast to schizophrenia in which auditory hallucinations are prominent. Auditory hallucinations if present are elementary and devoid of derogatory content, and thus can be easily differentiated from schizophrenia or other psychotic disorder. Rarely, frank *psychotic symptoms* are seen including hallucinations and delusions making the diagnosis difficult. The delusions most commonly reported are referential or persecutory in nature, which may include ideas that people are trying to kill or poison them. Most of such psychotic episodes occur for very brief periods and resolve spontaneously in few hours or days. The presence of frank symptoms may lead to a mistaken diagnosis of acute psychosis, specifically during the first episode of KLS in a teenager presenting with prominent delusions and hallucinations.

These periods (median duration of 10 days) tend to recur every few months (1–12 months, median 6 months). The onset and offset of the KLS episodes are fairly abrupt (i.e., in hours) in almost half of the cases, unlike mood disorders where it is over days. However, in almost half of patients the onset is less abrupt, and develops progressively over several days, making differentiation from mood disorders difficult. Longer episodes are more likely in adults, whereas it is brief in children and

adolescents. In almost one-third individuals one episode more than a month occurs and occasionally may last for up to 6 months. Alcohol use and infections are often reported as triggers for the episodes. The age of onset is usually after puberty (12 years) and not after 20 years. Males are affected more than females (2:1 ratio). Hypersomnia becomes less over the course of illness, when other symptoms such as extreme fatigue and derealization tend to predominate. In most cases, there is spontaneous recovery by 30 years of age. Arnulf et al. [26] reported a series of 108 cases, in which patients had a median of 19 episodes, with episode duration of 12.5 days and asymptomatic interval of 5.7 months. The median duration of KLS is approximately 8 years [27].

In between the episodes, patients have normal mood, behavior, cognitive function, and sleep. However, recent studies have found mild cognitive dysfunction in asymptomatic periods in one-third of patients with KLS. The most common psychiatric disorders that are reported to co-occur with KLS includes depressive and anxiety disorders. Emerging psychiatric disorders were more common among females, those with long-standing disorder and having frequent psychiatric symptoms during the KLS episodes [28].

Atypical depression, which presents with reverse vegetative signs (hypersomnia, hyperphagia, and hypersexuality), is a close differential diagnosis in such cases. The presence of recurrent episodes of hypersomnia, hyperphagia, and hypersexuality seen in KLS may lead to mistaken diagnosis of recurrent depressive disorder or even bipolar disorder. Occasionally, anxiety may be more prominent than depression. Rarely, there have been reports of bipolar disorders being comorbid with KLS, raising the possibility of overlap between the two syndromes [29]. Bipolar disorder being more common than KLS makes it more likely that some cases of KLS may be misdiagnosed as bipolar disorder, rather than other way round.

There are several analogies between KLS and bipolar disorder, even though the onset and offset of KLS episodes are quite abrupt in contrast to episodes in bipolar disorder. Depression is common during hypersomnia episodes, and at resolution of hypersomnia, elation is frequently seen. In some individuals, there is an alteration between hypersomnia episodes and typical manic-depressive episodes. The illness resembles the mythological character, *Kumbhakarna*, described in the epic *Ramayana* [30]. It has also been referred to as "sleeping beauty syndrome" in the literature.

KLS without compulsive eating is an atypical presentation in which all the features are presented less frequently, except for derealization. Menstrual-related hypersomnia is considered as a variant form of KLS, which occurs with menstrual cycle and sometimes with puerperium. Secondary KLS is reported in 10% patients in which neurological symptoms are present prior to the onset and persist between the episodes. KLS and its variants have been reported in association with stroke, head trauma, viral encephalitis, genetic and developmental diseases including mosaicism, mental retardation, multiple sclerosis, hydrocephalus, paraneoplasia, and autoimmune encephalitis. Rarely, KLS may be associated with autism spectrum disorder including Prader–Willi and Asperger's syndromes.

13.4 Hypersomnia Due to a Medical Disorder

Hypersomnia is seen in several medical conditions (Table 13.5). If hypersomnia appears after the diagnosis of the medical condition, the diagnosis is easy. However, in several conditions sleepiness predates the onset of symptoms diagnostic of the medical disorder, and a high index of suspicion is necessary. For example, hypersomnia may appear in Parkinson's disease 4-12 years prior to onset of motor symptoms. In such situations, presence of parasomnias such as REM sleep behavior disorder could provide clues to presence of possible neurodegenerative disorder [31]. Such patients with hypersomnia associated with dream enactment symptoms should be assessed for the presence of subtle early extrapyramidal signs such as glabellar tap or mild cogwheeling in limbs, orthostatic changes in blood pressure, or reduced acuity of smell.

Both insomnia and hypersomnia are reported to occur with acute stroke. Strokes affecting reticular activating system can present with hypersomnia. Hemispheric strokes reduce total sleep time and sleep efficiency leading to daytime sleepiness. Hypothalamic strokes affecting orexin-producing neurons can cause narcolepsy. Also, sleep disordered breathing is commonly comorbid in individuals presenting with stroke.

Tumors in thalamus, hypothalamus, and brain stem present with hypersomnia. Craniopharyngioma, a pituitary tumor, is commonly associated with hypersomnia. In multiple sclerosis, lesions involving similar areas lead to hypersomnia. Excessive

Table 13.5 Hypersomnia associated with medical conditions

	Medical condition	Comments
1	Neurodegenerative disorders (Parkinson's disease, Alzheimer's disease)	Daytime hypersomnia and disturbed nocturnal sleep related to sleep-disordered breathing, parasomnias, and circadian rhythm disorders
2	Endocrine disorders (hypothyroidism, hyperprolactinemia)	Obstructive sleep apnea is common cause of hypersomnia
3	Sleep-related breathing disorder (OSA)	This is commonly associated with obesity
4	Infectious diseases (HIV, infectious mononucleosis, Lyme disease, neurocysticercosis, trypanosomiasis)	Disordered nocturnal sleep and hypersomnia
5	Brain tumors (craniopharyngioma, brainstem glioma, subependymoma)	Hypersomnia is common with craniopharyngioma
6	Strokes (subthalamic, pontine, mesencephalic, thalamic)	Can present with features of narcolepsy when affect the hypocretin-producing neurons.
7	Demyelinating disorders (multiple sclerosis)	Hypersomnia is related to symptoms such as insomnia, fatigue, depression, periodic limb movements, and pain
8	Genetic syndromes (Arnold-Chiari malformations, Norrie disease, myotonic dystrophy)	May be related to sleep-related breathing disorder

daytime sleepiness can also be associated with epilepsy, specifically uncontrolled epilepsy, and nocturnal frontal lobe epilepsy.

Sleeping-related breathing disorder such as obstructive sleep apnea is a common cause of excessive daytime sleepiness. This is common in endocrine disorders such as hypothyroidism. These patients commonly report hypersomnia, attention disturbances, fatigue, and snoring. In all cases with endocrine disorders, there should be a thorough evaluation of sleep-related breathing disorder. Hypersomnia is also common in overweight and obese individuals, who are also at risk for obstructive sleep apnea. Comorbid depression and metabolic derangements in these patients also could cause hypersomnia.

Infectious diseases can cause hypersomnia as a result of infection itself or related to the medications used in their treatment. Meningitis and encephalitis associated with viral and bacterial infections can cause disturbed nighttime sleep and daytime sleepiness as a result of cerebral edema and hydrocephalus. Trypanosomiasis is associated with sleepiness, hence also called "sleeping sickness." Sometimes, sleepiness can persist much longer beyond the acute infections.

13.5 Hypersomnia Due to a Medication or Substance

Several medications are known to cause excessive daytime sedation (Table 13.6). Most of the hypnotics such as benzodiazepines and barbiturates are associated with daytime sleepiness. Medications with long half-life are associated with higher daytime sleepiness, whereas those with short half-life including the Z-drugs such as zolpidem have lower propensity to cause such effect.

Table 13.6 Hypersomnia associated with medications

	Medication category	Comments
1	Hypnotics (benzodiazepines, Z-drugs, melatonin agonists)	Residual daytime sedation can be seen with medications with longer half-life
2	Antidepressants (tricyclics, occasionally SSRIs)	Sedation, sleep disruption and REM sleep suppression is seen
3	Antipsychotics (thioridazine, chlorpromazine, quetiapine, olanzapine, clozapine)	Can cause daytime sleepiness
4	Antihistamines (chlorpheniramine, diphenhydramine, cyproheptadine, doxylamine, hydroxyzine, promethazine)	Increased sleepiness, but tolerance develops after consistent use
5	Antiepileptics (phenobarbital, carbamazepine, phenytoin, gabapentin)	Daytime sleepiness common
6	Antihypertensives (clonidine, methyldopa, carvedilol, prazosin)	Sedation and fatigue common
7	Dopamine agonists (pramipexole, ropinirole, rotigotine)	Sleepiness and sleep attacks are frequent
8	Alcohol	Sleep-disruption in later two-third of night and leads to daytime sleepiness

Several medications other than the hypnotics are associated with excessive daytime sleepiness. Among antidepressants, the tricyclics are highly sedating and as a consequence cause daytime sleepiness. Other sedating antidepressants include trazodone and mirtazapine.

Antipsychotics that are highly sedating include chlorpromazine, thioridazine, olanzapine, quetiapine, and clozapine. Antihistamines of the first generation such as chlorpheniramine, diphenhydramine, hydroxyzine, promethazine, and cyproheptadine are highly sedating drugs. Antihypertensives can cause sedation and fatigue. Opioid use is associated with central sleep apnea, leading to daytime sleepiness. Triptans for the treatment of migraine are associated with sedation.

13.6 Hypersomnia Associated with a Psychiatric Disorder

Excessive daytime sleepiness is frequently reported in patients with psychiatric disorders, specifically in context of mood disorders. Most of the studies in depressive disorder have found high rates of hypersomnolence, more so in adults than in children. Almost two-third patients with seasonal affective disorder have symptoms of hypersomnolence. Although insomnia is common in depressive disorder, 6% have hypersomnia. In atypical depression, hypersomnia is common and is considered as a reverse vegetative sign along with hyperphagia and hypersexuality. The complaints of excessive daytime sleepiness may be related to apathy, withdrawal, poor motivation, lack of energy, anhedonia, or reduced psychomotor activity in patients with depression. In patients with narcolepsy, 33% had any forms of depressive disorder in a nation-wide study in Taiwan [32].

High rates of hypersomnolence (up to 30%) are reported in bipolar disorder [33]. Specifically, in those with bipolar depression, hypersomnia is common. Psychotic symptoms in patients with narcolepsy can lead to mistaken diagnosis of schizophrenia. It has been estimated that up to 7% of patients with schizophrenia may have a psychotic variant of narcolepsy [34]. Several medications used in the treatment of mood disorder are associated with excessive sleepiness.

In these disorders, although patients report of excessive daytime sleepiness, the degree of sleepiness varies with days and the nighttime sleep is of poor quality. Furthermore, objective sleepiness is nor demonstrated in MSLT. Sleep inertia is also frequent in patients with mood disorder, though sleep drunkenness, which is characteristic of idiopathic hypersomnia, is uncommon.

13.7 Insufficient Sleep Syndrome

Behaviorally induced insufficient sleep syndrome refers to having less sleep than the biologically determined sleep duration. This happens when subjects deprive themselves of sleep because of social or personal reason. Typically, those who overwork during weekdays tend to oversleep during weekends to compensate for the sleep debt. The presenting symptom is sleepiness for more than 3 months. In adolescents,

the phase delay in circadian rhythm and slowed sleep drive associated with puberty coupled with external factors such as homework, extracurricular activities, and excess use of electronic media could potentially contribute to insufficient sleep [35]. Sometimes, the daily loss of sleep can be quite small, hence, not perceived as a possible cause of hypersomnolence.

Although not well studied, self-induced sleep restriction could be highly prevalent, specifically among adolescents. For example, in among Norwegian students the estimated prevalence was 10% [36]. Furthermore, in that study presence of insufficient sleep was associated with higher self-reported depression. Among Korean adolescents, it was not only associated with depression but also with higher suicidal behavior [37]. Those having insufficient sleep syndrome have higher rates of accidents [38]. In addition, adolescents with insufficient sleep may have poor attention, poor academic performance, higher risk of obesity, increased alcohol and substance use, and increased rates of car accidents and sports-related injuries [35]. It has been found that there is an increased risk-taking behavior in chronically sleep restricted subjects, which was associated with low slow-wave sleep intensity over the right prefrontal cortex [39].

In those with insufficient sleep syndrome, hypersomnolence predominates in the afternoon and evening hours, in contrast to idiopathic hypersomnia. Subjective complaints are common which includes fatigue, lower energy levels, and tiredness. Other features include reduced concentration, poor memory, impaired learning capacity, and impaired psychomotor performance. Mood symptoms such as irritability and fluctuations in mood with poor impulse control may be present with insufficient sleep. In sleep history, the disparity between the sleep duration between weekdays and weekends could alert toward a possibility of insufficient sleep syndrome, in contrast to narcolepsy [40].

13.8 Evaluation of Excessive Daytime Sleepiness

Evaluation of patients with sleepiness includes careful history followed by focused examination, use of questionnaires, and if possible laboratory testing including a sleep study.

One of the common features of all central disorders of hypersomnolence is that *excessive daytime sleepiness* occurs despite sufficient sleep (except insufficient sleep syndrome). Excessive daytime sleepiness should not be caused by sleep deprivation, obstructive sleep apnea syndrome, circadian rhythm disorders, or because of medication or substance use. The subjects report poor quality or difficulty in maintaining wakefulness. Increased nighttime sleep duration is commonly associated with excessive daytime sleepiness.

Excessive daytime sleepiness can present with *sleep attacks*, which are severe, sudden episodes of irresistible sleep that are characteristically seen in narcolepsy. Such episodes not only occur during relaxing periods such as watching television or reading quietly but also during active tasks such as during a conversation or while

driving. Although excessive daytime sleepiness is seen in other disorders of hypersomnolence, these are not as marked and "sleep attacks" are uncommon.

Insufficient sleep syndrome is the most common and correctable cause for excessive daytime sleepiness. A good sleep history including sleep duration during weekdays and weekends is essential. This can be augmented with sleep logs, and if necessary actigraphy measures for 1 week. Extending the sleep time during weekends usually leads to resolution of symptoms.

Long sleepers, a normal variant, may require 9-10 h of sleep to feel refreshed. Younger individuals tend to sleep more than older adults. If relatively sleep deprived, they present with excessive daytime sleepiness that reverses with ensuring their habitual sleep. Diagnosis is easy if the habitual sleep pattern is enquired; typically, such sleep pattern is present since childhood. Similarly, *shift workers* may present with excessive daytime sleepiness.

Clinophilia is the tendency to maintain reclining positions, which may be seen in some healthy individuals and in mood disorders. This has to be distinguished from sleepiness using a thorough history.

Many patients with sleepiness do not complain of this, but rather present with fatigue, tiredness, moodiness, or difficulty in concentration. How sleepiness affects the daily activities and functioning should be explored. Patients report inability to stay awake to complete the tasks, difficulty in studies, recreational activities, and relationships.

Excessive daytime sleepiness has to be distinguished from *fatigue*, which is unrelated to the quantity and quality of sleep, and does not improve with increasing duration of sleep. Presence of fatigue should alert the physician to look for symptoms of depression or other medical illness.

Sleep history includes information on the patient's bedtime, time to fall asleep, waking time, number of awakenings, day time naps, periods of dozing during the day, and any time spent lying on bed. A *sleep diary* can be helpful to record the sleep-wake patterns over weekdays and weekends over at least 2 weeks. This can identify poor sleep hygiene and circadian sleep disorders. However, the limitations include discordance with the objective measures of actual sleep duration.

Sleep-related breathing disorders such as obstructive sleep apnea and upper airways resistance syndrome are associated with daytime sleepiness. Obstructive sleep apnea includes periods of apneas or hypopneas lasting more than 10 s, which leads to hypoxemia, snoring, and disrupted sleep. Typically, there is history of snoring and episodes of choking or gasping that are self-reported or witnessed and reported by the bed partner. Other features associated with sleep apnea are awakening with dry mouth, nasal congestion, nocturnal cough or enuresis, and morning headaches.

A thorough medical and psychiatric history is essential in identifying conditions associated with hypersomnia. Medical history should focus on cardiovascular, cerebrovascular, and nasopharyngeal disease. Pain syndromes can fragment sleep and present with sleepiness. Presence of parasomnias (e.g., REM sleep behavior disorder) could provide clues to presence of possible medical condition such as degenerative disorders. Psychiatric history should include exploring mood disorders

including depression and bipolar disorder as they can present with hypersomnia. Specifically, depression with atypical features is commonly associated with hypersomnia. Nocturnal panic attacks in panic disorder can disrupt sleep and present with daytime sleepiness. In addition, prescription medications as well as over-the-counter medications can be associated with hypersomnia. Specifically, several psychotropic medications cause sedation that has next day carryover effects. It is also important to enquire about herbal supplements or Ayurvedic preparations that may be associated with excessive daytime sleepiness. Additionally, history of consumption of alcohol, tobacco, caffeine and other psychoactive substances need to be asked. Some conditions such as narcolepsy, restless leg syndrome, and obstructive sleep apnea can be familial. Hence, a detailed family history provides a clue to the diagnosis. Rarely, substance users may feign symptoms of narcolepsy to obtain stimulant prescriptions.

Careful physical examination may provide clues to the diagnosis. Obesity is one of the major risk factors for obstructive sleep apnea that is associated with sleepiness. BMI, waist circumference, and waist-hip ratio measurements are useful in assessment of obesity. Respiratory rate and pulse oximetry may be useful to assess obstructive sleep apnea. Neck circumference and nasal and oropharyngeal examination may aid in diagnosis of OSA.

Wrist actigraphy may be used to validate the data obtained from sleep diary. Actigraphy is a noninvasive method to monitor the activity-rest cycle and gives objective estimates of total sleep time, sleep efficiency, and wake time after sleep onset. However, this may overestimate sleep and underestimate waking period. The standard objective measure of nighttime sleep is *polysomnogram*, which is invaluable in recording total sleep time, percentage of time spent in each stage, sleep fragmentation, as well as its possible causes.

There are standard measures for recording excessive daytime sleepiness (Table 13.7). The standard objective measure of daytime sleepiness is *multiple sleep latency test* (MSLT). It is also used to document the presence of sleep-onset REM periods (SOREMPs). Differential diagnosis of SOREMPs includes narcolepsy, sleep deprivation, untreated OSA, rebound from REM suppressing drugs, delayed sleep phase syndrome and as a normal variant seen in 3–17% of population. Several subjective rating scales such as *Epworth Sleepiness Scale* (ESS) and *Stanford Sleepiness Scale* (SSS) are available to assess the presence and severity of excessive daytime sleepiness. A combination of subjective and objective measure along with the clinical history and examination assesses the clinical significance of excessive daytime sleepiness. Other sleep questionnaires that could be useful in the assessment include Pittsburg Sleep Quality Index (PSQI) and Swiss Narcolepsy Scale (SNS).

A diagnosis of narcolepsy is based on history of sleepiness, cataplexy, sleep paralysis, hypnogogic or hypnopompic hallucinations, and disturbed nocturnal sleep, with unremarkable physical and neurologic examination. Specifically, the presence of cataplexy need to be established based on history alone, and rarely, it may be witnessed in the clinic. However, cataplexy mimics such as syncope, basilar migraine, and conversion disorder can confound the diagnosis. Video

Table 13.7 Assessment of excessive daytime sleepiness

	Measure	Description	Comments
1	Multiple sleep latency test (MSLT)	Four or five 20-min nap opportunities at 2-h intervals in a sleep-inducing environment	Well-defined standard protocol that is reliable for multiple sleep latency and SOREMPs
2	Maintenance of wakefulness test (MWT)	Daytime polysomnography that objectively measures the ability of a person to remain awake (40 min four trial protocol)	No universally accepted standard protocol
3	Oxford sleep resistance (OSLER) test	Similar to MWT, in which behavioral criteria is used instead of polysomnography	Simple, lower cost, automatic reading and lower technical requirement
4	Psychomotor vigilance testing (PVT)	Sustained attention by measuring response times to stimuli at random intervals for 10 min	Reliable changes with varying degree of sleep deprivation
5	Epworth sleepiness scale (ESS)	Subjective sleep propensity in eight ordinary life situations	Score more than 10 correlates with EDS, and score more than 16 is seen in narcolepsy, idiopathic hypersomnia, or severe OSA
6	Stanford sleepiness scale (SSS)	Subjects choose one of seven statements that best describes their state of sleepiness	Best validated, easy to use multiple times
7	Karolinska sleepiness scale (KSS)	Subjects choose one of nine statements that best describes their state of sleepiness	Similar to SSS
8	Visual analog scale (VAS)	Subjects choose the level of sleepiness or alertness on a 10 cm line	Not very useful

documentation of such episodes is useful to distinguish from related events such as pseudocataplexy. Also, the onset of cataplexy may be much later than the onset of excessive daytime sleepiness. The other features such as sleep paralysis and hallucinations do not help in diagnosis as they are inconsistent and may be present in other conditions, such as idiopathic hypersomnia. For the same reason, diagnosis of type 2 narcolepsy is difficult, in the absence of cataplexy. Isolated hypnogogic hallucinations and sleep paralysis are not uncommon in general population.

Diagnosis of narcolepsy is confirmed with objective testing with polysomnography followed by MSLT or hypocretin-1 levels in CSF. Polysomnography allows ruling out obstructive sleep apnea as a cause for excessive daytime sleepiness. MSLT involves 4-5 nap opportunities during which the mean latency to sleep and the number of naps containing REM sleep are quantified. On MSLT, the mean sleep latency is 8 min or more on multiple occasions in narcolepsy. Sleep-onset REM periods (SOREMPs) during PSG or MSLT are characteristic feature of narcolepsy. However, MSLT can be falsely negative in a small proportion of narcolepsy patients. CSF hypocretin-1 levels are lower than 110 pg/mL in narcolepsy type I, which is a highly specific biological measure. The levels are

typically normal in narcolepsy type II. HLA genotyping may be helpful sometimes, if clinical features are doubtful. The HLA class II HLADQB1*0602 allele is found in more than 98% of those with narcolepsy type I, as compared to only 12–30% of general population.

Presence of sleep-drunkenness or severe sleep inertia gives clues toward a diagnosis of idiopathic hypersomnia. However, this needs to be differentiated from milder, physiologic state of *sleep inertia* that is common in healthy individuals. The *Sleep Inertia Questionnaire* can be used to assess sleep inertia in the context of depression. Sleep drunkenness is also seen in delayed sleep phase syndrome, which can be ruled out on careful history. Idiopathic hypersomnia patients usually do not have sleep paralysis or hypnogogic hallucinations but may be present in some individuals. Furthermore, patients with idiopathic hypersomnia sleep longer, more than 10 h every night. *Nap history* can be useful in distinguishing idiopathic hypersomnia from narcolepsy. Typically, naps are short and refreshing in narcolepsy, whereas those with idiopathic hypersomnia have longer, non-refreshing naps and difficulty waking from naps. Sleep efficiency is higher in idiopathic hypersomnia (>95%) than narcolepsy, and there are no SOREMPs in MSLT.

Chronic sleep deprivation, sometimes associated with shift work, can affect MSLT results. In those with insufficient sleep syndrome, longer sleep duration in weekends or holidays as recorded by sleep log or actigraphy may help in distinguishing this from narcolepsy. Neurological signs in narcolepsy patients are suggestive of secondary narcolepsy, which requires investigations including neuroimaging.

Excessive daytime sleepiness in young children may present with symptoms related to attention, concentration, behavior and mood symptoms, and not as sleepiness, and hence are likely to be misdiagnosed. Sometimes, daytime napping in school is reported by teachers. The classic presentations of cataplexy in adults may be absent in children, whereas cataplectic facies may be common. Mild head nodding as a feature of cataplexy may be mistaken as sleepiness and dozing off by the caregivers, leading to delay in diagnosis.

13.9 Cognitive Dysfunction in Central Disorders of Hypersomnolence

Narcolepsy patients have impairments in several cognitive domains [41, 42]. Usually, patients with narcolepsy appear to be alert after naps during daytime. However, even during those periods patients have reduced vigilance which interferes with cognitive functions and performance. Younger individuals with narcolepsy show significant impairment in attention, concentration, delayed recall, recalling names, or recognizing known persons. Older individuals have more cognitive impairments including attention, concentration, praxis, delayed recall, temporal orientation, and prospective memory. Children with narcolepsy are at a higher risk of cognitive impairment and emotional problems including depression, anxiety, and low self-esteem [43]. Subjective reports of attention deficits are much more common and

could be related to moments of sleepiness as well as anxiety and depression. However, there is a poor correlation of these complaints with objectively assessed cognitive measure [44]. However, there are reports of higher creative thinking in patients with narcolepsy, which could be associated with higher REM sleep and dreaming [45].

In KLS, cognitive impairment was believed to be associated with the episodes of hypersomnolence. However, recent studies have shown the impairments to persist during inter-episode intervals, with lower nonverbal IQ, reduced processing speed, impaired attention, and impaired episodic memory retrieval [46].

Subjective cognitive complaints are common in idiopathic hypersomnia. Memory problems, attentional disturbances, feeling of "mind going blank," and making mistakes in usual activities are commonly reported. Sometimes, the cognitive symptoms are pronounced, and patients may actually meet criteria for attention deficit disorder [21].

Sleep deprivation, even if behaviorally induced, lead to impairment in several mental tasks such as sustained attention, information processing speed, working memory, and multitasking. Sleep drunkenness or sleep inertia may be associated with transient decrease in cognitive performance, which may be further amplified by sleep deprivation. It can be problematic in occupational setting when immediate decision-making is required following waking abruptly, specifically in shift workers.

13.10 Conclusion

Daytime sleepiness is a common symptom that may be associated with primary disorders of hypersomnolence such as narcolepsy, idiopathic hypersomnia, as well as secondary to a gamut of medical and neurological disorders, psychiatric disorders, and medications. Behavioral, cognitive, and affective symptoms are common with the disorders associated with hypersomnolence. Comorbid psychiatric disorders may pose diagnostic challenges in differentiating the causes of sleepiness. A thorough clinical assessment which includes sleep history, along with medical and psychiatric history and physical and mental status examination, will be required to clarify the diagnosis. Several subjective and objective measures including rating scales and other sleep diagnostic tests may aid to differentiate between these conditions, so as to institute appropriate treatment strategies.

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Behavioral Presentations of Circadian Rhythm Sleep Disorders

14

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Abstract

Circadian rhythm sleep disorders (CRSD) are a group of sleep disorders characterized by a de-synchronization between a person's biological clock and the environmental 24-h schedule. There are six main types of CRSD, namely, advanced sleep phase syndrome (ASPD), delayed sleep phase disorder (DSPD), irregular sleep-wake rhythm (ISWR), free running disorder (FRD), shift work type (SWD), and jet lag disorder (JLD). Physiological data and genetic studies in patients with CRSDs suggest that these disorders result from abnormal functioning of the circadian rhythm system. The diagnosis of CRSD is based on clinical interview and sleep log diaries and/or actigraphic monitoring under a free condition schedule. Bright-light therapy and melatonin administration have proved to be the most effective treatments for CRSD. Difficulties in daytime functioning are one of the prominent characteristics of CRSDs. Individuals with CRSDs frequently fail to adjust to the normal accepted hours of activity. It is common that the daytime functional difficulties that accompany CRSDs are misinterpreted as symptoms of psychopathology or daily dysfunction. CRSDs are underrecognized and frequently misdiagnosed, and therefore treated as psychological, psychiatric, and/or sleep disorders. Recognition and awareness of the characterization of these disorders should improve the diagnosis and treatment of these patients.

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Keywords

Circadian rhythm sleep disorders · Insomnia · Hypersomnia · Depression

14.1 Introduction

Humans need to adjust their behavior and physiological processes to the conditions of a 24-h day-night (light-dark) period. Synchronization of the endogenous clock with environmental conditions enables the rhythmic changes of behavior and physiological processes to be in phase with the external world. The synchronizing factors are clear environmental cues (so-called time givers—"zeitgebers"), the most prominent of which to the central clock in the SCN is light. Alternating periods of light and dark, day and night, are cues that enforce the period of activity and sleep.

Sleep is regulated by two main factors [1]: the model posits that a homeostatic process (Process S) interacts with a process controlled by the circadian pacemaker (Process C), with time-courses derived from physiological and behavioral variables—the homeostatic pressure and the circadian timing—and the interaction between them. The homeostatic pressure to sleep accumulates as long as a person is awake and therefore the pressure to sleep increases in a positive correlation with the awake time. The circadian factor plays a role in the timing of the sleep; this means that there is a time of day that the probability to fall asleep is higher, for example, in the afternoon between 1 and 4 p.m. and at night between 0 and 4 a.m. The interaction between these two factors will determine the timing and length of sleep [1].

Circadian rhythm sleep disorders (CRSDs) are a group of sleep disorders characterized by an asynchronization between a person's biological clock and the environmental 24-h schedule. These disorders can lead to harmful psychological and functional difficulties and are often misdiagnosed and incorrectly treated due to the fact that physicians are unaware of their existence. In the current chapter we describe the characteristics of CRSDs, its diagnosis and treatment, as well as the relationship to daily dysfunction and disabilities.

The timing and length of sleep display large interindividual differences in human behavior. Sleep and wake times show a near-Gaussian distribution in a given population, with extreme early types (larks) waking up when extreme late types (owls) fall asleep. This distribution is predominantly based on differences in an individual's circadian clock. Circadian rhythm sleep disorders (CRSDs) are caused by disruption of the synchronization of the endogenous circadian rhythm system and the external 24 h of the dark-light period of the earth. Almost by definition, a CRSD involves an abnormality in the timing of sleep relative to the conventional circadian phase for sleep.

Six distinct CRSDs were characterized and are currently recognized in the International Classification of Sleep Disorders (ICSD-3) [2]: delayed sleep-wake phase disorder (DSPD), advanced sleep-wake phase disorder (ASPD), irregular sleep-wake phase type (ISWR), non-24 h sleep-wake rhythm disorder, jet lag type (JLD), and shift-work type (SWD) [2]. The prevalence of CRSDs is unknown;

although if we take into account the enormous number of people who do shift-work or fly, it must be high. There are very limited community-based epidemiological studies of CRSDs [3, 4]. A clinical experience review regarding the proportion of CRSDs by Dagan and Eisenstein [5] found that DSWPD was the most common CRSD diagnosis, followed by non-24 h sleep-wake rhythm disorder; on the other hand, ASWPD and ISWR were very rarely diagnosed, accounting for less than 2% of the CRSD patients.

14.2 Assessment and Measurements of CRSD

14.2.1 Sleep Logs/Diaries

The sleep-wake cycle is a rough indicator of circadian phase, but it is strongly influenced by homeostatic sleep drive, as well as many other factors that make unclear or "mask" the underlying circadian signal. Sleep logs/sleep-wake diaries are consistently recommended as a method for evaluating sleep schedules in CRSD patients; however, there are no widely accepted, standardized sleep logs, and investigators and clinicians often construct their own. Sleep logs have apparent face validity and can provide data on qualitative as well as quantitative aspects of sleep. Although they are commonly used in sleep clinics, the reliability or validity of sleep logs and sleep diaries has not been tested as a clinical assessment tool for CRSDs.

14.2.2 Actigraphy-Watch Monitoring

The common and standard biological method for assessing the circadian rhythm is to assess the rhythm of rest and activity, using an actigraphy watch. Actigraphy monitoring is the recommended and the best manner for assessing CRSD; sleep polysomnography is not applicable to assess CRSD. The measurement is done with a small watch-like device that is equipped with motion and light sensors and is usually placed on the wrist of the nondominant hand. In general, the actigraphy and sleep diaries/logs are collectively used in the diagnosis of CRSD because they allow measuring sleep in both an objective and a subjective manner. Several studies have demonstrated that human wrist activity often shows a robust circadian pattern. Morgenthaler et al. [3] reported that the circadian period of the actigraph-defined sleep/wake rhythm accurately predicted the period of the PSG-defined sleep/wake rhythm, measured simultaneously. Actigraphy provides an accurate estimation of the sleep and wakefulness cycle that can be readily obtained over multiple sleep cycles and is thus very useful for the longitudinal assessment of sleep patterns or rhythm disturbances. The use of actigraphy for evaluation of sleep and wake cycles is a common practice in sleep labs when there is a need for an objective way to assess CRSD. In practice, actigraphy monitoring should be performed for a period of 1 week (at a minimum) to 2 weeks, in "free condition"—the patient is free to go

to sleep and wake up according to his own choice without any obligation (e.g., work, study).

14.2.3 Questionnaire

The "Morningness-Eveningness Questionnaire" (MEQ), developed by Horne and Ostberg in 1976, aimed to determine when the respondent's natural tendency to be active lies during the daily temporal span [6]. The MEQ has become a widely used instrument to classify circadian tendencies in studies of normal subjects as well as patients. The MEQ score is often assumed to be correlated with core parameters of human circadian organization such as the timing of sleep [7, 8] and possibly an endogenous circadian period [9]. Another questionnaire, the Munich Chronotype Questionnaire (MCQ), was developed to assess morning and evening preferences [10, 11].

For research and not clinical needs, circadian rhythms can be quantitatively estimated by the measurement of the clock-controlled physiological processes. Such measurements include the onset of melatonin secretion in the dark (dim light melatonin onset—DLMO), daily changes in the concentration of 6-sulphatoxymelatonin (6-SMT) in the urine, and the circadian rhythm of core body temperature.

14.2.4 Patient's Medical History by Physicians

Patients need to be asked about the chief circadian sleep wake symptom: time onset of routine activity in the patient's daily life (wake time, daily activities, daytime napping habit, activities before sleep, time to go to bed, activities in bed before falling asleep, and sleep description), alertness during the day, timing of hunger and eating habits, timing of best cognitive performance, preferred sleeping time during vacation in order to assess the natural sleeping time, family history with sleep and CRSD disturbance, and type and amount of drugs and alcohol consumption during the day. Patients are suggested to keep a sleep diary or sleep logs for a 1- to 2-week period.

In sum, the best method to make the diagnosis of CRSD is by a clinical interview and 1-2 weeks of actigraphy monitoring or sleep log in free schedule conditions.

14.3 Risk Factors of CRSD

14.3.1 Head Trauma

Minor traumatic brain injury (mTBI) might contribute to the emergence of circadian rhythm sleep disorders. One-third of the patients with complaints of insomnia following mTBI were diagnosed with CRSD of DSWPD and IRSWD types.

14.3.2 Age

Although there are few reports that ASWPD is associated with older age and DSWPD is associated with the age of adolescence, we did not find that age is a risk factor for CRSD. We may suggest that the circadian system endures some changes over the course of the life cycle.

14.3.3 Gender

We found no evidence suggesting any gender differences in CRSD, or that gender might be a risk factor for CRSD per se.

14.3.4 Drugs Side-Effect

Several studies found that administration of antipsychotic drugs such as haloperidol or fluvoxamine can induce CRSD such as DSWPD [12, 13].

14.3.5 Exposure to Artificial Light at Night (ALAN)

Negative physiological outcomes due to exposure to artificial light at night (ALAN) have been a focus of research in the last two decades. Results of studies in recent years show a wide range of ALAN effects, arising from indoor and outdoor lighting, on the human biological clock. Such effects include pineal melatonin suppression, changes in body temperature regulation, and development of circadian and other sleep disorders [14–20]. Modern living styles characterized by nocturnal living patterns, shift-time work, and working in offices with little variation in illumination throughout the day and night may also induce disorders in biological rhythm. Moreover, in recent years several studies found that exposure to ALAN illumination from digital media devices can disrupt circadian rhythm. Green et al. [21, 22] report that exposure to illumination prior to bedtime interfered with markers of human chronobiology known to play a role in sleep regulation. We noted that ALAN from digital media devices suppressed both secretion of melatonin and normative thermoregulation. Therefore, continuous exposure to nighttime illumination from digital media devices may be a risk factor to developing sleep or sleep/wake circadian disorders. It is well-established in the sleep literature that targeted exposure to bright ALAN can delay sleep onset and melatonin secretion [14–16, 23, 24], and therefore is considered an effective treatment for circadian rhythms sleep disorders [25, 26]. In our opinion, extended exposure to light from digital screens at night is in practice a form of unintended “light therapy” that affects the circadian clock and its derivatives and consequently influences sleep capacity and quality.

14.4 Advanced Sleep Wake Phase Disorder (ASWPD)

Advanced sleep phase disorder (ASWPD) is characterized and defined by a stable sleep schedule that is several hours earlier than the conventional or desired time. There is no standard for how much earlier a sleep schedule needs to be in order to qualify as pathological. Diagnosis depends on the amount of discomfort the patient expresses about being unable to adapt to a more conventional sleep schedule after ruling out other causes of sleep maintenance insomnia. The prevalence of ASWPD is about 1–2% and ASWPD is thought to be much less common than DSPD, but because an early sleep pattern results in fewer social conflicts the incidence may be underestimated. The mechanisms leading to this condition are unknown, but hypotheses have usually been the opposite of those thought to underlie DSWPD.

Diagnosis of ASWPD is characterized by an advance in the phase of the major sleep period in relation to the desired sleep and wake times; individuals with this condition would be predicted to score as morning types (M-type) with high values on the MEQ. Several studies report ASWPD patients scored high on the MEQ indicating morning-lark traits [27–29]. Age is associated with increased ASWPD with age; several studies using the MEQ questionnaire found that age was associated with morningness type of sleep-awake schedule (M-type) [30, 31]. There are no gender differences associated with ASWPD according to available data.

A few years ago, a young girl (age 11) was referred to our sleep clinic. Her mother described an unusual sleep-wake schedule; according to the mother's description, the girl sleeps once she comes home from school until the middle of the night. An actigraphy recording for a week, in free-schedule condition, showed that the girl is falling asleep at 3–4 p.m. and waking up at 1–2 a.m. This type of ASWPD is very extreme, leading to social isolation and psychological distress since her ASWPD does not leave this young girl any free time, or time for social interaction with her friends in addition to long hours alone and awake at night. Since treatment of ASWPD includes bright light therapy given as close to sleep time as possible, this might delay sleep onset. In addition, melatonin should be taken in the morning. We prescribed treatment of light therapy with a light box during the afternoon (4–5 p.m.) and melatonin administration in the morning (Fig. 14.1).

14.5 Delayed Sleep Wake Phase Disorder (DSWPD)

Delayed sleep phase disorder (DSPD) is characterized by a stable sleep schedule that begins substantially later than the conventional or desired time (2–4 a.m.), and by the inability to fall asleep and awaken at a desired time, leading to significantly later sleep onset and wake times (10 a.m.–12 p.m.). The first description of the disorder was by Weitzman and colleagues [32]. The pathophysiology of DSWPD is attributed to longer τ (see Chap. 3), misaligned phase relationship between endogenous clock and sleep-wake cycles, reduced photic entrainment, and/or altered sleep homeostasis. Patients suffering from DSWPD are often required to rise early in the morning in order to adhere to domestic, school, or job obligations. Due to late sleep

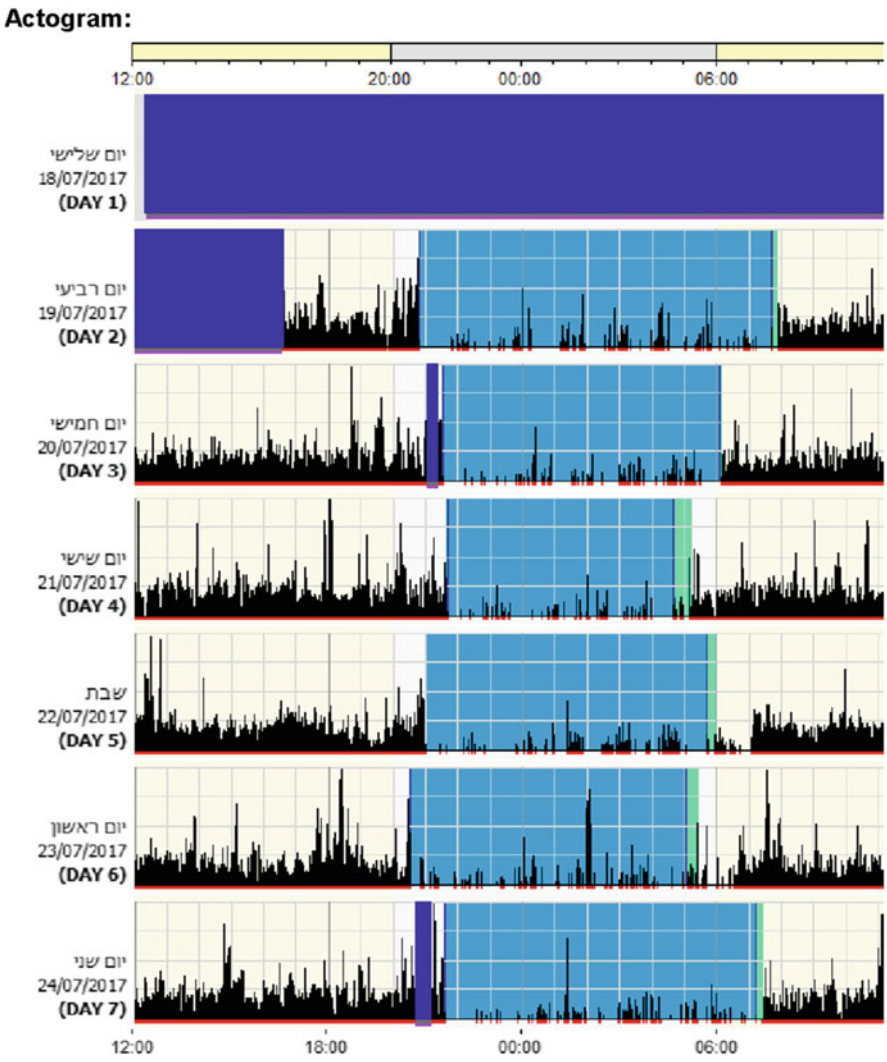

Fig. 14.1 Actigraphy recording of advanced sleep wake phase disorder (ASWPD) patient

onset, chronic sleep loss is, therefore, a common consequence. DSWPD has been shown to have high comorbidity with other conditions, such as depression, hypochondria, and personality disorders [33]. Patients with DSWPD have sleep onset insomnia and extreme difficulty arising when they attempt to conform to a conventional work schedule or other social demands. A tendency for a delayed sleep schedule is very common during teenage years; nevertheless, this seems to be an outcome of social interaction rather than physiological trait. Psychophysiological insomnia must be ruled out as a cause for the sleep onset insomnia characteristic of DSWPD. Weitzman et al. [32] proposed that a significant number of patients with

sleep onset insomnia may have underlying DSWPD, but this hypothesis has not been systematically pursued. We tend to agree with Weitzman et al.'s [32] claim that since both disorders, DSWPD and insomnia, exhibit prolonged sleep onset, some clinician's may misdiagnosis DSWPD as insomnia. The differential diagnosis between DSWPD and insomnia is important for precise therapeutic intervention, since Insomnia should be treated with psychological treatment such as CBT-I or hypnotic treatment, while DSWPD is conventionally treated with melatonin and light therapy. The etiology of DSWPD is unknown, and it is unclear whether this is a manifestation of intrinsic pathology or a socially reinforced sleep-wake schedule that can be readily modified if circumstances require it. There is solid evidence that melatonin administered 2 h before the desired sleep time to promote a corrective phase advance is an effective treatment for DSWPD. Light therapy with bright light in the morning at close to waking appears to be a reasonable and effective intervention for DSWPD (Fig. 14.2).

14.6 Irregular Sleep-Wake Rhythm (ISWR)

Irregular sleep-wake rhythm (ISWR) is characterized by the relative absence of a circadian pattern to the sleep-wake cycle. Total sleep time may be comparatively normal, but instead of being consolidated into a distinct bout or bouts, sleep times are shortened, and in extreme cases, almost randomly distributed throughout the day and night. ISWR is commonly associated with neurological impairment, such as mental retardation in children and dementia in older adults. The cause (or more likely, the causes) of this association are unknown, but damage to the circadian pacemaker in the suprachiasmatic nucleus (SCN) is clearly implicated as an important, if not a major, etiological factor.

A 47-year-old male was admitted to the Institute for Fatigue and Sleep Medicine complaining of severe fatigue and daytime sleepiness. He described a gradual evolvement of an irregular sleep-wake pattern within the past 20 years, causing marked distress and severe impairment of daily functioning. A 10-day actigraphy record revealed an ISWR pattern with extensive day-to-day variability in sleep onset time and sleep duration. In addition, melatonin level and oral temperature showed abnormal patterns. A further investigation of the patient's daily habits and environmental conditions revealed two important facts. First, his occupation required work under a daylight intensity lamp (professional diamond-grading equipment of more than 8000 lux), and second, since the patient tended to work late, the exposure to bright light occurred mostly at night. To recover his circadian rhythmicity and stabilize his sleep-wake pattern, we recommended combined treatment consisting of evening melatonin administration combined with morning (09:00) bright light therapy (8000 lux for 1 h), plus the avoidance of bright light in the evening. A follow-up 10-day actigraphy monitoring done 1 month after initiating the combined treatment protocol revealed stabilization of the sleep-wake pattern with advancement of sleep phase. In addition, the patient reported profound improvement in maintaining wakefulness during the day. This case study shows that chronic

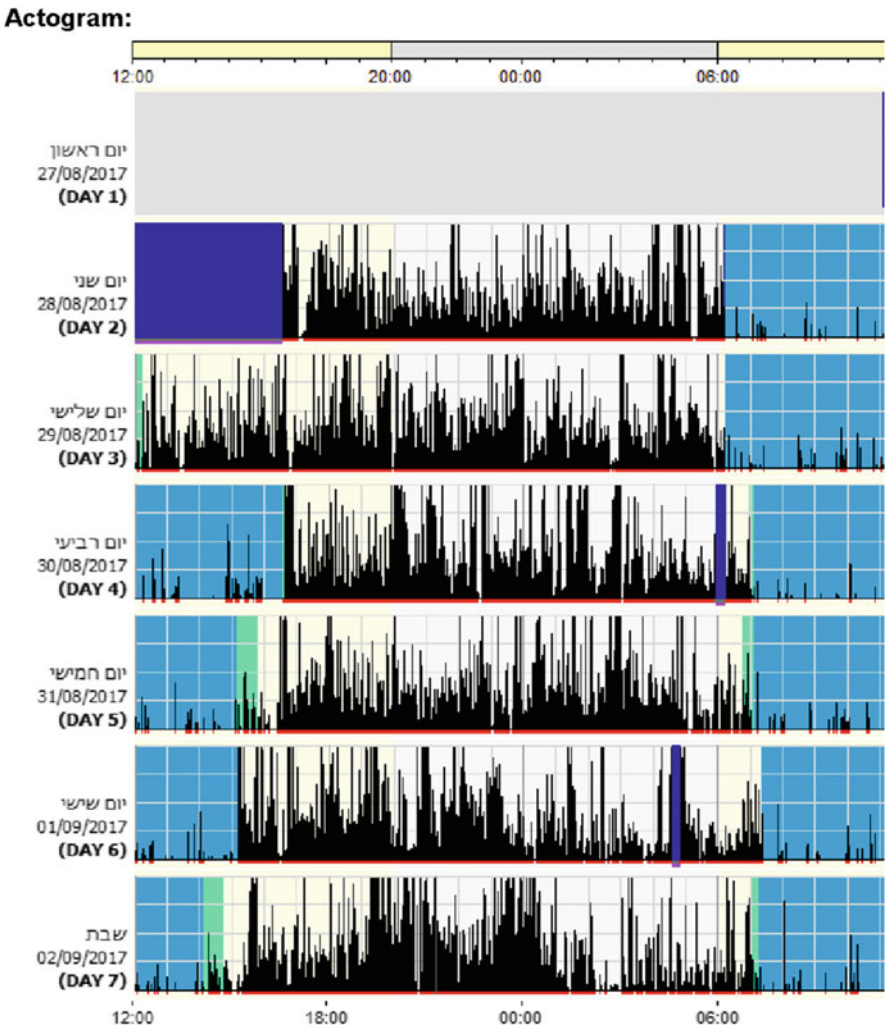

Fig. 14.2 Actigraphy recording of DSPD patient

exposure to bright light at the wrong biological time, during the nighttime, may have serious effects on the circadian sleep-wake patterns and circadian time structure. Therefore, night bright light exposure must be considered to be a risk factor of previously unrecognized occupational diseases of altered circadian time structure manifested as irregularity of the 24-h sleep-wake cycle and melancholy (Fig. 14.3).

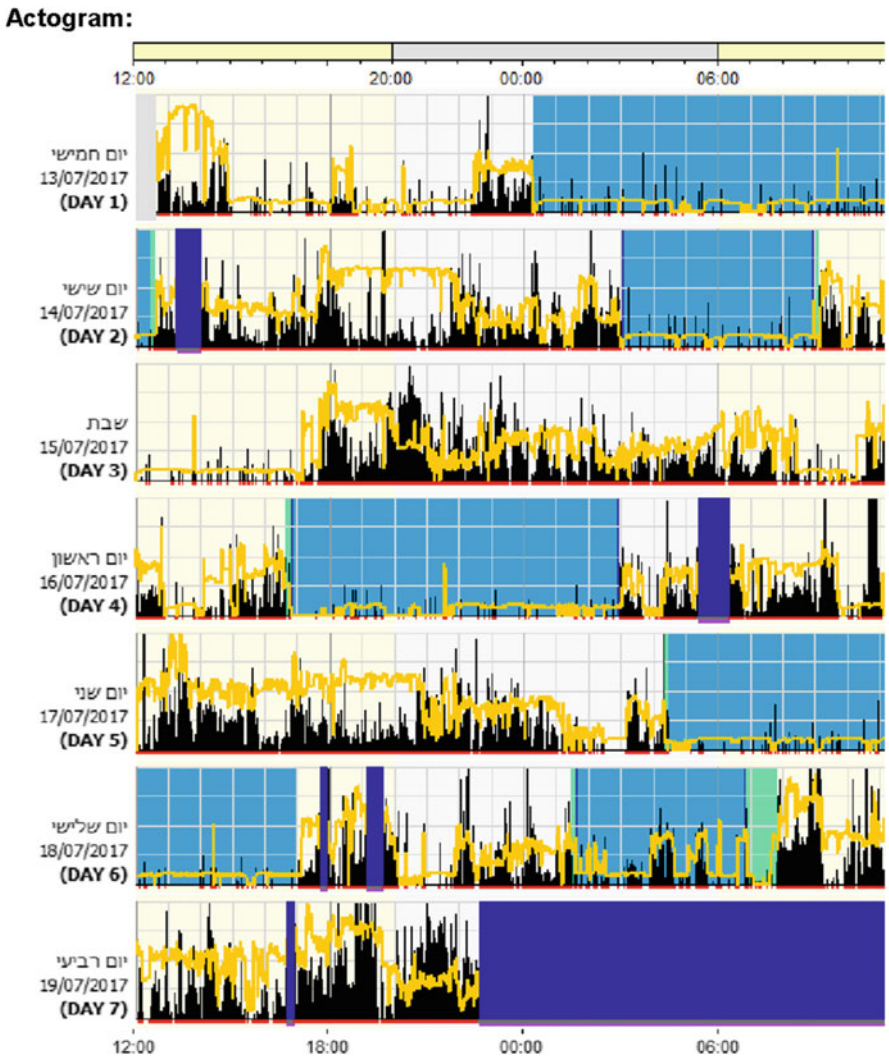

Fig. 14.3 Actigraphy recording of patient with irregular sleep-wake rhythm (ISWR) disorder

14.7 Non-24 h Sleep Wake Rhythm Disorder (NSWRD)

The human circadian period is usually longer than 24 h; the earliest studies of human subjects in free environments concluded that most people have an intrinsic circadian period longer than 24 h, averaging about 24.2 h [34]. Patients with free-running rhythms have circadian cycles that mimic those of subjects in time-free environments, and thus are thought to reflect a failure of entrainment. The condition

is very rare in normally sighted people, but quite common in the totally blind who have no access to the entraining effects of the light/dark cycle [35]. Roughly one-fourth of sighted individuals with NSWRD have related psychiatric diagnoses. Appropriately timed melatonin doses from 0.5 to 10 mg have been shown to entrain totally blind people who have NSWRD.

Dagan and Ayalon [36] reported about a 14-year-old male suffering from significant academic and personal difficulties, who had been diagnosed with depression, schizotypal personality disorder, and learning disabilities. Because of excessive sleepiness, assessment for a potential sleep disorder was performed. An overnight polysomnographic study revealed no primary sleep disorders. Wrist actigraphy revealed an NSWRD (non-24-h sleep-wake pattern). Delay in temperature rhythm and dissociation from melatonin rhythms were also noted. Treatment with oral melatonin restored normal sleep-wake schedule. In a follow-up psychiatric evaluation, none of the above diagnoses were present. This case, from our point of view, is an excellent example how the difficulties to adjust the normal requirements of the society, being awake and active during daylight hours and to sleep during night time, is problematic for CRSD patients in general, and in this case for this young boy with NSWRD. These difficulties in adjusting to the social norm may be misdiagnosed by physicians and psychologists as a psychiatric and/or psychologic disorder and leads to not suitable treatment (Fig. 14.4).

14.8 Shift Work Disorder (SWD)

Shift work refers to nontypical work schedules, including permanent or intermittent night work, early morning work, and rotating schedules. Shift work has become a common practice in the modern Western world and it is estimated that about 15–20% of the workers are working shift-work schedules. There is common agreement that shift-work is associated with a number of health problems, for example, poor sleep, gastrointestinal disorders, abnormal metabolic responses, and increased risk of accidents. Disturbed sleep is perhaps the most dramatic and dominant result of shift-work. A number of survey studies have shown that shift workers have sleep complaints, mainly maintaining sleep after the night shift and initiating sleep before the morning shift [37, 38]. The major effect on sleep architecture is reduced stage 2 and rapid-eye movement (REM) sleep with minor effect on slow wave sleep (SWS). In addition, sleep latency is positively associated with morning shift and is shortened after night shift. Several studies have reported that shift workers report more sleepiness and fatigue than do daytime workers [39, 40]. As with sleepiness, the main reason for night shift deterioration in performance is circadian rhythmicity and sleep loss [41, 42]. Several studies showed decreased performance in parameters of capacity, accuracy, and quality of workers during the night shift [43–45]. In sum, several lines of evidence suggest that rotating shift work might directly or indirectly contribute to decrements in cognitive function.

A long-term risk of major disease such as heart disease and cancer are beginning to be appreciated. Recently, rotating night shifts have been linked to adverse health

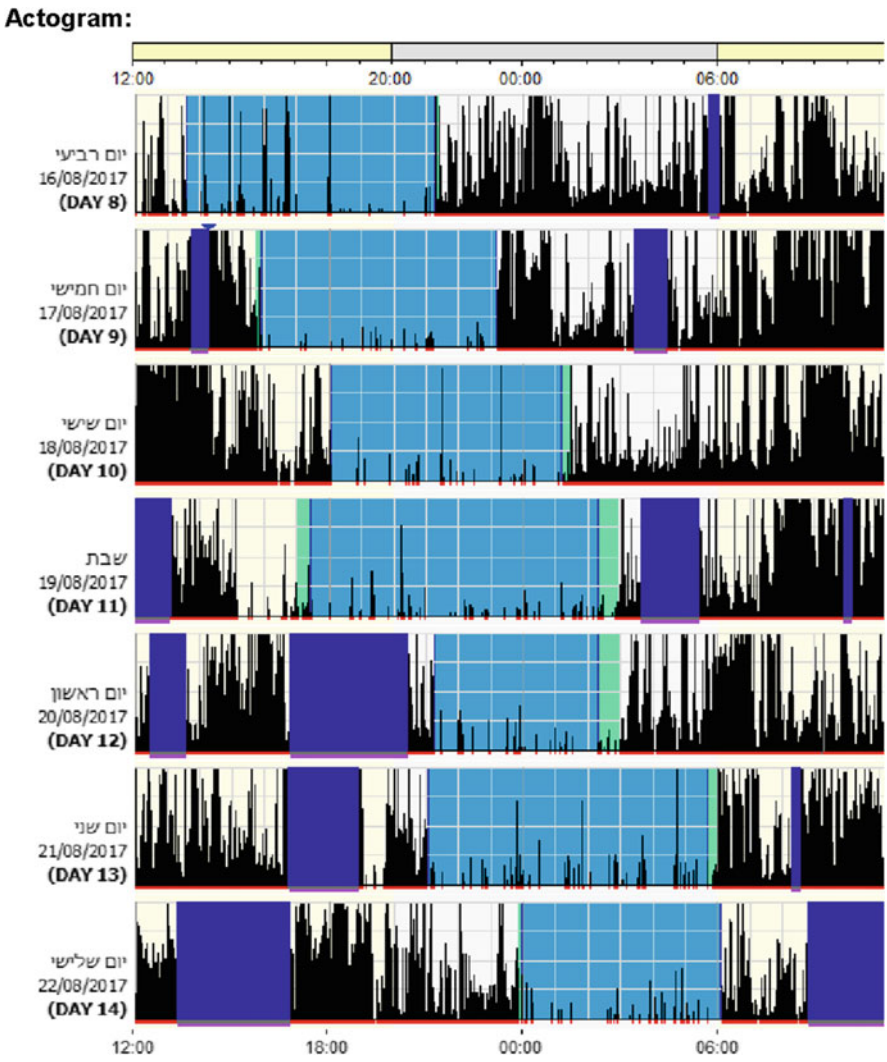

Fig. 14.4 Actigraphy recording of patient with non-24 h sleep wake rhythm disorder (NSWRD)

outcomes, including obesity, type 2 diabetes, and cardiovascular disease [46]. Moreover, Koller [47] noted that reduced health appeared to be earlier among shift workers than among day workers, reflecting the effect of long-term stress due to shift work hours.

Several factors influence the adjustment to shift work. One such factor is the direction of rotation of the shift schedule. A previous study reports that phase delay is easier to accomplish than phase advance [48]. In addition, the length of the work shift is another parameter that influences sleepiness and performance. Moreover, apparently, a rotating shift work schedule causes greater disturbance to the

individual than does an unchanging work schedule. The trait of morningness (the propensity toward preferring morning sleep-wake) has frequently been associated with poor adjustment to shift work [41, 44]. This has also been the case for the trait of sleep rigidity [49]. Finally, inappropriate light exposure during night shifts, which can disrupt circadian rhythm, might adversely affect shift workers' health and performance [50, 51].

14.9 Jet Lag Disorder (JLD)

Jet lag disorder (JLD) is a transient circadian rhythm disorder related to travel across time zones in which there is a discrepancy between the timing of the sleep and wake cycles generated by the endogenous circadian clock and the environmental clock (day-night) in the new time zone. Jet lag results from the new time zone of a biological clock unadjusted to the environmental clock. This absence of rapid adjustment results in loss of sleep at night, and all the daily (circadian) rhythms that are controlled by the body clock are inappropriately phased.

Why does it happen? A recorded rhythm can be regarded as a mixture of components because of effects of the body clock (the endogenous component) coupled with effects of the individual's environment and lifestyle (the exogenous component). These components are usually synchronized, but this synchronicity is lost in the days after a time-zone transition, since, unlike the exogenous component, the endogenous component has not adjusted. Therefore, explicit circadian rhythms will adjust to time-zone transitions at different rates. Those with a larger exogenous component, for example, food intake and physical activity, will seem to adjust more rapidly than those with a larger endogenous component, for example, sleep, mood, and mental performance.

When several (usually three or more) time zones are crossed, JLD is noticed. The subjective symptoms of JLD usually occur within 1-2 days after travel and include a complaint of insomnia or excessive daytime sleepiness and may also include general malaise, somatic symptoms, or other impairments of daytime function. The severity of JLD increases with the number of time zones crossed in flight. In addition, JLD severity of symptoms is positively associated with age for older travelers. Travelers with rigid sleeping habits had more symptoms of JLD than did those with less rigid sleeping habits. Moreover, the incidence and severity of JLD symptoms depends on the direction of the time-zone transition—flights to the east are associated with more JLD than flights westward. JLD symptoms include poor sleep during the new night-time, including delayed sleep onset (after eastward flights); early awakening (after westward flights); fractionated sleep (after flights in either direction); poor performance during the new daytime at both physical and mental tasks; negative subjective changes, which include increased fatigue, frequency of headaches and irritability, and decreased ability to concentrate; gastrointestinal disturbances (indigestion, the frequency of defecation, and the consistency of the stools); and decreased interest in, and enjoyment of, meals.

The best way to lighten JLD is by adjustment of the body clock. The main zeitgebers in individuals are the light-dark cycle and the nocturnal secretion of melatonin. Sleep, physical activity, and food intake have also been implicated. The effects of light exposure and melatonin secretion act to synchronize the body clock with the sleep-wake and light-dark cycles.

Treatments for JLD include: (1) The combination of morning exposure to bright light and shifting the sleep schedule 1 h earlier each day for 3 days prior to eastward travel may lessen symptoms of JLD. (2) Melatonin administered at the appropriate time is indicated to reduce symptoms of JLD and improve sleep following travel across multiple time zones. (3) Short-term use of a sleeping hypnotic is optional for the treatment of jet lag-induced insomnia.

14.10 Types of Treatment for CRSD

14.10.1 Light Therapy

Light therapy is a treatment method in which the therapeutic effect results from exposure to bright light. It is considered the method of choice for the treatment of seasonal affective disorder (SAD) and is often used to treat circadian rhythm disorders. It has been well-established that the solar light-dark cycle is the primary environmental time cue for synchronizing the circadian system of most living plants and animals to the 24-h day. Light/dark cycles are the most common zeitgebers (time keepers) for terrestrial animals, and play an important role in the entrainment of the circadian clock within the SCN. External light cues are transmitted via retinal non-image-forming photoreceptors to the SCN via the retinohypothalamic tract [52, 53].

One of the major functions of the SCN is to regulate the production and secretion of the circadian neurohormone melatonin (MLT) by the pineal gland. MLT production is inhibited by light during the day and facilitated during darkness at night, so that the majority of melatonin secretion takes place in the hours of darkness [14]. In synchrony with MLT secretion is the circadian core body temperature (CBT) rhythm, which peaks in the afternoon, gradually declines in the time for sleep at night, and remains low until the early morning hours. CBT has also been shown to be regulated via transmission of nonvisual information to the anterior hypothalamus by means of preoptic nerves [54, 55]. In sum, light/dark cycles seem to play an important role in relaying external information to the SCN, thereby synchronizing a range of circadian rhythms to each other and the external environment.

The light exposure schedule, intensity, and wavelength, and history of light exposure affect the size and direction of the phase shift of the circadian rhythm caused by exposure to light. Exposure to bright light in the morning causes an advance in the circadian rhythm. In contrast, exposure to bright light in the evening or at night will lead to delay in the circadian phase. In sum, bright light just after waking up, and/or in the last 2 h of the sleep period, causes a circadian phase advance, while the light therapy exposure in the evening/nighttime will cause a circadian phase delay. Another major factor for the success of the light therapy is the

duration and intensity of the light. In practice, with lamps with light intensity of 2500 lux, the recommended exposure duration is generally 2 h, while for those with light intensity of 5000–10,000 lux, 30 min of exposure is sufficient. In clinical practice, patients might not routinely follow instructions as precisely as prescribed. Therefore, the effectiveness of light therapy in clinical practice is usually lower than that observed in empirical studies. The circadian clock is very sensitive to short wavelength; it has been demonstrated that the retinal photoreceptors involved in the regulation of the circadian rhythm containing melanopsin are most sensitive to blue light with a wavelength of 480 nm. Several studies found that exposure to light in short wavelengths (460–480 nm) can affect circadian phase and sleep. It is also important to explain in what part of a 24-h period one should avoid artificial light, especially that emitted by computer screens, TV screens, tablets, and smartphones [56]. DSWPD patients should not use such devices 2 h before their usual bedtime, and not stay in brightly lighted rooms as well. Conversely, patients with ASWPD should not be exposed to artificial light from digital media screens after awakening at night, because it may result in further phase advance of their sleep-wake rhythm [22, 56].

14.10.2 Melatonin Treatment

A variety of doses of melatonin have been given to subjects for phase shifting. The threshold for a chronobiological effect occurs at physiological blood levels (about or below 50 pg/mL). The common doses for treatment of CRSD are usually between 3 and 5 mg/day. Recent studies suggest that timing of taking the pills is more important than the dose itself [57]. There may be some synergistic effect when light and melatonin are used to promote shifts in the same direction. Studies on biological markers implicated in circadian rhythms have established the optimal timing of melatonin and/or light therapy administration. These studies [58, 59] showed that the largest phase shift occurs when melatonin and light therapy are applied in concordance with DLMO occurrence and a core body temperature minimum. Revell and her colleagues [60] demonstrated that a combination of a gradual advancement of the sleep schedule (wake time 1 h earlier each morning) combined with bright light upon awakening and melatonin (0.5 or 5 mg) in the afternoon, induced a maximal phase advance while maintaining circadian alignment, suggesting a synergistic effect of the treatments. In sum, the robust phase advance occurs when melatonin is administered at least 10 h before a usual time of getting up and light therapy is used during the last 2 h of the usual sleep period. The strongest phase delay occurs when melatonin is administered in the last 2 h of the usual sleep period and light therapy is used during the first half of a usual sleep period.

14.11 Psychological, Behavioral, and Cognitive Consequences of CRSD

14.11.1 Psychological and Emotional Aspects

Several studies report that patients having CRSD are at high risk to suffer from psychological distress, mainly since they suffer from difficulty to adjust to general and common hours of activity. DSWPD patients, for example, have been reported to shown high comorbidity with depression, hypochondriasis, and personality disorders [61, 62]. In addition, patients with DSWPD are shown to have an elevated score on the Minnesota Multiphasic Personality Inventory–Second Edition [61, 63]. In one study, the DSWPD group scored higher than the control group on anxiety and depression assessments [64]. Studies have shown a consistent association between eveningness and depressive symptoms and/or depressive disorder [65–68]. Eveningness was associated with an increased risk of depression, even after adjusting for sleep-related factors (Kitamura et al. 2010). Furthermore, eveningness and insomnia were recently found to be independent predictors of non-remission in depressed patients [69]. A study designed to examine whether sleep problems (daytime sleepiness, insomnia, and circadian misalignment) mediate the association between eveningness and negative emotionality found that eveningness was an independent risk factor for negative mood [70]. Similarly, eveningness and subjective sleep quality were independent risk factors for increased depressive symptomatology, and sleep quality failed to explain the link between eveningness and depressive symptoms [71]. Along the same lines, we previously found that the evening type was associated with clinically diagnosed major depression [65]. In addition, Costa and McCrae [72] showed that young adults with DSWPD scored higher on neuroticism and lower on conscientiousness compared to the control group. The neuroticism dimension represents the individual's tendency to experience psychological distress, and most psychiatric conditions yield elevated scores on neuroticism. The low scores on the conscientiousness dimension, according to the authors, may explain the notion that some patients with DSWPD are difficult to treat, noncompliant with light therapy and melatonin administration, and become school or academic dropouts. In a recent study performed by Micic et al. [73], DSWPD and NSWRD patients showed higher neuroticism compared to control, and significantly lower extraversion, conscientiousness, and agreeableness. Conscientiousness was associated with phase timings of circadian rhythms and lifestyle factors within the DSWPD patients. According to the authors, these findings suggest that CSRD may not only stem from circadian abnormalities, but personality factors may also drive lifestyle [73]. A good example of how complicated and tricky the association between CRSD and psychological state might be can be understood by this example: Several years ago, a young boy was referred to our sleep institute from day-care hospitalization of the psychiatric clinic. This 14-year-old male was suffering from significant academic and personal difficulties, had been diagnosed with depression, schizotypal personality disorder, and learning disabilities. Because of excessive sleepiness, assessment for a potential sleep disorder was performed. An overnight

polysomnographic study revealed no primary sleep disorders. Wrist actigraphy revealed a non-24-h sleep-wake pattern. Delay in temperature rhythm and dissociation with melatonin rhythms were also noted. Treatment with oral melatonin restored normal sleep-wake schedule. In a follow-up psychiatric evaluation, none of the above diagnoses were present. Greater awareness of sleep disorders may prevent psychiatric misdiagnosis of treatable sleep-wake schedule disorders. In sum, a major difficulty and challenge facing CRSD patients is their effort to adjust the norms of awake-active during daytime and sleep in the night-time of the society. A failure to do so may lead to mood disorder such as anxiety, depression, and decrease in self-esteem of CRSD patients. In addition, lack of awareness to the symptoms CRSDs among physicians, psychologist, and parents of children with CRSD can cause misdiagnosis of the CRSD. This mistaken diagnosis can lead to fault attribution of the difficulties to motivational and psychological factors instead of the real problem.

14.11.2 Attentional, Memory, and Cognitive Performance

Circadian differences in cognitive performance have been the subject of scientific investigation since 1885, when Ebbinghaus first reported a remarkable effect of the time of day on the efficiency of learning serial lists of nonsense syllables [74]. In general, human cognitive performances are best between 12.00 and 18.00 h, just before body temperature reaches its highest, and worst when temperature was lowest, between 04.00 and 06.00 h. More specifically, performance on cognitively complex tasks, especially those that require verbal reasoning and/or short-term memory, is highest in the morning and steadily declines during the rest of the waking day [75, 76]. Johnson et al. [72] found prominent circadian variations in the mean 24-h patterns of short-term memory, subjective alertness, and calculation performance during the constant routine. The patterns of subjective alertness and cognitive performance paralleled the body temperature cycle and reached their lowest point just after the minimum of temperature. These outcomes became apparent when overall performance on short-term memory tasks in fact paralleled the body temperature cycle [72]. On the other hand, other studies that disassociated the circadian variable found an effect to the sleep/wake factor were noted, meaning that sleep deprivation also affects the cognitive performance. It appears that cognitive performance is influenced by two interacting factors: an endogenous circadian process that is coupled to the temperature cycle, and the sleep/wake-related process.

A major factor on our cognition is the attention dimension. Dagan and Borodkin [77] state that the association between CRSDs and attention deficit disorder (ADD) and attention deficit/hyperactivity disorder (ADHD) should also be revealed. A relatively high prevalence (19.3%) of these disorders was reported in a large sample of patients with CRSDs attending a sleep clinic. In a retrospective study of 45 children and adolescents with DSPS (aged 6–18) who were treated with melatonin, almost half of the sample had a comorbid diagnosis of ADD or ADHD pretreatment.

Gamble et al. [78] conclude that ADHD symptom severity correlates with delayed sleep timing and daytime sleepiness, suggesting that treatment interventions

aimed at advancing circadian phase may improve daytime sleepiness and attention abilities. In addition, ADHD adults with combined hyperactive-impulsive and inattentive symptoms have decreased sleep quality as well as the delayed sleep timing of predominately inattentive subtypes. The understanding that sleep disorder in general, but CRSD specifically, can increase or impair symptoms of ADHD, and that good sleep hygiene improves attention and concentration tasks, has sparked interest in the investigation of possible etiological relationships between sleep disorders and ADHD. Recent studies indicate that one-third of children and two-thirds of adults with ADHD have symptoms of sleep disorders such as daytime sleepiness, insomnia, delayed sleep phase syndrome, and fractured sleep [79]. Treatment of adolescents suffering from DSWPD with melatonin was reported to improve not only the circadian disorder but also their academic performance [80]. A recent study in the Netherlands, conducted to evaluate whether the association between ADHD and Seasonal Affective Disorder was mediated by the circadian rhythm, found that late self-reported sleep onset was an important mediator in the significant relationship between ADHD symptoms and probable SAD, even after correction for confounders. This implies that treating patients with SAD for possible ADHD and delayed sleep onset time may reduce symptom severity in these complex patients [81]. In line with the above, a recent study reports high impulsive individuals displayed phase-delayed patterns of sleep, a decreased total sleep time and sleep efficiency, and disrupted circadian sleep-wake cycle [82]. These outcomes revealed the association between attention deficit hyperactivity disorder symptoms and sleep and circadian rhythm disturbances, and this may be associated with impulsive traits illnesses in which impulsivity is one of the core features of the ADHD disorder. In sum, we find reliable evidence for circadian rhythm disruption in ADHD and this disruption may present a therapeutic target for future ADHD research.

14.11.3 Behavioral and Physical Activity and CRSD

Consider, for example, a patient with DSPS who is expected to come to his workplace by 8 or 9 a.m. In order to fulfill this requirement, this individual is forced to wake up at what might be the middle of his internal night. It is not surprising, therefore, that he will frequently be late and/or absent, a pattern that will most likely subject him to disciplinary actions up to firing. If, however, he manages to meet the attendance standards, his performance will be subject to the detrimental effects of sleep loss and time of day. In childhood and adolescence, when CRSDs usually emerge, the impairment of daytime functioning can be even more remarkable than in adults. Unlike adults, who can at times choose a lifestyle that corresponds to their sleep-wake cycle, the activity hours of persons of younger age are constrained by a strictly predetermined school timetable. The inability to adjust to this timetable may be associated with deteriorated school performance.

Sleep deficiency due to either circadian rhythm sleep disorder or insufficient sleep duration is strongly associated with motor vehicle crashes in the general population, independent of self-reported excessive sleepiness [83, 84]. Patients that suffer from

CRSD tend to have insufficient sleep hours due to their irregular circadian sleep wake disorder. For example, DSPD patients tend to go to sleep late at night and therefore are more vulnerable to suffering from sleep loss. ASWPD patients in contrast tend to go to sleep early and they get sleepy and tired in the early evening. Patients with NSWRD and IRSD tend to have an unusual sleep schedule. All of these can lead to excessive sleepiness during the day and night hours and therefore put CRSD patients at a high risk for work accident and motor vehicle crashes.

There is evidence that many aspects of physical activity display circadian rhythms that are closely in phase with that of core body temperature. These aspects include peak force of muscle contraction, anaerobic power output, performance in long-jump and high-jump, and an individual's motivation to undertake sustained effort. Furthermore, sports that simulate contests or that involve timing skills, for example, swimming, football, and tennis, show circadian variation.

We believe that if we consider any CRSD as discrepancies between the inner-biological clock and the outer-environmental clock, we will expect to find decline and lower abilities and performance when the environmental clock is not in phase with their inner-biological clock. Some examples of human rhythms in disease processes include nighttime asthma, early morning increases in blood pressure, death rate from cardiovascular disease and stroke, and disrupted menstrual cycles. Thus, diagnostic tests should be aware of these rhythms. Measurement of a given rhythmic variable in someone who suffers from CRSD (DSWPD, ASWPD, NSWRD) or has just crossed several time zones (JLD), or worked several night shifts, can give false-negative or false-positive results. This means that if DSWPD patients are evaluated in early morning hours in psychological, behavioral, and cognitive tests, we will expect to find low abilities compared to evening assessment. In contrast, ASWPD patients will show better results in the early morning hours compared to evening-night hours.

14.12 Conclusion

Circadian rhythm sleep disorders (CRSDs) arise when an individual's sleep-wake rhythm does not match the environmental 24-h schedule.

Difficulties in daytime functioning are one of the prominent characteristics of CRSDs. Individuals with CRSDs frequently fail to adjust to the activity hours accepted in most social, occupational, and academic settings, due to incompatibility of their internal biological rhythms with the environmental timetable. Daytime functional difficulties that accompany CRSDs are frequently misinterpreted by parents, teachers, psychologists, and physicians as symptoms of psychopathology or maladaptive behavior. Although these disorders can be relatively easily diagnosed and treated, as mentioned, until now many cases of CRSDs are underrecognized and/or misdiagnosed and wrongly treated as psychiatric disorder, insomnia, maladaptive function due to excessive day somnolence or sleepiness. Consequently, these patients receive inappropriate treatment, such as hypnotics or stimulants, which can enhance the psychological distress and add to the adjustment difficulties

that accompany CRSDs. It is of great importance to raise the awareness of these disorders on the part of pediatricians, physicians, neurologists, psychiatrists, and psychologists.

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Behavioral Presentations of Parasomnias

15

Srikant Yadav and Ravi Yadav

Abstract

Parasomnias are defined as a group of sleep disorders that are characterized by abnormal, unpleasant motor, verbal, or behavioral events that occur during entry into sleep, within sleep, and during arousals from sleep. Hence unusual behavioral events are an integral part and parcel of these disorders. They may be associated with a variety of sensory, motor, and emotional phenomena that may mimic a number of other disorders, most commonly sleep-related hypermotor epilepsy. This chapter focuses on behavioral presentations of parasomnia and its differentiation with sleep-related hypermotor epilepsy.

Keywords

Parasomnia · Sleep-related hypermotor epilepsy · Differentiation

15.1 Introduction

The formal study of sleep medicine is a few decades old. The scientific understanding of the various neuronal circuits and neurotransmitters has paved the way for a better understanding of sleep medicine. Sleep-related behavioral problems have been known to humanity from time immemorial. The dream content during sleep has been a topic of many mythological stories in various cultures of the world. Parasomnias are a fascinating group of sleep disorders. Parasomnias are defined as a group of sleep disorders that are characterized by abnormal, unpleasant motor, verbal, or behavioral events that occur during entry into sleep, within sleep, and during

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Table 15.1 Classification of parasomnias according to International Classification of Sleep Disorders-3 (ICSD-3)

NREM-related parasomnias	REM-related parasomnias	Others
• Confusional arousals • Sleepwalking • Sleep-related eating disorder • Sleep terrors	• REM sleep behavior disorder • Recurrent isolated sleep paralysis • Nightmare disorder	• Exploding head syndrome • Sleep-related hallucinations • Sleep enuresis • Parasomnia due to a medical disorder • Parasomnia due to a medication or substance • Parasomnia, unspecified

arousals from sleep. Hence unusual behavioral events are an integral part and parcel of these disorders.

The term "parasomnia" was first used by a French researcher Henri Roger in 1932. This word is taken from the Greek word "para" meaning beside or along the side of and Latin term "somnus" meaning sleep [1]. The current classification given by International Classification of Sleep Disorders divides the parasomnias into REM related, NREM related, and others [2] (Table 15.1).

Understanding these parasomnias is vital for the clinicians as there are significant implications on the management in these conditions [3]. In this chapter, we discuss the behavioral presentation of parasomnias (Table 15.1). Each of these parasomnias is associated with some form of change in behavior, although the patterns of these changes need to be recognized by the clinician to reach a differential diagnosis.

15.2 History and Examination

The patients presenting with a history of parasomnia should undergo detailed history and examination. The history derived from the bed partner is of utmost importance and the abnormal behavior at night should be corroborated by the spouse. Particular attention should be paid to the semiology of the behavioral alteration, duration of the episode, the time elapsed since the first attack, any features of Parkinsonism (tremor, rigidity, bradykinesia, postural instability), any injury to bed partner, frequency of such attacks, and the medication history. Here the pattern of nocturnal behavior needs special attention. In case the patient is fearful, angry, aroused, aggressive, or appears in panic the implications are mainly the REM sleep behavioral disorder, nightmares, night terrors, and will need further probing about the timing of night and also associated injuries. The patients should be examined for the orthostatic hypotension, parkinsonian symptoms, injury marks, obesity, features of sleep-disordered breathing, pulmonary and cardiac abnormalities.

The patients should be investigated based on clinical suspicion. The patient may be evaluated by electroencephalogram, neuroimaging, video-polysomnography,

hemogram, renal functions, liver functions, pulmonary functions, and iron studies [2].

15.3 Differentiating Nocturnal Seizures from Parasomnias:

Effect of sleep on epilepsy: In epileptic patients, NREM sleep acts as a proconvulsant, causing excessive synchronization and activation of seizures in an already hyperexcitable cortex. In REM sleep, there is desynchronization of EEG coupled with an inhibition of interhemispheric transfer of impulses, causing attenuation of epileptiform discharges and limitation of propagation of generalized epileptic discharges to a focal area. Thus, REM sleep acts as an anticonvulsant. Sleep deprivation increases epileptiform discharges by causing sleepiness as well as by increasing cortical excitability. Approximately 10% of epileptic patients experience nocturnal seizures. The patient may present with violent episodic behavior at night or in the setting of harm/injury to someone or sleep partner. In such situations the physician may be asked to evaluate and opine. One has to take a thorough history and clinical examination followed by a video-polysomnography to document the episode. In our experience there is always a challenge in diagnosis when there is a forensic angle in the diagnosis. The availability of mobile video shot during the episode is beneficial [4] (Table 15.2).

15.4 What Is Sleep-Related Hypermotor Epilepsy (SHE)?

In the year 2014 during a consensus meeting of a group of epileptologists, sleep experts, and epidemiologists it was decided to describe the disorder "Nocturnal frontal lobe epilepsy" (NFLE) in a better way [5]. A new term "Sleep-Related Hypermotor Epilepsy (SHE)" was coined to replace NFLE (Table 15.3). The term "nocturnal" was replaced as these episodes were not only confined to night but also occurred during the day. As the origin in this type of epilepsy was not only frontal but also extra-frontal (temporal, parietal, etc.) parts of the brain so the "frontal" term was also abolished. Hence, SHE was identified as a distinct syndrome independent of the cause and the brain region involved. The diagnostic criteria included brief

Table 15.2 Physiological differences between NREM and REM sleep

NREM sleep	REM sleep
Promotes seizure	Protects from seizure
Synchronized thalamocortical activity of synapses	Desynchronized patterns of neuron discharges
Chances of spread of epileptic activity is higher	Less likelihood of propagation of ictal activity
Increased cortical and interhemispheric synchronizations	Inhibited thalamocortical synchronization Reduced interhemishpheric traffic

Table 15.3 Seizures that are characteristically observed during sleep

1.	Sleep related hypermotor epilepsy (SHE) (old nocturnal frontal lobe epilepsy (NFLE))
2.	Tonic seizure as a component of Lennox- Gastaut syndrome
3.	Benign focal epilepsy of childhood with rolandic spikes
4.	Juvenile myoclonic epilepsy
5.	Early- or late onset childhood occipital epilepsy
6.	Benign focal epilepsy with occipital paroxysms in EEG
7.	Generalized tonic-clonic seizures on awakening
8.	Nocturnal temporal lobe epilepsy (a sub group of partial complex seizures)
9.	Landau-Kleffner syndrome
10.	Panayiotopoulos syndrome

seizure attacks (<2 min), abrupt onset and offset, stereotypical nature, many attacks every night, "hypermotor" semiology, asymmetric tonic/dystonic posturing of body with a clearly suggestive history, and semiology of seizure.

SHE consists of approximately 13% of all the referrals to a tertiary care center for video PSG evaluation of nocturnal motor disorders. It is predominantly seen in males and the seizure onset is typically seen in childhood before 20 years of age. A genetic mutation of CHRNA4 gene of neuronal nicotinic acetylcholine receptor has been found to be associated with SHE. Also mutations in several other genes have been reported.

There is a clear difficulty for the clinicians in differentiating the parasomnia from SHE. Hence, a clinically validated scale was developed and named as Frontal Lobe Epilepsy and Parasomnia scale (FLEP). This scale is very useful but is unable to differentiate between nocturnal wandering from sleepwalking. There is another Structured interview for NFLE/SHE (SINFLE) that relies on the presence or absence of two major motor seizure patterns and other forms of important features (duration, aura, vocalization, sleep-related convulsive seizures).

Prognosis is variable. Those patients who have drug refractory seizures and have drug refractory seizures and have undergone epilepsy surgery have shown more than 70% seizure free rate over 5 years follow-up (Ref). Good prognostic factors are absence of brain disorders with normal intellect and normal neurological examination and typical SHE (100% having sleep-related seizure episodes) (Ref).

Carbamazepine is the drug of choice in the patients with SHE. Also oxcarbamazepine, acetazolamide, levetracetam, lacosamide, and nicotine patches have been found beneficial [5].

Among these seizure disorders, the frontal lobe seizures are the ones that need to be differentiated from parasomnias (see Table 15.4).

15.5 NREM Parasomnias (Disorders of Arousals)

The disorders of arousal have certain common features. They have recurrent episodes of awakening, inappropriate or absent responsiveness, partial or complete loss of recall for the event, and absence of any medical condition or drug abuse. The

Table 15.4 Differences between the nocturnal frontal lobe epilepsy, arousal disorders, and REM sleep behavior disorder

Characteristic	Sleep related hypermotor seizures (SHE)	Disorders of arousal	REM sleep behavior disorder
Age of onset	First or second decade	First decade	Fifth or sixth decade
Sleep stage	Non REM (N1/N2)	N3 (NREM)	REM
Timing of event	Anytime	1st third of sleep time	Last third of sleep time
Duration of event	5–60 s	2–30 min	Seconds to 2 min
Frequency	Night clusters	Sporadic	Sporadic
Onset/offset	Sudden	Gradual	Sudden
Semiology	Highly stereotyped, hypermotor, asymmetric tonic/dystonic	Not stereotyped	Not stereotyped, vocalization, dream recall
Consciousness	Preserved usually	Variable	Poorly responsive
Post ictal confusion	Absent	Present	Absent
Risk of body injury	Low	High	Moderate
Video-polysomnography	Epileptic discharges <50%	Slow wave sleep arousals, rhythmic delta	REM sleep without atonia

patient may remain confused or disoriented for many minutes after the episode [1, 6, 7]. The disorders of arousal are as follows:

1. Confusional arousals
2. Sleep terrors
3. Sleepwalking

15.5.1 Confusional Arousal

This is diagnosed by the presence of broad features of disorders of arousal along with the episodic confusing behavior in the bed and absence of terror or ambulation outside the bed. A typical episode often starts with an individual sitting up in bed and looking around in the confused manner. There is a lack of autonomic arousal such as mydriasis, tachycardia, tachypnea, and diaphoresis during the event.

15.5.2 Sleep Walking

Sleepwalking is diagnosed by the presence of general criteria for arousal disorder along with the ambulation and other complex behaviors out of bed. The event begins as a confusional arousal, the individual then leaves the bed and starts walking or running. Highly inappropriate, agitated, aggressive, or violent behavior can also

occur. Behaviors can be simple and non-goal directed or complex and protracted and may involve inappropriate sexual activity with oneself or an individual close. The ambulation may terminate at inappropriate places or may return back to bed, lie down, and continue sleep without reaching conscious awareness at any point. The sleep walking individual is disoriented to time and place, with slow speech and severely diminished mentation and blunted response to questions or requests. There is prominent antegrade and retrograde memory impairment associated with the impairment.

15.5.3 Sleep Terrors

This is also known as night terrors/pavor nocturnus. This is characterized by an episode of abrupt terror which begins with a loud scream which is frightening. This is associated with intense fear and increased autonomic activity like pupil dilatation, tachycardia, tachypnea, and diaphoresis. He should also satisfy the general criteria for arousal disorder.

During the episode, the person sits up in bed, indifferent to external stimuli and if awakened is confused and disoriented. However, bolting out of bed and running is not uncommon in adults and also can be associated with violent behaviors particularly when attempt is made to restrain the individual. It may be accompanied by incoherent vocalization sometimes inconsolably in children or adults. The important thing to note is that these are usually seen among children and resolve by puberty but may sometimes persist in adolescence or adulthood. It occurs during partial arousal from slow-wave (N3) sleep and usually emerges in the first third or first half of a typical sleep period. They rarely arise from daytime naps.

These episodes are brief but may last as long as 30–40 min in some children. The eyes are usually open during episodes and not uncommonly are wide open with a confused glary stare. They do not have planning and memory of the event. Patients are not consciously aware and behaviors are often thought to be automatic. If we consider the disorder of arousal in particular, sleepwalking can involve healthy routine practices that are inappropriate only regarding their timing but more often inappropriate behaviors such as urinating in a waste-basket, moving furniture around haphazardly, or climbing out a window are seen. Self-injury is not unusual and can result in death and this was given a term— parasomnia-pseudosuicide (Ref). Sleepwalkers are reported to have high tolerance for pain and knife cuts, and burns may not awaken them (Ref).

Violence to others can occur with adult men with sleepwalking and the sleepwalker does not search for the object of the attack. More typically a person attempting to block, grab, restrain, redirect, or awaken a sleepwalker may be attacked, even if they are family members or friends. This may result in the form of primitive defensive aggression including pushing, hitting, kicking, or throwing objects. This pattern has been reported in sleep laboratories when a technical personnel has attempted to return sleepwalking patients to bed. These behaviors have legal and forensic implications.

15.6 Epidemiology and Pathogenesis of Disorders of Arousal

They are prevalent in children and adults younger than 35 years. Prevalence of confusional arousals in children aged 3–13 years in a large population-based study was 17.3% and in adults older than 15 years is 2.9–4.2% (Ref). The lifetime prevalence of sleepwalking is as high as 18.3% (Ref). A Swedish study of children aged 6–16 years found incidence of sleepwalking to be 40% (Ref). Up to 4.3% of adults sleepwalk (Ref). The prevalence of sleep terrors is 1–6.5% in children and 2.2% in adults (Ref). A genetic predisposition has been hypothesized especially in sleepwalking (see below). In childhood disorders of arousal can usually be considered as an expected and normal developmental sleep phenomenon. However, when it persists beyond adolescence or begins in adulthood it requires clinical attention. Priming factors for disorder of arousal especially for sleepwalking include sleep deprivation and stress. Hyperthyroidism, migraine, head injury, encephalitis, and stroke are other potential priming factors (Ref). OSA is increasingly recognized as precipitants of disorder of arousal (Ref). They may also be triggered by environmental stimuli such as telephone calls, pagers, etc. Travel, sleeping in unfamiliar surroundings, febrile states in children, premenstrual period in women, use of psychotropic medications such as lithium, phenothiazines, anticholinergics, and sedative-hypnotic agents have also been found associated with onset of sleepwalking but a causal relationship has not been established. Moreover, internal stimuli such as distended bladder or external stimuli such as noise or light can also precipitate episodes. Alcohol was previously reported as a potential sleepwalking trigger but recent evidence-based reviews have found no compelling relationship (Ref). There is no significant association between disorders of arousals and psychopathology as control of psychiatric disorder does not control the parasomnia [6].

Genetic factors appear to play an essential role in all disorders of arousal. However, published data exists primarily for patients who sleepwalk. Rate of sleepwalking in child increases in relation to number of parents affected—22% if neither of parent is affected, 45% if one parent is affected, and 60% if both the parents are affected (Ref).

15.7 Onset, Course, and Complications

Confusional arousals most often appear in childhood around 2 years of age, benign and diminish after 5 years of age. Sleepwalking can begin as soon as a child is able to walk but may start at almost any time in life cycle, including as late as seventh-decade. Sleepwalking is often preceded by confusional arousals. Childhood sleepwalking usually disappears spontaneously around puberty but may persist into adolescence. Episodes can occur sporadically or multiple times nightly. Sleepwalking may occur for the first time in adulthood or may recur in adulthood during periods of sleep deprivation or stress. Sleep terrors usually emerge in children 4–12 years of age and resolve by early adolescence.

The overwhelming majority of individuals with disorders of arousals do not have neurological or psychological pathology. There are reported cases of confusional arousals associated with brain lesions in areas subserving arousals such as posterior hypothalamus, midbrain reticular area, and periventricular gray matter (Ref). Data from single patients with confusional arousal suggest that they may be due to functional abnormality in brain that leaves some brain regions such as hippocampus and frontal associative cortices asleep while other parts of brain such as motor, cingulate, insular, amygdala, and temporopolar cortices active or awake. It is generally considered that disorders of arousal represent a dissociation of different regions of the brain in addition to activation of locomotor centers/central pattern generators, accompanied by sleep inertia and sleep state instability.

Polysomnography studies demonstrate that disorders of arousal typically begin after arousal from slow-wave sleep, most commonly toward the end of first or second episodes of slow wave sleep. High amplitude hypersynchronous delta waves and frequent arousals from slow wave sleep are noted in polysomnography but these have low specificity and have been reported in OSA and asymptomatic individuals. Post arousal electroencephalography (EEG) recordings in children and adults with sleepwalking often demonstrate a partial or complete persistence of sleep with diffuse rhythmic delta activity; diffuse delta and theta activity mixed delta, theta, alpha, and beta activity; or at times alpha and beta activity. A sleep study may assist in ruling out disorders with similar presentations like REM sleep behavior disorder (RBD) or SHE and is useful in identifying potential triggers like periodic limb movements during sleep (PLMS) and sleep-related breathing disorder.

The differential diagnosis of this condition includes (1) RBD Dream enactment behavior seen during the second half of night and usually affects middle-aged men. Sleepwalking in adults can also present with dream enactment behavior and video polysomnography can help distinguish primary RBD from sleepwalking. (2) Sleep-related hypermotor epilepsy can manifest as wandering behavior or frenzied walking or running. (3) Alcohol intoxication may resemble that of sleepwalker but cognitive functioning is reduced, not absent as observed during sleep-walking, and lastly, (4) Malingering.

15.7.1 Sleep-Related Eating Disorder

The diagnosis is made by a history of recurrent episodes of disordered eating that occurs after arousal during main sleep period and the presence of at least one of the following in association with repeated episodes of involuntary eating. During these episodes, consumption of peculiar forms or combinations of food or inedible or toxic substances can be observed which may lead to sleep-related injurious or potentially injurious behaviors performed while in pursuit of food or while cooking food, and adverse health consequences from recurrent nocturnal eating. Also noted is partial or complete loss of conscious awareness during the eating episode, with substantially impaired recall. Also, any other sleep disorder/mental disorder/medical

condition/medication or substance abuse should be excluded before making this diagnosis.

There are many features that can be associated like nightly eating, episodes occur during any time in sleep cycle with a preference to the high caloric foods. Rarely simple foods or entire hot or cold meals may be prepared and consumed. Consumption of alcoholic beverages is not seen and any interference in the eating episode may lead to aggression or irritability.

There are many adverse implications of this eating disorder like injuries, poisoning, dental caries, weight gain/obesity, dyslipidemia, depression, and insomnia.

The mean age onset of SRED is reported to be 22–39 years and is seen in females predominantly. Sleepwalking is the most common sleep disorder associated with SRED. Sexomnia, a variant of confusional arousals, has also been reported with SRED. Medication-induced SRED has been reported with zolpidem but also with a broad range of sedative-hypnotics including benzodiazepines, benzodiazepines receptor agonists, mirtazapine, risperidone, quetiapine, lithium, and anticholinergics. Onset of SRED has also been reported with cessation of alcohol/smoking and substance abuse, acute stress, after daytime dieting, and with onset of narcolepsy, autoimmune hepatitis, encephalitis, and other conditions.

The two basic states of sleeping and eating are abnormally intermingled in SRED. Video polysomnography shows multiple confusional arousals with or without eating, arising from slow wave sleep but has been documented from all stages of NREM sleep and occasionally from REM sleep.

The differential diagnosis of SRED are night eating syndrome (NES) (characterized by excess eating between dinner and bedtime and during full awakening during sleep period), and Kleine Levin syndrome (inappropriate nocturnal eating, periodic hypersomnia, hypersexuality), hypoglycemic states, peptic ulcer disease, reflux esophagitis, Kluver Bucy syndrome—medical conditions associated with abnormal recurrent eating during main sleep period (usually with full or almost full alertness) should also be considered during diagnosis.

15.8 Parasomnia Overlap Disorder

In conditions of parasomnia overlap disorder, the patients may have an overlap of multiple parasomnias existing in the same patient like RBD, SRED, and sexsomnia. Sexsomnia has been proposed to be an NREM parasomnia with significant forensic implications. Many studies have demonstrated cases of marital rape and other sexual assaults attributed to this [8, 9].

15.9 REM-Related Parasomnias

15.9.1 REM Sleep Behavior Disorder (RBD)

RBD is diagnosed by a history of repeated episodes of sleep-related vocalization or complex motor behaviors. These behaviors are documented by polysomnography to occur during REM sleep and there is a history of dream enactment. The PSG shows REM sleep without atonia (RWA). The other conditions like sleep-related breathing disorder, mental disorders, alcohol and sedative hypnotic agents, or substance abuse should be ruled out before making the diagnosis [10–12].

RBD occurs predominantly in males and usually emerges after the age of 50 years. RBD emerging before 50 years of age has greater sex parity, increased rates of idiopathic RBD, comorbid narcolepsy, parasomnia overlap, antidepressant medication use, possibly autoimmune disease, and clinical presentation is also less aggressive and violent (probably due to greater female representation and narcolepsy association). Prevalence rates range from 0.38–0.5% [13, 14].

RBD manifests as an attempted enactment of unpleasant, action-filled, violent dreams in which an individual is being confronted, attacked, or chased by unfamiliar people or animals. Typically, at the end of episode the individual awakens quickly, becomes rapidly alert, and reports a dream with a coherent story. The dream action corresponds closely to observed sleep behaviors. Nonviolent behaviors like talking, smiling, laughing, singing, whistling, chewing, etc. also are noted. RBD is seen in REM sleep, which usually appears at least 90 minutes after sleep onset unless there is co-existing narcolepsy in which case RBD emerges shortly after sleep-onset [15].

Complications include sleep-related injuries to self and to bed partner that at times are life-threatening. Delayed emergence of a neurodegenerative disorder, often more than a decade after the onset of idiopathic RBD, is very common in men 50 years of age and older. These disorders include Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB) [12]. Two recently reported series found 81% and 82% eventual conversion rates from idiopathic RBD to parkinsonism/dementia (and also mild cognitive impairment in the latter study) [11]. Conversely, RBD is present in >90% of reported cases of MSA, in approximately 50% of reported cases of DLB, and in up to 46% of reported patients with PD. RBD can emerge in children, usually in association with narcolepsy-cataplexy, brainstem tumors, or antidepressant medications [13, 14].

Polysomnography demonstrates an excessive amount of sustained or intermittent loss of REM atonia and/or excessive phasic muscle twitch activity of the submental and/or limb EMGs during REM sleep. Some patients have almost exclusively arm and hand behaviors during REM sleep, indicating the need for both upper and lower extremity EMG monitoring in fully evaluating for RBD.

Here it is useful to mention the condition described as *Status dissociatus* as a subtype of REM sleep behavior disorder where there is complete breakdown of individual sleep stages. Here the patient may have the behavioral manifestation like RBD but then he feels he is awake. The sleep stages in polysomnograms are also

difficult to stage in this condition. The dream enactment behavior may persist like RBD [16].

15.9.2 Recurrent Isolated Sleep Paralysis

It is also known as hypnagogic and hypnopompic paralysis/predormital and postdormital paralysis. The patient has a recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep, and each episode lasts seconds to a few minutes associated with clinically significant distress including bedtime anxiety or fear of sleep. Other conditions like other sleep disorders (especially narcolepsy), mental disorder, medical condition, medication, or substance use should be excluded. The core features of the event consist of an inability to speak or to move the limbs, trunk, and head. Respiration is usually unaffected. Consciousness is preserved, and full recall is present. An episode of sleep paralysis lasts seconds to minutes. It usually resolves spontaneously but can be aborted by sensory stimulation, such as being touched or spoken to, or by the patient making intense efforts to move.

Intense anxiety is usually present during the initial episodes. Hallucinatory experiences accompany the paralysis in about 25–75% of patients. These may include auditory, visual, or tactile hallucinations or the sense of a presence in the room. Some patients experience predormital or postdormital hallucinations at separate times from episodes of sleep paralysis. There is up to 40% prevalence of at least one episode of sleep paralysis in general population. Sleep deprivation and irregular sleep-wake schedules have been identified as predisposing factors to episodes of sleep paralysis. Mental stress has been reported as a precipitating factor in some but not other studies. Other factors that have been noted on regression analysis include an association with bipolar disorder, the use of anxiolytic medication, and sleep-related leg cramps.

Analysis of sleep paralysis after forced awakenings during PSG studies reveals the event to be a dissociated state with the persistence of REM-related electromyographic atonia into conscious wakefulness. The differential diagnosis includes (1) Cataplexy produces similar generalized paralysis of skeletal muscles but occurs during wakefulness and is precipitated by emotion. (2) Atonic seizures occur during wakefulness. (3) Nocturnal panic attacks are not usually associated with paralysis. (4) Familial periodic paralysis syndromes, especially hypokalemic periodic paralysis, may occur at rest and awakening. However, the episodes usually last hours may be associated with carbohydrate intake, and are usually accompanied by hypokalemia. There are also hyperkalemic and normokalemic periodic paralysis syndromes.

15.10 Nightmare Disorder

Nightmare disorder includes mandatory inclusion of repeated occurrences of extended, extremely dysphoric, and completely remembered dreams that usually involve threats to survival, security, or physical integrity, the person rapidly becomes oriented and alert after awakening from the dysphoric dreams and the dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following. Along with mood disturbance, sleep resistance, cognitive impairments, behavioral problems like avoidance of bedtime and fear of dark and negative impact on caregiver or family. This may also be associated with sleepiness during day, low energy, impairment in work, interpersonal problems.

The most essential feature of the nightmare is that the episodes have a greater tendency to occur during the second half of the major sleep episode when the REM pressure is most pronounced. The ability to detail the nightmare's contents upon awakening is common in nightmare disorder. Multiple nightmares within a single sleep episode may occur and may bear similar themes.

Post-awakening anxiety and difficulty returning to sleep may be present. Nightmares are more common in those with higher levels of anxiety. Additionally, nightmares are commonly seen in those who have been physically or sexually abused and in those suffering from the posttraumatic stress disorder. Nightmares arising either immediately following a trauma (acute stress disorder [ASD]) or 1 month or more after a trauma (posttraumatic stress disorder [PTSD]) have been described during NREM sleep, especially N2, as well as during REM sleep and at sleep onset. Posttraumatic nightmares may take the form of a realistic reliving of a traumatic event or may depict only some of its elements or emotional content. Occasional nightmares in children are frequent and do not constitute a nightmare disorder. Patients with acute stress disorder and PTSD are at risk for developing mood disorders, substance abuse, and self-destructive behavior and the extent to which nightmares contribute to this complication is not known.

The differential diagnosis of nightmare disorder includes those conditions where night time acute behavioral changes are noted like cases of seizures presenting only as "nightmares" have, sleep terrors, RBD, patients with narcolepsy often report nightmares at sleep onset, nocturnal panic attacks, and finally sleep-related dissociative disorders include dissociative identity disorder (formerly called multiple personality disorder) and dissociative fugue.

15.10.1 Exploding Head Syndrome (Sensory Sleep Starts, Sensory Sleep Shocks)

Exploding head syndrome is diagnosed when there is a complaint of a sudden loud noise or sense of explosion in the head either at the wake-sleep transition or upon waking during the night, the individual experiences abrupt arousal following the

event, often with a sense of fright and the experience is not associated with significant complaints of pain.

A painless loud bang, an explosion, or a bomb exploding sense is a core feature but sometimes maybe a less alarming sound. A sense of fear is usually associated, and many patients believe they are having a stroke. This abnormal feeling may last for few seconds and then may recur many times. The episodes may occur many times in the night or may be clustered. Sometimes a flash of light may be associated with the sound, and a myoclonic jerk can occur. The episode is usually painless but the pain may appear like stab. The patient may report insomnia complaints due to the recurring arousals and anxiety about these events. The exploding head syndrome is more common in women than in men. It has a benign course and spontaneous remission [6].

15.10.2 Sleep Enuresis

Primary sleep enuresis is diagnosed when the patient is older than 5 years and the patient exhibits recurrent involuntary voiding during sleep, occurs at least twice a week for at least 3 months, and the patient has never been consistently dry during sleep.

In secondary sleep enuresis the patient is older than 5 years and exhibits recurrent involuntary voiding during sleep occurring at least twice a week for 3 months. Also, the patient has previously been consistently dry during sleep for at least 6 months. The patients and caregivers may be anxious and the frustration of dealing with sleep enuresis once the child had gained control over voiding could be challenging.

15.11 Conclusion

The behavior observed during parasomnias is multidimensional in nature. The manifestations predominantly are in the form of anxiety, fearfulness, and panic like in night terror (NREM) while anger, rage, and complex behaviors noticed in REM sleep behavior disorder. Also nightmares have fear and panic like response with visualization of dream content. Thus parasomnias have significant implications on the psychological, mental, and medical health of the individual. They may be harbingers of ominous neurodegeneration in some while in others a signal of old psychological scars due to traumatic experiences. They provide a fascinating window of intervention also and may be a health marker in many of these parasomnias.

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Behavioral Presentation of Sleep-Related Motor Disorders

16

Ambra Stefani and Evi Holzknecht

Abstract

Sleep-related movement disorders, for example, restless legs syndrome and sleep related bruxism, interfere with acquisition of good quality sleep. These disorders can interfere with onset or maintenance of sleep, and underlying motor events lead to micro-arousals during sleep. Hence, patients suffering from sleep-related movement disorders can show signs of sleep deprivation which possible result in daytime consequences including among others increased sensitivity to pain, distressed and anxious mood, headaches, generalized fatigue, loss of appetite, and cognitive impairment. These symptoms may be mistaken for psychiatric disorders or may pave way for psychiatric disorders. This chapter reviews though scant but available literature in this area.

Keywords

Restless legs syndrome · Bruxism · Depression · Anxiety · Headache

16.1 Introduction

Sleep-related movement disorders (SRMD) are characterized by movements, which usually are relatively simple and often stereotyped, that disturb sleep or sleep onset. This is a heterogeneous category including, according to the International Classification of Sleep Disorder 3rd edition (ICSD 3), restless legs syndrome (RLS), periodic limb movement disorder (PLMD), sleep-related leg cramps, sleep-related bruxism, sleep-related rhythmic movement disorder, benign sleep myoclonus of infancy, and propriospinal myoclonus at sleep onset. Additionally, the category of

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"isolated symptoms and normal variants" includes excessive fragmentary myoclonus (EFM), hypnagogic foot tremor (HFT) and alternating leg muscle activation (ALMA), and sleep starts [1]. Neck myoclonus during (REM) sleep can also be considered a SRMD, although it has not yet been included in the ICSD 3 classification.

Neuropsychiatric disorders are considered to play a role in the manifestation of some SRMD, or to be associated with them [2]. At least in some cases, this association can be explained by a common pathophysiological mechanism, for example, neurotransmitter dysfunction. In other cases, the sleep disorder may be secondary to or aggravated by drugs used to treat a neuropsychiatric disorder. For example, RLS can cause insomnia and therefore alters the normal circadian pattern with consequent alterations in neurotransmitter function leading to depression or mood disorders. Moreover, sleep deprivation (which may be secondary to RLS in severe cases or in patients with augmentation) also increases the risk of depression.

Therefore, behavioral symptoms may be present in patients with SRMD and need to be identified, as they may confound the clinical picture and make the diagnostic process more difficult. This chapter will focus on the behavioral presentation of those SRMD, in which neuropsychiatric disorders may be relevant, that is, RLS, PLMD, sleep-related bruxism, and sleep-related rhythmic movement disorder.

16.2 Behavioral Presentations of RLS

RLS is a common neurological disorder with a reported prevalence up to 10% in European and North American populations [3–6]. It is characterized by an urge to move the legs, mostly accompanied by uncomfortable sensations, beginning or worsening during rest and at evening/at night, and being totally or partially relieved by movement [7]. The symptoms cause concern, distress, sleep disturbances, or impairment of important areas of functioning. In RLS pathophysiology, brain iron deficiency, dopamine dysregulation, genetic risk factors [1], and peripheral hypoxia [8, 9] play a role.

Behavioral manifestations have been often reported in association with RLS, including several psychiatric disorders and namely depression, anxiety disorder, schizophrenia, attention deficit hyperactivity disorder (ADHD), Tourette syndrome, and impulse behavior disorder. Behavioral presentation of RLS is even more common in children, as almost two-thirds of children with RLS have been reported to have a concomitant psychiatric disease [10]. Moreover, an effect of drugs used to treat psychiatric conditions on RLS symptoms has been reported. These aspects will be reviewed in detail below. Genetic studies are summarized in Tables 16.1, 16.2.

16.2.1 RLS and Depression

Depression has been reported as a frequent comorbidity in children (27.8%) [11] and in adults with RLS (19%) [12, 13]. On the one side, sleep disturbances due to RLS

Table 16.1 Genetic studies on psychiatric disorders and restless legs syndrome

Study	*N*	Investigated genes	Investigated polymorphisms	Findings
Jensen et al. 2014	6725	MAP2K5	rs41305272	rs41305272 associated with agoraphobia in European-Americans, with major depressive disorder in African Americans rs41305272 carrier frequency correlated with number of anxiety and depressive disorders diagnosed per subject
Kang et al. 2018	190	MAP2K5	rs1026732, rs11635424, rs12593813, rs4489954, rs3784709	G-G-G-G-T (rs1026732-rs11635424-rs12593813-rs4489954-rs3784709) haplotype was associated with RLS symptoms in schizophrenic patients the G-A-A-T-C genotype was also associated with RLS symptoms
Kang et al. 2013	190	BTBD9	rs9357271, rs3923809	Difference in the rs9357271 polymorphism between schizophrenic patients with and without RLS symptoms Genotypic association of rs9357271 with RLS symptoms in the dominant and heterozygous model Difference in overall haplotype difference of rs3923809–rs9357271 between schizophrenic patients with and without RLS symptoms
Kang et al. 2015	190	MEIS1	*rs*2300478, *rs*671034	No differences in genotype or allele frequencies between schizophrenic patients with or and without RLS symptoms
Jung et al. 2014	190	CLOCK NPAS2	rs2412646, rs1801260 rs2305160, rs6725296	CLOCK polymorphisms associated with RLS symptoms in schizophrenic patients No association of allelic, genotypic, and haplotypic variants of NPAS2 with RLS in schizophrenic patients
Cho et al. 2009	190	TH gene	rs6356	rs6356 polymorphism associated with increased RLS frequency only in women
Riviere et al. 2009	322	MEIS1 BTBD9 MAP2K5/ LBXCOR1	rs12469063, rs2300478 rs9394492, rs4717156, rs9296249, rs9357271, rs3923809 rs12593813, rs11635424, rs884202, rs4489954, rs3784709, rs1026732, rs6494696	3 SNPs within BTBD9 associated with Tourette Syndrome, risk alleles for RLS and PLMS were overrepresented in patients with Tourette syndrome; variants in BTBD9 strongly associated with Tourette's syndrome without obsessive-compulsive disorder

N number of subjects investigated; *PLMS* periodic limb movements during sleep; *RLS* restless legs syndrome

Table 16.2 Genetic studies on psychiatric disorders and bruxism

Study	*N*	Investigated genes	Investigated polymorphisms	Findings
Cruz-Fierro et al. 2018	171	HTR2A	rs6313	No significant differences in allele frequency
Oporto et al. 2016	130	HTR1A HTR2A HTR2C SLC6A4	rs6295 rs1923884, rs4941573, rs6313, rs2770304 rs17260565 rs63749047	In the HTR2A rs2770304 polymorphism, the C allele associated with increased risk of sleep bruxism

symptoms may lead to depression, and it has been reported that treatment of RLS improves symptoms of depression [12]. Moreover, drugs used to treat depression may induce or worsen RLS symptoms [14].

The association between RLS and depression has been reported in several populations and ethnicities. In a study conducted in Germany, depressive disorders were present in 34% of patients with RLS versus 5.4% of controls [15]. RLS has been reported in up to 52% of subjects with depression in a Finnish study, with RLS prevalence increasing with increasing severity of depressive symptoms [16]. RLS was associated with higher prevalence of depressive disorder also in a Danish general population study: RLS patients had higher odds for depressive disorders (men: OR = 3.60; women: OR = 4.08) as compared to non-RLS patients. This was true also for patients with mild or infrequent RLS symptoms (women: OR = 1.59; men: OR = 1.79) [17]. Similar results were reported in a US population study assessing 982 men, where depression was associated with moderate to severe RLS (OR 2.85, 95% CI 1.23,6.64) [18], as well as in a Korean population (OR for depression in patients with RLS: mild depression 1.95, moderate depression 6.15, severe depression 56.54) [19]. In a population-based survey conducted in rural Ecuador, symptoms of depression were reported by 30% of participants with RLS, as compared to 10.2% of participants without RLS ($p < 0.001$) [20]. As the population included in this study was medication naïve, an exacerbation of RLS due to antidepressant can be excluded.

An epidemiological study in the Turkish community-dwelling elderly in an urban area reported depressive mood as risk factor for RLS (depressive mood in 32.4% of RLS vs 18% without RLS, $p = 0.001$) [21]. Studies investigating the temporal relationship between RLS and depression reported that RLS often preceded depression [13, 22], or that a previous diagnosis of depression was associated with presence of RLS [17].

In a European community-based cohort of patients with RLS conducted in Serbia, the severity of RLS—in particular frequency of symptoms—negatively influenced quality of life. In this study, the severity of depressive and anxiety symptoms was negatively associated with quality of life, and these were the most significant negative contributors to scores of quality of life in patients with RLS [23]. On the

other hand, a study investigating depression and quality of life in RLS, primary insomnia, and healthy controls showed that RLS severity was the most overall predictive factor for depression and quality of life among patients with RLS [24].

Also in a cohort of women with symptoms of postpartum depression, prevalence of RLS in the last trimester of pregnancy has been reported to be high (48.3%, vs. 28.4% in women without symptoms of postpartum depression, OR 2.837 CI 1.18–6.84) [25].

Due to the frequent overlap of these two conditions, it has even been suggested, that RLS subjects with comorbid depression and anxiety may represent a distinct RLS subtype, without PLMS [26]. This association seems to have an anatomical correlate, as depressive symptoms in RLS patients have been associated with gray matter abnormalities in the anterior cingulate cortex [27]. Common genetic risk factors may also be the reason for this strong association. SNPs in mitogen-activated protein kinase 5 (MAP 2K5) have been reported as risk factors for RLS in GWAS studies [28–30]. Interestingly, a study reported that the carrier frequency of the SNP rs41305272*T in MAP 2K5 (not reported as a risk factor for RLS) was correlated with the number of anxiety and depressive disorders diagnosed per subject [31]. These findings suggest that MAP 2K5, which is involved in growth factor stimulated cell proliferation and muscle cell differentiation, plays a role in both RLS and anxiety/depression.

Complicating the tangled relationship between RLS and depression, SSRI, SNRI, and mirtazapine have been reported to worsen symptoms of RLS. However, these data are mostly based on case reports, so that evidence is poor. Mirtazapine may be associated with higher rates of RLS. On the other hand, bupropion may even reduce RLS symptoms, at least in the short term [14, 32, 33]. Antipsychotics, in particular olanzapine, quetiapine, and clozapine, have been also reported to induce RLS in single cases (reviewed in Patatanian et al., Annals of Pharmacotherapy 2018 [33]). Moreover, due to some overlapping symptoms (e.g., insomnia, nonrestorative sleep, and irritable mood), diagnosis of RLS or depression may be delayed in patients with both conditions [32].

16.2.2 RLS and Anxiety Disorder

Anxiety disorder is more frequent in RLS patients as compared to the general population [12, 34]. As for depression, this has been reported in several studies investigating different ethnicity. A study conducted in Turkey reported that RLS patients had higher anxiety scores, compared to healthy controls, and that anxiety scores correlated positively with RLS severity [35]. A study carried out in rural Ecuador reported that, in a regression model adjusted for age and sex, the prevalence of anxiety was 30% among persons with RLS as compared to 13% in the general population (OR 3.6, 95% CI 1.7–7.7; $p = 0.001$) [20]. Very similar data came from a survey carried out in Germany, where patients with RLS reported higher rates of generalized anxiety disorder compared to controls (OR 3.7, 95% CI 1.8–7.4). Moreover, when evaluating the temporal relationship between the two diseases,

this latter study reported that symptoms of RLS occurred before onset of the psychiatric disorder. Therefore, the anxiety disorder might be a consequence of sleep disturbances due to RLS.

A community-based RLS prevalence study conducted in Serbia focused on quality of life in RLS patients and showed that the severity of depressive and anxiety symptoms were the most significant negative contributors to quality of life in RLS subjects [23].

In a small study investigating nocturnal eating in RLS, untreated RLS patients had higher scores for harm avoidance than controls. These patients, particularly those with nocturnal eating, perceived stressful situations as dangerous and threatening and tended to respond with anxiety to such situations [36].

Interestingly, a study investigating RLS patients subgroups based on the PLMS index (without PLMS if PLMI < 5, mild PLMS if PLMI 5–30, and moderate-severe PLMS if PLMI > 30) revealed that RLS subjects without PLMS had higher anxiety scores than the two groups of RLS patients with PLMS. The authors hypothesized that RLS without PLMS might be a phenotypically distinct clinical subtype of RLS, associated with higher anxiety [26].

There might also be common genetic risk factors for RLS, depression, and anxiety. As reported before, the SNP rs41305272 in MAP 2K5 is a risk factor for RLS. This SNP has been also associated with agoraphobia in European-Americans (OR $= 1.95$, $p = 0.007$; 195 cases) and African Americans (OR $= 3.2$, $p = 0.03$; 148 cases). Moreover, rs41305272*T carrier frequency correlated with the number of anxiety and depressive disorders per participant [31].

16.2.3 RLS and Schizophrenia

Among patients with schizophrenia, a study conducted in South Korea reported higher prevalence of RLS (21.4%) as compared to controls (9.3, $p = 0.009$, OR $= 2.67$, 95% CI $= 1.27$–5.61). Moreover, RLS severity as evaluated with the IRLS (International Restless Legs Syndrome Severity Scale) score was higher in RLS subjects with schizophrenia as compared to RLS subjects in the control group ($p < 0.001$). An association with antipsychotics, antidepressants, or anxiolytics was not present [37]. Several genetic risk factors for RLS have been investigated by a Korean group in patients with schizophrenia. Whereas a haplotype of MAP 2K5 polymorphisms confers increased susceptibility to antipsychotics-induced RLS symptoms in schizophrenic patients [38] and the rs9357271 alleles' frequency and rs3923809–rs9357271 haplotype of BTBD9 gene are associated with antipsychotic-induced RLS symptoms in schizophrenic patients [39], the rs2300478 and rs6710341 polymorphisms of the MEIS1 gene are not associated with the core symptoms of antipsychotic-induced RLS in schizophrenia [40]. CLOCK (Circadian Locomotor Output Cycles Kaput) polymorphisms (rs2412646, rs1801260, and rs2412646-rs1801260 haplotype) are associated with increased susceptibility of schizophrenic patients to RLS [41]. Interestingly, in the same cohort, the rs6356 polymorphism of tyrosine hydroxylase (the enzyme responsible for the conversion

of L–tyrosine to L-DOPA) gene was associated with increased RLS frequency only in women [42]. These and previous genetic studies on RLS in patients with schizophrenia are reviewed in Assimakopoulos et al. 2018 [43].

16.2.4 RLS and ADHD

Worldwide, up to 44% of children with ADHD have been reported to have RLS [44–47]. However, this association has not been reported in the Japanese population [48]. The relationship between RLS and ADHD seems to be bidirectional. On the one side, children with ADHD are more likely to have iron deficiency, and this might contribute to the high frequency of RLS in this population [49]. On the other side, RLS may worsen ADHD symptoms in subjects with both conditions [46].

In adult ADHD patients, an observational cross-sectional study conducted in The Netherlands reported an RLS and RLS symptoms prevalence of 34.5%. In this cohort, RLS symptoms were correlated with hyperactivity-impulsivity ($\rho = 0.742$; $p < 0.001$). This is also reflected in the fact that ADHD patients with positive RLS scores reported higher scores on the ADHD rating scale compared with patients with negative RLS scores (Z: −2.968, $p = 0.003$), mainly due to higher hyperactivity-impulsivity scores (Z: −3.145; $p = 0.002$) [50]. In a German community-based sample, adult ADHD was associated with statistically significant increases in the odds of meeting diagnostic criteria for RLS, even after adjusting for potential confounding variables (OR = 3.18, 95% CI = [1.29, 7.63], $p < 0.001$). However, the association did not hold true after adjusting for the presence of sleep disturbances (OR = 2.02, 95% CI = [0.82, 4.96], $p = 0.13$) [51].

A large cross-sectional study of 25,336 participants enrolled in the Danish. Blood Donor Study evaluated the presence of RLS using the Cambridge-Hopkins RLS questionnaire and ADHD based on the Adult ADHD Self-Report Scale (ASRS). About 1322 participants (5.2%) were classified with RLS, and 653 (2.6%) experienced ADHD symptoms. RLS sufferers were more prone to experience ADHD symptoms (OR: 3.57, 95% CI: 3.14–4.0), and they were also more likely to experience ADHD-subtype symptoms (inattention, OR:1.66, 95% CI: 1.43–1.90; hyperactivity-impulsivity, OR: 1.90, 95% CI: 1.66–2.14) [52].

In adult patients with RLS, ADHD symptoms have been reported to be more frequent (26%) than in insomnia patients (6%) or controls (5%, $P < 0.01$). Moreover, in RLS patients with ADHD symptoms the RLS symptom severity (as evaluated with the IRLS score) was greater than in RLS patients without ADHD symptoms ($P < 0.04$) [53]. In a large sample of adult patients with RLS in France, ADHD and obsessive compulsive disorders (OCD) symptoms were evaluated through questionnaires. A high prevalence of ADHD (27.6%) and OCD (7.6%) symptoms in RLS was described, except for women with ADHD symptoms either alone or in combination with OCD symptoms [54].

It has been suggested that an overlapping neurobiological dopaminergic and serotoninergic dysfunction in ADHD, OCD, and RLS could be responsible for this

overlap [54]. RLS and ADHD may alternatively be considered part of a single symptom complex, due to dopaminergic deficiency [53].

Another possible common pathophysiological mechanism is iron deficiency. A recent study investigated 200 adults with ADHD (112 males, median age 31 years) on lifetime ADHD symptoms and sleep characteristics. RLS was diagnosed in 33.0%, and was associated with earlier onset of ADHD, hyperactive presentation, and more severe lifetime ADHD symptoms. Iron deficiency (defined as serum ferritin levels <50 ng/mL) was found in 35.5%, with higher frequency in patients with RLS (OR = 1.37, 95% CI: 1.10–1.72). In this large sample of adults with ADHD, a subgroup could be identified, characterized by earlier and severe ADHD symptoms, RLS, and iron deficiency. The authors suggested that this endophenotype may reflect a different neurobiological mechanism [55].

Another aspect to be considered is that the differential diagnosis between RLS and ADHD is not always easy, in particular in children. Some common features, for example, motor restlessness, need to be accurately investigated and interpreted, and this might represent a diagnostic challenge. Urge to move due to RLS symptoms in children may be misinterpreted as ADHD. Moreover, leg discomfort or poor quality of sleep due to RLS symptoms may theoretically lead to hyperactivity, lack of concentration, inner restlessness, and inability to relax, mimicking ADHD.

16.2.5 RLS and Tourette's Syndrome

As RLS and Tourette's syndrome share some common features, for example, symptoms relief with activity, some association between the two diseases might be expected [56]. In a study evaluating the presence of RLS in 144 subjects with Tourette syndrome or chronic tics and their parents, RLS was described in 10% of probands and 23% of parents. Interestingly, in those subjects RLS was linked to maternal RLS, so that the authors suggested a contribution of maternal RLS factors to the variable expression of Tourette's syndrome [57]. As RLS is linked to mitochondrial iron deficiency and associated impairment of mitochondrial function, this could also be explained by the maternal mitochondrial heritability [58].

A case-control association study conducted in Montreal provided three SNPs polymorphisms within BTBD9 associated with Tourette syndrome, with the risk alleles for RLS and PLMS overrepresented in the Tourette's syndrome cohort. After stratification, variants in BTBD9 were strongly associated with Tourette's syndrome without obsessive-compulsive disorder. Furthermore, allele frequency of rs9357271 inversely correlated with severity of obsessive-compulsive disorder [59].

16.2.6 RLS and Impulse Control Disorder (ICD)

ICD symptoms have been reported in up to 40% of patients with RLS [60, 61], and correlate with dosage of dopaminergic medication as well as with augmentation. In

particular, patients with RLS with augmentation have an almost sixfold increased risk of exhibiting ICD symptoms ($p = 0.007$, OR 5.64, 95% CI 1.59–20.02) [60].

The same group reported that RLS patients treated with dopaminergic drugs, regardless of having augmentation or not, jumped to conclusions and decided significantly more often against the evidence they had at the time of their decision. However, those with augmentation performed worse and made more often irrational decisions [62].

Interestingly, reflection impulsivity has been reported to be common in RLS patients, regardless whether they are drug naive or treated with dopaminergic therapy. This could have a negative effect on decision-making in daily life [63].

Of note, also nocturnal eating disorder (NED) has been described in RLS patients. An Italian study analyzed the psychopathological profile of patients with RLS and NED, as compared to RLS without NED and controls. The authors reported more severe obsessive-compulsive symptoms in RLS patients with NED [36].

16.3 Behavioral Presentation of PLMD

Periodic limb movements during sleep (PLMS) are repetitive and highly stereotyped movements, typically involving extension of the big toe often combined with partial flexion of the ankle, knee, and sometimes the hip. In periodic limb movement disorder (PLMD), PLMS causes clinically significant sleep disturbance or impairment in important areas of functioning, not better explained by other disorders (including RLS) (Fig. 16.1).

The exact prevalence of PLMD is not known, but it seems to be rare [1]. In a large retrospective study conducted at the sleep center of a mental hospital in Taiwan, patients with depression had higher proportions of PLMD (12.7%, as compared to 5.9% in patients without depression, $p = 0.004$). In this cohort, patients with depression and PLMD had a higher rate of initial insomnia [64]. On the other hand, there is some evidence that antidepressant may cause PLMS [65]. However, data on PLMD and antidepressant use are missing.

Data from the Netherlands sleep registry also showed a positive association between ADHD and prevalence of PLMD. The prevalence of PLMD was 6.2% in this study. The presence of ADHD symptoms (overall) was associated with PLMD (OR 1.32, 95% CI 1.12–1.55, $p = 0.001$). When examining inattention and hyperactivity symptoms separately, the association was still present only for hyperactivity symptoms (OR 1.81, 95% CI 1.28–2.56, $p = 0.001$) [66]. As reported previously, dopamine deficiency is involved in ADHD. Therefore, common pathophysiological mechanisms can explain the association with RLS and PLMD.

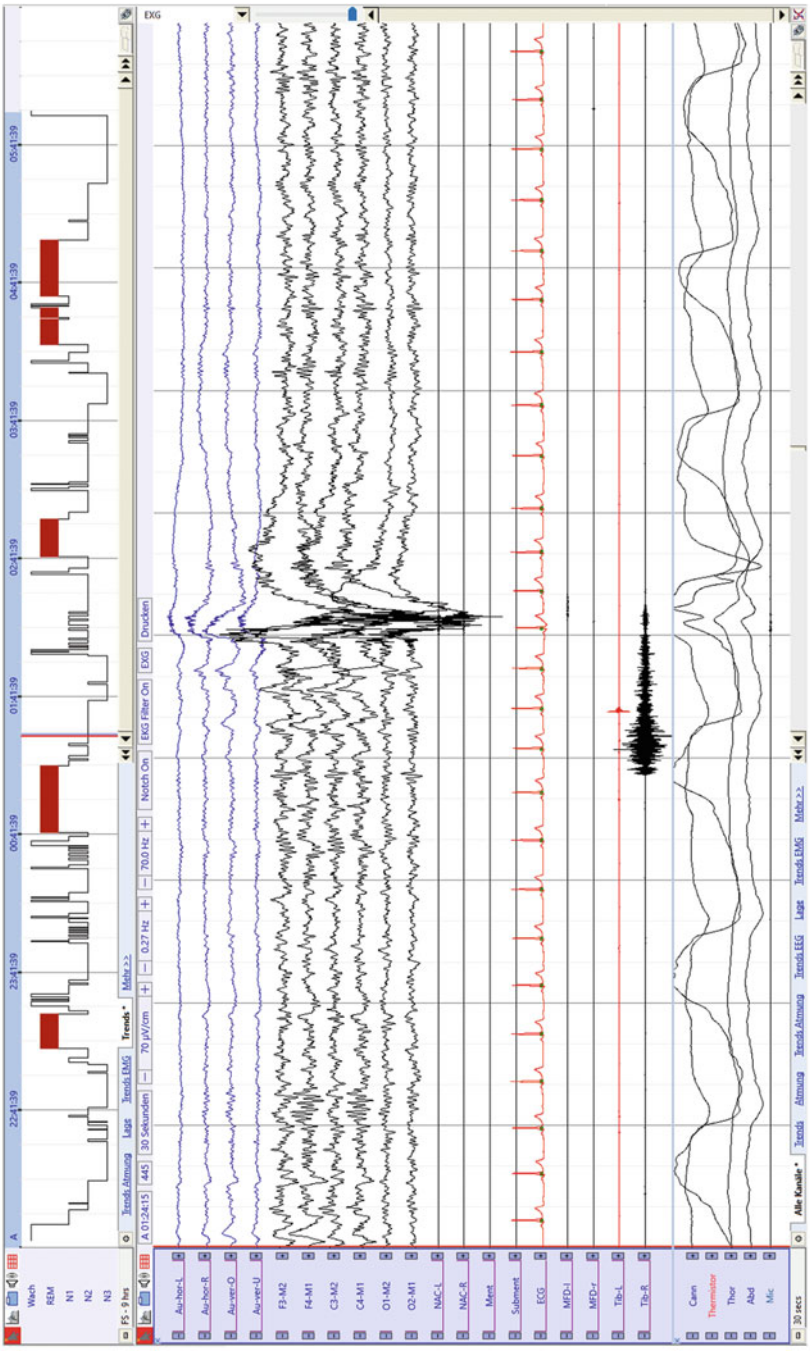

Fig. 16.1 The microarousals associated with PLMS

16.4 Behavioral Presentation of Sleep-Related Bruxism

Bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible, in the presence of consistent abnormal tooth wear, transient morning muscle pain/muscle fatigue, or jaw locking on awakening. The activity can occur during sleep (i.e., sleep bruxism [SB]) and/or during wakefulness (i.e., awake bruxism [AB]) [1]. SB has a high incidence in childhood and may perpetuate to adulthood. Personality features, such as anxiety traits and stress sensitivity, are the main psychological factors that have been reported to be associated with bruxism, both in children/adolescents and in adults. As possible pathophysiological mechanism it has been proposed that individuals with high levels of neuroticism and responsibility traits, as well as anxious expectations, may tend to engage in SB and/or AB activities to release emotional tension.

Data about behavioral presentation of sleep-related bruxism presented below (summarized in Table 16.3) suggest that psychopathological aspects should be evaluated when taking the clinical history. In particular, depression, anxiety, perceived stress (including also work-related aspects in adults) should be assessed in patients presenting with SB (Table 16.3).

16.4.1 Sleep Bruxism and Depression

A cross-sectional study nested in a cohort evaluated a sample of 536 mothers and their children aged 24–36 months. Prevalence of SB was 25.93% (95% CI 22.2–29.7). After adjustments, there was a significant association between maternal major depression disorder [PR 1.43 (95% CI 1.06–1.92)] and the presence of stressful events, mainly environmental changes, [PR 1.47 (95% CI 1.08–2.00)] with bruxism in children [67].

16.4.2 Sleep Bruxism and Anxiety Disorder

A study performed in 84 six- to eight-years-old children assessing bruxism and anxiety revealed that children with bruxism reached higher levels of anxiety than the non-bruxism group. These data indicate a direct relationship between the presence of anxiety disorder and the onset of bruxism in children [68].

A recent study examined rates of PSG-detected compared to parent-reported SB in 31 children, aged 7–11 years. Almost one-third of children showed evidence of SB based on PSG. Interestingly, no associations were identified between parent-reported and PSG-detected SB. Rates of SB did not differ between anxious (generalized anxiety disorder) and control groups, though children with generalized anxiety disorder showed more tonic bruxisms during stage REM sleep. Presence of SB predicted more muscle aches and stomach aches, and children with SB had more awake time after sleep onset than those without bruxism. The lack of association

Table 16.3 Behavioral presentation of sleep-related bruxism

Study	N	Age (range or mean ± SD, y)	Prevalence, %
Depression			
Goettems et al. 2017	536	2–3	25.93
Anxiety			
Oliveira et al. 2015	84	6–8	50
Alfano et al. 2018	31	7–11	SB by parents reports: 26.7 SB by PSG: 32.3
Drumond et al. 2018	440	8–10	Probable SB: 40
Yu et al. 2015	616	23–52	33.3
Manfredini et al. 2016	36	25–37	38.8
Cruz-Fierro et al. 2018	171	14–53	Signs and symptoms of bruxism: 71.3 SB: 18 AB: 25.7 Combined bruxism: 26.9
Montero & Gomez-Polo. 2017	526	18–94	Bruxism: 35.9 SB: 20.2 AB: 15.8
Hermesh et al. 2015	75	20–65	SB in social phobia patients: 26.1
Tavares et al. 2016	181	19–77	Only SB 16.6 Only AB: 18.8
Perceived stress			
Emodi Perlman et al. 2016	1000	12–18	SB: 9.2 (10.6/8.7) AB: 19.2 (19.2/19.2)
Cavallo et al. 2016	278	mean 23.7	SB 31.8 (29.1/33.3) AB: 37.9 (34.2/40.8)
Huhtela et al. 2016	4403	19–35	SB: 17.9 (12.5/21) AB 2.3 (2.8/2) Combined bruxism: 5.7
Ohlmann et al. 2018	67	20–80	SB 56.7
Karakoulaki et al. 2015	45	25–52	55.6
Psychopathological factors in general			
Shen et al. 2018	50	27.84 ± 5.60	50
Van Selms et al. 2017	618	46.9 ± 13.6	TMD pain: 43.4
Quality of life			
Gomes et al. 2018	761	5	SB: 26.9
De Alencar et al. 2017	66	3–7	51
Circadian rhythm			
Oporto et al. 2016	130	Data not shown	SB: 20 AB 46.9 SB and AB: 33

AB awake bruxism; *PSG* polysomnography; *SB* sleep bruxism; *TMD* temporomandibular disorder

between SB and anxiety status in this study suggests that stress sensitivity rather than anxiety per se may be predictive of SB [69].

A cross-sectional study of a representative sample of 440 schoolchildren evaluated tooth wear and/or muscle discomfort through a clinical oral examination. The prevalence of probable SB in this sample was 40.0% ($n = 176$). Probable SB was significantly more prevalent in children with a history of nail biting (PR: 1.50; 95% CI: 1.19–1.90; $p = 0.001$) and biting objects (PR: 1.30; 95% CI: 1.03–1.63; $p = 0.025$), which might be considered signs of anxiety [70].

In adults, less data about SB and anxiety are available. A cross-sectional epidemiological survey in 616 male Chinese civilian pilots (aged 23–52 years) did not address SB but investigated temporomandibular disorders (TMD) and anxiety. This survey reported a 33.3% prevalence of TMD, and showed that high anxiety was associated with TMD (OR 2.48; 95% CI 1.25–4.90) [71].

Thirty-six healthy volunteers underwent an in-home evaluation with a portable device using EMG for the diagnosis of SB. Even the SB index was not correlated with any of the psychological scales, there were some significant correlations (r values range from 0.393 to 0.458) between the SB index and the specific items from the trait anxiety and coping scales. Significant correlations between the prevalence of SB in higher-scoring subjects for state anxiety scores (Phi coefficient = 0.456; $P = 0.006$), trait anxiety scores (Phi = 0.369; $P = 0.027$), and social support coping strategy (Phi = 0.387; $P = 0.020$) were observed [72].

An interesting study aimed to determine the associations between self-reported bruxism, anxiety, and neuroticism personality trait with the rs6313 polymorphism in the gene HTR2A (a serotonin receptor). A sample of 171 subjects aged 14–53 years was included. The control group ($n = 60$) exhibited no signs or symptoms of bruxism, the patients group had signs and symptoms of bruxism ($n = 112$). The patients group was subdivided into SB ($n = 22$), AB ($n = 44$), and combined bruxism ($n = 46$). The combined bruxism group reported higher scores in bruxism symptoms, anxiety symptoms, and neuroticism. Accordingly, combined bruxism was associated with a higher degree of neuroticism (OR = 15.0; 95% CI 1.52–148.32), moderate anxiety (OR = 3.56; 95% CI 1.27–10.03), and severe anxiety (OR = 8.40; 95% CI 1.45–48.61). Allele frequency did not differ among the four groups [73].

A large sample size study recruited 526 subjects, over 18 years old and not seeking dental treatment. About 35.9% of this adults sample was classified as being bruxers, where sleep bruxers comprised more than half of the sample at 20.2%. Bruxers tended to perceive more anxiety in all situations assessed, and exhibited a higher level of phobia toward the teeth scaling and local anesthetic injection. The risk of being considered a bruxer was reduced with age (OR: 0.99), and increased proportionally for some personality traits, such as neuroticism (OR: 1.06) and extraversion (OR: 1.04), to the total score of the modified dental anxiety scale (OR: 1.08) and in smokers (OR: 1.61), after controlling for all potentially confounding factors. These data showed that self-reported bruxism was significantly associated to several personality traits (mainly neuroticism and extraversion) and to the level of dental anxiety [74].

The influence of anxiety, depression, and SSRI on bruxism in social phobia has been analyzed in 23 drug naïve and 17 SSRI-treated social phobia patients, and 33 healthy controls. Social phobia, but not depression, was associated with higher risk of oral parafunctional activity and AB. Chronic SSRI treatment of social phobia did not affect SB and AB [75].

In contrast with abovementioned data from the literature, a study conducted in 181 female patients, aged 19–77 years, reported a positive and statistically significant relationship between anxiety levels and self-reported AB, but not with SB [76].

16.4.3 Sleep Bruxism and Perceived Stress

A questionnaire-based study in Israeli adolescents included 1000 students from different high schools in the center of Israel. Prevalence of self-reported SB was 9.2% and no gender difference was found. Predicting variables related to SB included temporomandibular joint sounds ($p = 0.002$) and feeling stressed ($p = 0.001$). A significant association was found between SB and AB: an individual reporting SB had a higher probability of reporting AB compared with an individual who did not report SB (odds ratio = 5.099) [77].

In a group of 278 Italian undergraduate students (117 males), the perceived stress score (evaluated using the perceived stress scale) was higher in females. The prevalence of sleep bruxism was 31.8% (F 33.3%, M 29.1%), without significant gender differences. A positive correlation with perceived stress was present in male students for awake bruxism, but not with sleep bruxism [78].

In 4403 Finnish students (academic and applied science university students), SB was reported by 21.0% of women and 12.5% of men, whereas both sleep and awake bruxism were reported by 7.2% of women and 3.2% of men. Pain due to temporomandibular joint disorder (TMD) was reported by 25.9% of women and by 11.4% of men, and temporomandibular joint pain on jaw movement by 9.6% of women and 4.2% of men. In both genders, report of SB increased the risk for all TMD symptoms and reporting stress as a perpetuating factor for TMD pain increased the risk for SB [79].

In contrast with these data, a study including 67 participants (38 bruxers and 29 non-bruxers) found no statistically significant association between SB and self-reported stress or sleep quality [80].

An interesting study used objective measures of stress through the estimation of stress-related biomarkers (cortisol, alpha-amylase) in saliva. The 45 participants (20 men, 25 women) were divided into bruxers and nonbruxers based on questionnaires and perceived stress was measured by questionnaire. In self-reported bruxers, SB was confirmed using a miniature, single use electromyography device for SB detection (BiteStrip). Bruxers showed higher levels of perceived stress than nonbruxers ($p < 0.001$). Moreover, there was a moderate positive correlation between the 25 bruxers' BiteStrip scores and the salivary cortisol levels (Spearman rank correlation = 0.401, $p = 0.047$). In general, bruxers showed higher levels of cortisol than nonbruxers ($p < 0.001$) [81].

A study investigated 44 females recruited in five dental practices in Germany, aged between 18 and 65, without somatization or depression, without pain medication, and without relevant chronic pain. Temporalis muscle activity was measured for four nights using a portable electromyographic device. The factors "work overload" (adulthood chronic stress because of too many demands at work) and "pressure to perform" (necessity to be successful at work) were significantly correlated with the number of temporalis muscle episodes per hour. In contrast, no correlation with anxiety was present [82].

16.4.4 Sleep Bruxism and Psychopathological Factors in General

A recent review and meta-analysis evaluated the risk factors related to bruxism in children. Reported risk factors included among others some which can be related to psychopathological factors, and namely, mixed position, moves a lot, anxiety, the nervous, psychological reactions, responsibility, restless sleep, sleep with light on, noise in room, "sleep hours, $\leq$8 h," headache, objects biting, conduct problems, peer problems, emotional symptoms, and mental health problems [83].

A recent study investigated 25 patients (9 males, 16 females, with a mean age of 27.84 $\pm$ 5.60), who self-reported having SB, and 25 normal subjects. SB was diagnosed by polysomnography, and rhythmic masticatory muscle activity (RMMA) was recorded. In normal subjects, 15.89 $\pm$ 4.23 RMMA episodes per hour were detected, whereas 41.23 $\pm$ 16.78 RMMA episodes per hour were recorded in patients with SB ($p = 0.001$). Paired t-test revealed significant differences between SB patients and normal subjects in any of the subscales of the Symptom Checklist-90, which was used to assess the psychopathological status ($p = 0.001$). Regarding total psychopathological scores, the positive rate was 40% in patients with SB. In addition, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, paranoid ideation, and psychoticism were all statistically associated with RMMA ($p < 0.05$). This study confirmed previous data that patients with SB tend to have poor psychological status, and reported that obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, paranoid ideation, and psychoticism are related to onset of SB [84].

A study aiming to investigate the association between pain-related TMD, bruxism, and psychological factors assessed 268 patients with TMD pain (85.8% women; age 40.1 $\pm$ 14.5 y) and a control group of 254 patients without any pain in the orofacial area (50.8% women; age 46.9 $\pm$ 13.6 y). Patients with TMD reported significantly more bruxism than patients without any report of orofacial pain. Moreover, bruxism intensity was associated with a variety of psychological factors (depression, somatic symptoms, anxiety, and psychological stress) and to the clinical presence of TMD pain [85].

16.4.5 Sleep Bruxism and Quality of Life

A preschool-based cross-sectional study in 761 children reported a prevalence of sleep bruxism of 26.9%. The multivariate analysis revealed that bruxism was associated with poor sleep quality (OR = 2.93; 95 CI: 1.52–5.65) and tooth wear (OR = 2.34; 95%CI: 1.39–3.96). Psychosocial aspects were not associated with SB [86].

In a study investigating healthy children aged 3–7 years, with (n = 34) and without (n = 32) bruxism, no association between SB and all evaluated sociodemographic/socioeconomic conditions were observed, with exception of being the only child ($p = 0.029$). An association between bruxism and quality of life ($p = 0.015$) was observed, but it was dropped ($p = 0.336$; OR = 1.77) in the logistic regression model. As trait anxiety was the variable responsible for the impact on the quality of life of children ($p = 0.012$; OR = 1.05), these data indicate that anxiety is the main factor interfering in the quality of life of children with SB [87].

16.4.6 Sleep Bruxism and Circadian Rhythm

Due to the relationship that both the chronotype and bruxism have with psychological factors, and the fact that performing tasks not compatible with chronotype can trigger stress, it has been hypothesized that the prevalence of SB can differ with the various chronotype profiles [88]. Moreover, as serotonin is involved in circadian rhythm regulation, a role of serotonin in bruxism pathogenesis has been postulated. A study including 61 AB patients, 26 SB patients, and 43 patients with both AB and SB, as well as a control group of 59 healthy patients with no signs of bruxism, investigated genetic polymorphisms in serotonin receptors. In particular, the frequency of genetic polymorphisms in the genes HTR1A (rs6295), HTR2A (rs1923884, rs4941573, rs6313, rs2770304), HTR2C (rs17260565), and SLC6A4 (rs63749047) was evaluated. Data showed significant differences among groups in allelic frequencies for the HTR2A rs2770304 polymorphism, where the C allele was associated with increased risk of SB (odds ratio = 2.13, 95% confidence interval: 1.08–4.21, $p = 0.03$). These results support the hypothesis that polymorphisms in serotoninergic pathways are involved in sleep bruxism [89]. Genetic findings are summarized in Tables 16.1, 16.2.

16.5 Behavioral Presentation of Sleep-Related Rhythmic Movement Disorders

Sleep-related rhythmic movement disorders (RMDs) are repetitive, stereotyped, rhythmic motor behaviors that occur predominantly during drowsiness or sleep, and result in interference with normal sleep, impairment in daytime function, or the likelihood of self-inflicted injury. Sleep-related rhythmic movement disorders are typically seen in infants and children, but can also be present in adults [1]. The

reported prevalence is high in infants (59%), dropping to 5% at the age of 5 years. However, a recent prevalence study in infants and toddlers using both parental report and confirmatory home video-polysomnography reported a lower prevalence (maximal prevalence 2.87%, likely prevalence 0.96%) [90]. When sleep-related rhythmic movement disorders persist to older childhood or beyond, an association with mental retardation, autism, or other significant pathology is reported [91].

A strong association with attention deficit hyperactivity disorder has also been reported, suggesting a similar pathogenetic mechanism [92]. However, available data are scarce.

Sleep-related rhythmic movement disorders share similarities with the rhythmic habit patterns which are expressed during early normal development, and seen in normal children in early life. These habit patterns increase under emotional disturbance and boredom, and seem to satisfy some inner need or allay frustrations. Like habit patterns, persistence into adulthood is particularly frequent in autistic or mentally retarded individuals. Sleep-related rhythmic movement disorders may also be associated with Tourette's syndrome [93].

Another relevant aspect when considering sleep-related rhythmic movement disorders is the differential diagnosis with seizures. In doubtful cases, video polysomnography and an expanded EEG montage might be useful.

16.6 Conclusion

Behavioral manifestations are common in sleep-related movement disorders.

In most of the cases, the relationship between the neuropsychiatric disorders and the sleep-related movement disorders seems to be bilateral. Common pathophysiological mechanisms are responsible for the coexistence of these disorders in some cases. Moreover, sleep-related movement disorders can be secondary to or aggravated by drugs used to treat a neuropsychiatric disorder. When evaluating patients with sleep-related motor disorders, the investigation of behavioral symptoms should be part of the history taking, in order to get a complete clinical picture of the patients and to be able to better address their symptoms with pharmacological and non-pharmacological treatments.

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Part III

Sleep Disorders and Psychiatric Disorders

Sleep in Depression

17

David N. Neubauer

Abstract

Sleep and mood are closely linked as each influences the other. The relationship is most evident with insomnia and depression. Episodes of insomnia increase the risk of future depression. Episodes of depression nearly always are associated with insomnia, though occasionally with hypersomnia. This chapter reviews several perspectives on sleep and depression, including epidemiologic evidence, insomnia and antidepressant therapy, historic polysomnographic studies in depressed patients, and suicide risk with insomnia.

Keywords

Antidepressant · Insomnia · Mood · Polysomnogram · Sleep · Suicide

17.1 Introduction

Episodes of depression nearly universally are associated with sleep disturbances that often predate the worst depressive symptoms and remain residual problems as the rest of the depressive syndrome resolves. Writers for millennia have noted the depression and insomnia connection, now culminated in diagnostic criteria [1]. The recognition of this apparent bidirectional relationship of mood and sleep (depression and insomnia) raises questions about underlying mechanisms and optimum treatment strategies [2]. Additional dimensions of this mood-sleep realm include alterations in sleep architecture and the effects antidepressant treatments have on sleep [3]. This chapter will provide an overview of this complex relationship and will suggest key questions for future investigation.

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17.2 Epidemiologic Studies of Insomnia and Depression

Difficulty falling asleep or remaining asleep are relatively common problems in the general population. Studies typically suggest that insomnia symptoms occur occasionally in approximately one-third of the adult population, with about 10–15% of adults experiencing associated daytime impairments and about 6–10% meeting the full criteria for insomnia disorder (nighttime sleep disturbance and daytime consequences when the individual has an adequate opportunity for sleep) [4]. In a recent study, Perlis and colleagues [5] evaluated the natural history of insomnia in 1248 good sleepers who kept daily online sleep diaries for 1 year. Acute episodes of sleep disturbance occurred in 27% of the participants with 72.4% of them returning to good sleep, 19.3% continuing with poor sleep, and 6.7% ultimately meeting chronic insomnia criteria. The researchers estimated an annual incidence rate of chronic insomnia as 1.8%. Epidemiologic studies also have shown the prevalence of insomnia to be increased among women and older individuals.

Abundant longitudinal research has provided strong evidence that even a history of insomnia represents an elevated risk for the development of a future depressive episode [6–8]. This increased depression risk following a baseline insomnia history was documented in the landmark 1989 Ford and Kamerow [9] publication of baseline and one-year follow-up assessments with general population subjects. Their findings subsequently were replicated in numerous studies with different populations, including adolescents and older adults.

While insomnia increases future depression risk, people experiencing episodes of major depression have a very high prevalence of sleep disturbances. The Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) includes reports of insomnia or hypersomnia diagnostic criteria options [1]. The DSM-5 text notes that typically depressed individuals experience difficulty remaining asleep during the night or early morning awakenings, but that difficulty falling asleep also may occur. The relatively high frequency of sleep onset difficulty reports among depressed patients has been represented in multiple recent studies, therein questioning the traditional teaching of early morning awakening as the key insomnia indicator of major depression.

In 2006, Steward et al. [10] published the results of a general population survey of 8580 adults in the United Kingdom. Insomnia of any degree of severity was present in 37% of the sample; however, the insomnia prevalence was 83% among the individuals meeting the study criteria for depression.

Sunderajan and colleagues [11] examined specific insomnia complaints among 3743 adults diagnosed with nonpsychotic major depressive disorder participating in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Overall, 84.7% of the depressed patients endorsed at least one insomnia symptom. Among the options that included sleep onset, mid-nocturnal, and early morning insomnia symptoms individually or in any combination, the most common presentation was 27.1% reporting sleep difficulty during all three time periods. Mid-nocturnal insomnia was the category most commonly reported (13.5%) when

sleep difficulty occurred during a single portion of the night. The authors also pointed out that insomnia was indicative of a more severe depression.

In 2013, Park and colleagues [12] reported the findings of the Clinical Research Center for Depression of South Korea (CRESCEND) study that included 944 patients with depressive disorders who were starting new treatment for an initial or recurrent depressive episode. They analyzed responses (range 0–2) to the three Hamilton Depression Rating Scale (HDRS) insomnia questions, thus a combined insomnia total range of zero to six. An insomnia score of at least 1 was present in 93% of the patients. Simultaneous responses of 1 or greater for early, middle, and late insomnia were given by 64.1% of the individuals. Only 7.1% of the subjects reported no insomnia symptom. The most common total insomnia score (20.9%) was 6, representing the maximum severity of all three time periods.

Several longitudinal studies have examined the timing of insomnia symptoms in relation to depressive episodes. The general conclusion has been that insomnia often is the earliest manifestation of a depressive episode, whether first-onset or recurrent, and it commonly lingers as other mood-related symptoms improve. Ohayon and Roth [13] presented findings of a large-scale ($n = 14{,}915$) general population survey in four European countries. Insomnia accompanied with daytime impairment was endorsed by 19.1% of the sample, with 90% of these individuals having insomnia lasting at least 6 months. Among the insomnia subjects, approximately 28% had a current mental health disorder diagnosis. More than 40% of the individuals with a mood disorder reported that insomnia predated their depressive symptoms.

17.3 Residual Insomnia Following Antidepressant Therapy

Persistent insomnia continuing after successful antidepressant treatment has been assessed in numerous studies, including pharmacologic and CBT-I approaches [14]. In 1999, Nierenberg and colleagues [15] reported that residual sleep disturbance was present in patients with major depression who were considered full responders to treatment with fluoxetine, having HDRS scores of 7 or less. Iovieno et al. [16] reported on a study of 576 major depressive disorder patients in a 12-week open-label fluoxetine study. The responders then were randomized in a double-blind manner to continue on fluoxetine or switch to placebo with monitoring for 52 weeks or until relapse. Among these remitted subjects, 48.2% continued to experience a sleep disturbance, with the most common individual symptom being middle insomnia at 33.5%. Of note, hypersomnia was reported by 35.9% of the patients in the remission group.

McClintock et al. [17] explored residual symptoms among STAR*D participants who responded to the initial antidepressant therapy by at least 50% but did not reach remission status ($n = 428$). Insomnia with at least mild severity was present in 94.6% of these patients. Mid-nocturnal insomnia was the symptom that was most frequently present from baseline throughout the study, occurring in 81.6% of these responders without full remission. Mid-nocturnal insomnia also was identified as a symptom emerging during the initial treatment phase of the trial. Nierenberg et al. [18]

reported on the residual symptoms in the patients who did attain full remission with citalopram in the STAR*D study ($n = 943$). At least mild residual symptoms continued for sleep onset insomnia (29.5%), mid-nocturnal insomnia (54.9%), and early morning insomnia (16.6%). At least moderate mid-nocturnal insomnia was endorsed by 40.5% of these remitted patients.

17.4 Hypersomnia and Depression

Hypersomnia (extended nighttime sleep with excessive daytime sleepiness) is a common report among depressed individuals and, as noted above, is included among the DSM-5 major depressive disorder diagnostic criteria options along with insomnia [1]. In the residual symptom assessment of the fluoxetine study described above, 35.9% of the patients who experienced remission from depression complained of persistent hypersomnia [15]. Residual hypersomnia also was reported by 24% of the STAR*D remitted subjects, with 2.4% describing it as at least moderate severity [18].

While a subjective hypersomnia complaint is common during and following a major depressive episode, it is debatable whether it represents the objectively measurable experience of patients diagnosed with narcolepsy, hypersomnolence disorder, or obstructive sleep apnea. For many individuals, the hypersomnia associated with depression may reflect low energy, fatigue, lack of motivation, social isolation, or a desire to spend increased time in bed. In a review of hypersomnia and depressive symptoms, Dauvilliers and colleagues [19] argued that there are no studies of mood disorder patients providing objective evidence of extended nocturnal sleep or abnormally short multiple sleep latency test (MSLT) mean sleep latencies.

17.5 EEG and Polysomnographic Studies of Sleep in Depressed Patients

A wealth of investigations have examined EEG and polysomnographic (PSG) features in populations of depressed patients. In 1946, years before the identification of REM sleep and the current classification of sleep stages, Diaz-Guerrero et al. [20] monitored the nighttime sleep of six depressed patients and compared the findings with data available on normal subjects. The EEG-defined categories included waking and four patterns based on amplitude and frequency (low voltage, spindles, spindles plus random, and random), essentially along a continuum of increasingly deep sleep with the last one roughly equivalent to modern slow wave sleep. They found that the depressed patients had longer sleep onset latencies, more and longer nighttime awakenings, more sleep level changes, and considerably less deep sleep, all implying "a change in the neurophysiologic status of these patients."

Zung and colleagues [21], employing the early A through E sleep stage categorization representing increasingly deep sleep, studied the EEG features of depressed

male inpatients and compared their findings with the Diaz-Guerrero group results and with available data from normal subjects. Although REM activity during sleep had been described and studied, REM sleep had not yet been standardized as a separate sleep stage [22]. As with the depressed patients studied by Diaz-Guerrero, early morning awakening was a much greater problem than sleep onset difficulty. The Zung group also assessed the depth of sleep with the likelihood of awakening with auditory stimulation during different stages and during study nights before and after treatment (amitriptyline and perphenazine). Compared with the normal controls, the before-treatment depressed patients were much more likely to awaken with an auditory stimulus during all sleep stages; however, following medication treatment (4–6 weeks), the awakenings among the depressed and control groups were no longer significantly different.

Gresham et al. [23] in 1965 performed all-night monitoring of EEG and eye movements in eight depressed inpatients and control subjects to assess sleep stages with a classification system of stages 1, 1 with rapid eye movements, 2, 3, and 4 [22]. The patients were drug-free for 3 days prior to the sleep recordings. Four of the patients were available for repeat sleep studies following treatment, and again were drug-free for 3 days prior to the recording. Compared with controls, the depressed patient group initially had a nonsignificant trend for longer initial sleep latency, but did show significantly greater wake after sleep onset and less stage 4 amount. On repeat monitoring near the time of discharge when depression scores were improved, the depressed patient group characteristics were similar to those of the control group. Especially interesting was the analysis of sleep stage by each third of the night on the initial baseline monitoring. The depressed patient group had 25% of their 1-REM sleep during the first third of the night, while the control subjects had 13% of their 1-REM sleep in that first period.

Mendels and Hawkins [24] in 1967 studied the sleep of 21 depressed inpatients and 15 control subjects with all-night recordings of the EEG, eye movements, and submental muscles. This research group also differentiated between Stage 1 and Stage 1-REM. Compared with the control subjects, the depressed patients had decreased REM and Stage 4 sleep, more awakenings and a greater time awake during the night, longer initial sleep onset, and more early morning wakefulness. They also suggested that the sleep disturbances of patients categorized as psychotic were greater than those with neurotic depressive subjects.

The intriguing evidence from these and other early studies comparing the EEG and PSG characteristics of depressed patients with controls and with themselves following treatment, as well as the effects of medications on sleep, ushered in a golden age of investigations seeking to establish sleep-related biological markers to discriminate among psychiatric disorders and their subtypes [25]. While several objectively measured characteristics differed between patients and normal controls, the outstanding findings were the shortened initial REM latency, relative shift of REM activity earlier during the night, and increased REM density among patients diagnosed with a depressive disorder [26]. Additional PSG findings closely associated with major depression were a sleep continuity disturbance represented by increased awakenings and decreased sleep amount, and a reduction in slow wave

activity. Attempts were made to employ PSG features to differentiate degrees of depression severity, primary (endogenous) vs. secondary (reactive) depression, neurotic vs. psychotic depression, and unipolar vs. bipolar depression [27, 28]. Studies examined whether PSG characteristics represented state or trait associations, and whether findings were evident in family members [29]. It was shown that a prolongation of the abnormally short REM latency in depressed patients during the first two nights after starting an antidepressant medication (amitriptyline) predicted a beneficial antidepressant effect on mood after 3–4 weeks of treatment [30]. Kupfer et al. [31] also proposed a delta sleep ratio calculation as a more "robust predictor" of a depressive episode recurrence compared with the initial REM latency. This measure was based on the slow wave activity during the first two non-REM periods, normally greater during the first non-REM period and declining during the night, but reduced during the first non-REM period in depressed subjects. It was found that the delta sleep ratio value could predict survival time without a recurrence following medication discontinuation.

The hope for a biological marker having high specificity and sensitivity for major depression diminished as further research found PSG features varying with demographic characteristics (e.g., shorted REM latency with aging) and the presence of PSG abnormalities in patients with a variety of psychiatric disorders. While abnormal PSG characteristics (shortened REM latency, decreased slow wave activity, and increased arousals and awakenings) are commonly observed in depressed patients, these now are regarded as transdiagnostic findings. The presence of these shared objective characteristics raises new questions regarding underlying pathologic mechanisms [25].

17.6 Sleep and Antidepressant Treatment

Clinical guidelines on the management of chronic insomnia typically recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line approach [32, 33]. Abundant evidence supports the efficacy of CBT-I for insomnia disorder patients, including groups with comorbid major depressive disorder [34]. Manber and colleagues [35] reported on a 12-week study of 30 adults dually diagnosed with major depression and chronic insomnia. All subjects were treated with the antidepressant escitalopram and were randomized to seven-session CBT-I or a control condition. The primary outcome measure was remission of depression (HDRS score items), which was found in 61.5% of the escitalopram with CBT-I group, but only in 33.3% of the escitalopram with control condition group. In addition, remission from insomnia (Insomnia Severity Index) occurred in 50% of the CBT-I group, but in only 7.7% of the controls.

Mention should be made here of the remarkable and paradoxical benefits of acute sleep deprivation therapy for depression. Total night sleep deprivation, as well as partial sleep deprivation during the latter portion of the night, has a significant mood elevating effect for roughly 50% of depressed individuals, though most revert to a depressed mood again following a subsequent night of sleep [36, 37]. Boland and

colleagues [38] published a meta-analysis of the antidepressant effects of acute sleep deprivation. The analysis included 66 studies (years 1974–2016) and demonstrated that the efficacy was not dependent on age, gender, the response definition, the clinical sample, and the type of sleep deprivation performed. The overall response rate for the six studies with a randomization protocol was 45%, while it was 50% for the other 60 studies.

The use of antidepressant medications is the mainstay of treatment for patients diagnosed with major depression and several other mental health conditions. Often insomnia symptoms co-occurring with depressive disorders improve as the mood symptoms resolve; however, antidepressant medications also may have direct effects on sleep that may be desirable or represent an adverse effect [39]. The sedating effects of an antidepressant (e.g., amitriptyline or mirtazapine) might be welcome at night, but undesired if lingering into the daytime. Antidepressants that may promote arousal (e.g., bupropion or venlafaxine) may contribute to insomnia symptoms [40]. Clinical trial data show that many antidepressants are associated with complaints of both insomnia and excessive sedation [41]. Periodic limb movements of sleep and restless legs syndrome symptoms may be caused or exacerbated with many antidepressants [42]. Parasomnias, including REM sleep behavior disorder, also may result from antidepressant use, particularly SNRI and SSRIs [43].

Antidepressant medications sometimes are associated with PSG changes that may or may not correspond to subjective reports [44]. Clearly, PSG evidence of improved total sleep duration and sleep efficiency may correspond to descriptions of improved sleep, and the opposite may occur—worsened PSG features with increased insomnia symptoms. With the use of fluoxetine and other SSRI antidepressants, there may be evidence of unusually slow eye movements [45]. In 1979, Chen [46] reviewed the available evidence regarding the REM suppressing effect of antidepressant medications that often decrease the amount of REM and delay the latency of REM onset [47]. The REM-suppressant effect is most prominent with monoamine oxidase inhibitors (MAOIs), but is common with nearly all tricyclic antidepressants and most other antidepressant pharmacologic categories. However, there is at least some evidence that the following antidepressants either do not suppress or may even increase REM sleep: bupropion, mirtazapine, nefazodone, trazodone, and trimipramine [39, 40].

17.7 Sleep, Insomnia, and Suicide

It is well established that a history of insomnia increases the future risk of a first-onset or recurrence of a depressive episode. Accordingly, an increased risk for suicide and suicidal ideation also would be expected to be higher among people with insomnia, especially if it exists comorbidly with depression [48, 49]. Pigeon et al. [50] published a meta-analysis of suicidal thoughts and behavior in relation to sleep disturbances. They identified 39 original studies (147,753 subjects) reporting both sleep disturbance and suicide outcomes. They performed global comparisons and specific analyses examining insomnia, insomnia subtypes, and nightmares, as

well as suicide ideation, suicide attempts, and suicide. Generally, sleep disturbance was associated with significantly elevated relative risk for suicidal ideation, suicide attempts, and suicide. The unadjusted risk ratio for any suicidal outcome in association with all types of sleep disturbances was 2.79. The unadjusted specific risk ratios associated with insomnia were 2.79 for suicidal ideation, 3.54 for suicide attempt, and 2.43 for suicide. In the adjusted studies, depression was not found to be a moderating factor, therein reinforcing the conclusion that sleep disturbance is an independent risk factor for suicidal thoughts and behaviors.

Vargas and colleagues [51] reported on the relationship of insomnia symptoms and suicide ideation among US Army service members (n = 1160). In their unadjusted model, global insomnia was significantly associated with all five suicide-related ideation types assessed: thoughts of death, thoughts of suicide, suicidal communication, suicidal plan, and suicidal intent. When controlling for depression, anxiety, PTSD symptoms, pain frequency, and demographic variables, insomnia symptoms remained significantly associated with increased thoughts of death and thoughts of suicide. Curiously, nocturnal awakenings were associated with an increased likelihood of endorsing thoughts of death or suicide; however, middle insomnia (presumably with extended awakenings) appeared to be protective against thoughts of suicide, suicidal plan, and suicidal intent.

The question of whether treating insomnia in a population of depressed patients who endorse suicidal thoughts (without intention or plan) was addressed in a randomized, placebo-controlled 8-week study by McCall et al. [52] They recruited 103 individuals who all were prescribed an SSRI antidepressant and randomized to zolpidem extended-release or placebo. The primary outcome was suicidal ideation as represented by the Scale for Suicide Ideation (SSI) and the Columbia-Suicide Severity Rating Scale (C-SSRS). As expected, the zolpidem ER was very beneficial for the insomnia symptoms. At the completion of the study, there was not a significant treatment effect reflected in the SSI scores, but the C-SSRS did show a significant effect that was most pronounced among the subjects with the more severe insomnia.

17.8 Conclusions

Sleep and mood are closely aligned in both illness and health, and interactions of sleep disturbance and depression are pervasive and complex. While no unitary field theory of the pathologic processes underlying sleep and mood connections exists, exciting insights have emerged from research utilizing the tools of neuroimaging, power spectral analysis, high density EEG, neurobiology, endocrinology, and genetics, among others. Explanatory models propose key roles for brain functional connectivity, inflammation, endocrine alterations, psychological processes, and genetic polymorphisms. While there is much to learn about integral relationship between sleep and mood, we certainly know enough to emphasize the critical role of identifying and treating disturbances of sleep and mood, as we synergistically leverage the clinical improvement of each to help the other.

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Sleep and Perinatal Depression

18

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Abstract

Clinically relevant depressive syndromes are estimated to occur in approximately 12% of women during pregnancy and the postpartum. Perinatal depression (PND) negatively impacts maternal self-care, nutrition, labor, and obstetric outcomes. Hormonal and physical modifications influence the circadian and homeostatic components of sleep regulation, leading to increased WASO, reduced TST, and a predominance of relatively more superficial NREM sleep, especially in the third trimester. Sleep-related breathing disorders, restless legs syndrome, insomnia, and circadian rhythm disorders also typically increase during pregnancy in predisposed women.

Of note, sleep disturbances are significantly more frequent in depressed pregnant women and might be an early predictor of mental health deterioration in the perinatal period. Therefore, sleep monitoring during pregnancy might contribute to the early detection of risk for PND. While polysomnography should be reserved for severe or diagnostically uncertain cases, sleep actigraphy can be used extensively due to its minor cost and major comfort, especially during pregnancy. Preliminary findings from this growing field of research encourage nonpharmacological approaches to sleep disturbances including clear communication of sleep hygiene to preserve positive sleep patterns, safe and effective chronotherapeutic measures such as bright light therapy to target circadian rhythm disruption, and cognitive-behavioral therapy to address insomnia. The combination of these interventions with conventional treatment approaches for

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PND is likely to improve mood and associated sleep disturbances in affected women.

Keywords

Prenatal depression · Postpartum depression · Mood disorders · Sleep-wake rhythms · Chronobiology

18.1 Introduction on Perinatal Depression

Perinatal depression (PND) is defined as a major depressive episode (MDE) with peripartum onset, that is, symptom onset during pregnancy or in the 4 weeks following delivery [1]. The extension of onset within pregnancy (antenatal depression, AD) is a major shift from the previous conceptualization of postpartum depression (PPD), classically restricted to the month following delivery. The American College of Obstetricians and Gynecologists (ACOG) has recently further extended the alert up to 1 year after delivery [2], suggesting the need to frame this disturbance in a span of 21 months (Fig. 18.1).

PND has a pooled prevalence of 12% (95% CI 11.4–12.5), which is significantly higher in women from low- and middle-income countries compared to those from high-income countries (OR 1.8, 95% CI 1.4–2.2) [3]. PND should be clearly distinguished from the so-called "baby blues": a brief, temporary state characterized by tearfulness and irritability that occurs in roughly 70% of new mothers. PND has

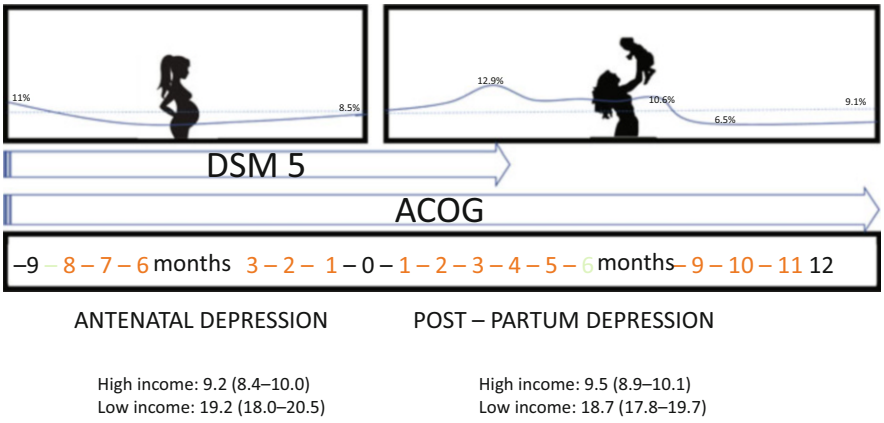

Fig. 18.1 Current DSM-5 definition of Perinatal Depression and extension suggested by ACOG. The continuous curve indicates estimated prevalence course across the 21 months: 11.0% in the first trimester which drops to 8.5% in the second and third trimesters. After delivery, prevalence of major and minor depression begins to rise and peaks in the third month at 12.9%. In the fourth through seventh months postpartum, prevalence declines slightly, staying in the range of 9.9–10.6%, after which it declines to 6.5%. The dotted line indicates the 9.1% prevalence of any form of depression in non-pregnant women of childbearing age

been shown to negatively impact the early stages of mother–infant bonding and adversely affect child development [4]. PND is linked to poor maternal self-care, inadequate nutrition, premature labor, and adverse obstetric outcomes [5–8]. Early detection is of paramount importance given the negative consequences of untreated depression on the mother and her unborn child. Whether PND should be considered a subtype of major depression that occurs in the perinatal period rather than a different form of depression remains unclear [9]. Multiple epidemiological studies have found depression to be more common following childbirth than at other times in a woman's life, suggesting an etiological link [10].

Several prenatal and perinatal risk factors for PND have been identified in childbearing women. The former group includes previous psychiatric disorders (especially history of PND or other mood/anxiety disorder), a family history of psychiatric disorders, a high level of neuroticism, and stressful life events in the previous year. In addition, lower socioeconomic status, low social support, daily hassles (work hassles, financial strain, time pressures), experiencing intimate partner violence, pregnancy complications, relatively younger (<24 years) or older (>35 years) age, and adverse obstetrical outcomes also increase risk for PND [11, 12].

18.2 Sleep and Pregnancy

Intense modifications of sleep can be observed among the several transformations that women endure during pregnancy, during which hormonal and physical modifications considerably impact both the circadian and homeostatic components of sleep regulation, leading to modifications of sleep architecture [13].

In human studies, progesterone and prolactin enhance non-rapid eye movement (NREM) sleep [14, 15], whereas rapid eye movement (REM) sleep is increased by estrogens and reduced by progesterone [16, 17]. Increased progesterone levels are also thought to be responsible for several modifications observed in sleep during the first trimester. Among these, increased urinary frequency, increased daytime sleepiness and shorter sleep onset latency (SOL) are noteworthy. Oxytocin peaks during the night, promoting uterine contractions leading to sleep fragmentation. Cortisol and growth hormone levels are also elevated, affecting sleep quality and inducing daytime sleepiness [13].

Nausea, shortness of breath, tender breasts, headache, constipation, and heartburn begin with pregnancy and often persist throughout, contributing further to sleep disruption. Sleep disruption and fragmentation typically characterize the antenatal period and the first few months after childbirth. The subjective quality of sleep is typically lower in pregnant women compared to control subjects, with perceived disruptions occurring as early as the first trimester despite an increase in sleep duration [18]. The amount of reported sleep begins to decrease in the second trimester. A recent meta-analysis showed that almost half of women experience poor sleep quality during pregnancy, with an average Pittsburgh Sleep Quality Index (PSQI) score of 6.4 (95% CI, 5.3–6.85) and a worsening trend from the second to the

third trimester by an average of 1.68 points (95% CI, 0.42–2.94) [19]. However, pregnancy is a risk factor for developing major polysomnography-assessed sleep disorders only in women with predisposing factors, such as obesity or hypertension. The physiological changes occurring during pregnancy in these women may contribute to the onset of pathological conditions, especially sleep-disordered breathing.

Some evidence suggests that obstructive sleep apneas (OSAs), short sleep duration, and poor sleep quality may be associated with preterm birth (PTB). Very few available studies all point to a slight increase in the risk for stillbirth for women who sleep in supine position during the third trimester [20]. Severely disrupted sleep in the third trimester has been found to be associated with longer labors and a fivefold increase in cesarean deliveries [21].

Polysomnographic (PSG) studies have shown that sleep undergoes several physiological modifications during pregnancy. A recent systematic review on PSG in pregnancy reported a correlation between subjective worsening of sleep quality across gestation and objective changes in sleep macrostructure, which become particularly evident in the third trimester [13].

Women have been found to have shorter sleep duration, poorer sleep efficiency, more awakenings, more stage N2 sleep, less slow wave sleep, less rapid eye movement (REM) sleep, higher apnea-hypopnea index (AHI), and higher periodic limb movement (PLM) index in late compared to early pregnancy. Quantitative analyses revealed a progressive decrease of delta and theta powers and an increase of beta-2 power suggesting frequent disruption of sleep during this period [22].

Overall, the main changes identified by PSG are increased WASO, reduced TST, and a transition from N3 and REM sleep to more superficial NREM sleep stages (N1, N2). These modifications become particularly evident in the third trimester and have been confirmed both by studies comparing pregnant with age-matched nonpregnant women and by a recent large analysis of PSG data collected among the same mothers during early and late pregnancy [13].

Suboptimal sleep duration has been associated with impaired glucose tolerance and gestational diabetes mellitus (GDM). This association has been confirmed after controlling for age, trimester of pregnancy, lifestyle, and metabolic risk factors. However, pooled data from prospective as well as cross-sectional studies have shown a close relationship between extreme (i.e., $\leq$4 or $\geq$10 h per night) rather than short sleep duration during the first half of pregnancy and incident GDM [23].

18.3 Sleep Disorders During Pregnancy

In addition to the physiological modifications that disrupt sleep during pregnancy, specific sleep disorders may appear for the first time, or may worsen during pregnancy. A full overview of these conditions is beyond the scope of this chapter, so we will briefly outline the clinical features of the most common conditions.

18.3.1 Sleep-Related Breathing Disorders (SRBDs)

The spectrum of sleep-related breathing disorders includes a set of disorders characterized by irregularity of respiratory pattern and/or abnormality in the quantity of ventilation during sleep. As defined by DSM–5, SRBDs include obstructive sleep apnea/hypopnea, central sleep apnea, and sleep-related hypoventilation.

SRBDs are quite common: approximately 20% of the general population are estimated to have an apnea-hypopnea index (AHI), calculated as the number of apnea and hypopnea episodes per hour, more than 5. These disorders are two to three times more common in pregnant than nonpregnant females, particularly during the third trimester [24, 25]. Snoring, a common sleep disorder reported by 4% of nonpregnant women, increases to 25% during pregnancy [26].

The prevalence of obstructive sleep apnea hypopnea syndrome (OSAHS) is approximately 2% in nonpregnant women but suspected to rise to almost 25% during pregnancy. However, the actual prevalence of OSAHS during gestation is not known [27]. OSAHS is characterized by repetitive episodes of obstruction of the upper airway which causes partial or complete interruption of the airflow resulting in oxygen desaturations. Patients usually report snoring, witnessed apneas, nocturnal awakenings, and poor sleep quality resulting in daytime sleepiness. SRBDs may develop or worsen during pregnancy and have a negative impact on maternal and fetal health. Snoring and OSAHS during gestation have been associated with an increased risk of GDM, preeclampsia, and pregnancy-induced hypertension [27, 28].

Considering the potential negative impact of SRBDs on maternal and fetal health, and the relatively high prevalence of this disease during gestation, an assessment of sleep quality and a query on snoring and other symptoms of OSAH should always be included in prenatal care. Behavioral changes, such as lateral sleeping position and/or head elevation, treatment of nasal congestion and avoidance of sedatives, excessive weight gain and sleep deprivation, should be recommended for all cases of pregnancy SRBDs. First-line treatment for OSAHS is positive airway pressure therapy (PAP). Various devices can be proposed, differing in the way of delivering the positive airway pressure; among them, the most common provides continuous positive airway pressure (CPAP), other possibilities are the auto-titrating devices (Auto-PAP) or bilevel delivery devices (Bilevel-PAP). Considering the increasing dimensions of the pregnant uterus and the weight gain, pressure needs have to be adjusted over time during the gestation.

The presence and severity of OSAH should be reassessed in the postpartum, as the severity may improve following delivery and some women may no longer require the treatment (Table 18.1).

18.3.2 Restless Legs Syndrome

Restless legs syndrome (RLS, or Willis–Ekbom disease) is a sensory-motor disorder characterized by unpleasant leg sensation occurring at rest or in the horizontal position (sensitive component) and irresistible urge to move the legs to relieve the

Table 18.1 Management of obstructive sleep apnea during pregnancy

	Method
1.	Behavioral • Sleeping in lateral position • Elevation of head end of the bed • Management of predisposing factors – Nasal congestion – Sleep deprivation – Use of hypnotic medications
2.	Disease-modifying strategies: • Use of positive airway pressure (PAP) devices – Continuous positive airway pressure therapy (CPAP) – Bi-level positive airway pressure therapy (BPAP) – Auto-titrating positive airway pressure therapy (APAP)

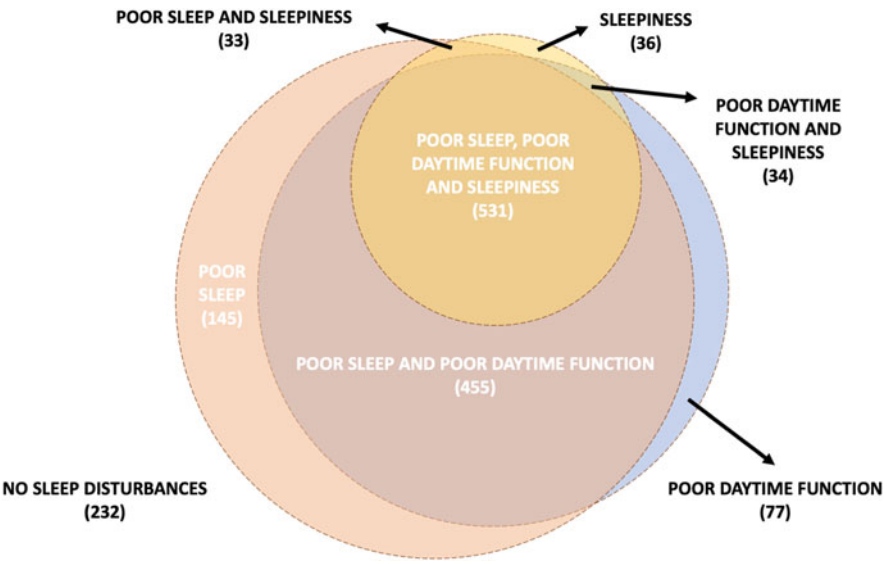

Fig. 18.2 Frequency of sleep-wake disturbances in a cohort of 1563 pregnant women, adapted from refs. [30, 31]. A substantial overlap can be observed among the three sleep-wake disturbances. Approximately one third of women reported all three disturbances and only 14.8% (=232) women had none

symptoms (motor component). The incidence of RLS in the general population is estimated to be 3.5–10%, and the syndrome is more common among women and older adults. Pregnancy is a risk factor for the emergency or exacerbation of preexisting RLS, and RLS symptoms are reported by as many as 27% of pregnant women [29]. RLS is strongly associated with sleep-wake disturbances (poor sleep quality, excessive daytime sleepiness, and poor daytime function) which are common in pregnancy and often overlap [30], as shown in Fig. 18.2.

The presence of transient RLS during gestation is a risk factor for subsequent development of chronic RLS. Furthermore, gestational RLS manifests in subsequent pregnancies in 60% of women [32].

For a long time, RLS was classified as idiopathic or secondary, depending on the presence of associated conditions. The idiopathic form is thought to be transmitted by autosomal dominant inheritance [33]. Conditions associated with RLS are iron deficiency anemia, folate deficiency, advanced renal disease, peripheral neuropathy, and pregnancy [34]. RLS can also emerge in association with Parkinson's disease, rheumatoid arthritis, and fibromyalgia, but these associations are less common [35]. However, the concept of primary and secondary RLS has been recently challenged, and "secondary" factors are now considered as conditions that facilitate the manifestation of RLS symptoms [36].

The pathogenesis of RLS in pregnancy, as in the general population, is still unclear, but there is evidence that the underlying mechanism could involve iron deficiency, along with alterations of dopaminergic transmission [37].

The therapeutic approach depends essentially on the severity of symptoms. In case of mild or moderate new-onset RLS, the conservative approach is recommended: sleep hygiene, avoidance of dietary stimulants, stretching, and moderate exercise during daytime. Serum levels of ferritin and folate should always be assessed and treated if abnormal.

When RLS symptoms are severe, a pharmacological intervention is recommended. Nonetheless, most of the drugs approved for RLS are not considered safe during pregnancy due to the poverty of studies on gestational RLS treatment. Recently, the International RLS Study Group developed some guidelines for the treatment of RLS in pregnancy and lactation [38]. Specifically, nonpharmacological treatment such as yoga, moderate exercise, and massage should be considered as first-line treatment as well as iron implementation if serum ferritin level is <75 mcg/L. For refractory cases, medication prescription is recommended at the lowest possible dose and for the shortest possible period of time. When medications need to be considered for refractory RLS during pregnancy, the guidelines recommend low doses of benzodiazepines (second and third trimester of pregnancy), combinations of levodopa/carbidopa (25/100 mg or 50/200 mg extended release), or low doses of oxycodone for very severe, refractory RLS (first trimester) [38].

18.3.3 Insomnia

Pregnant women often report disrupted sleep, reduced total sleep time, and decreased quality of sleep, particularly during the third trimester. More than one in two pregnant women (52–61%) complain about insomnia on an almost nightly basis, particularly during the last 8 weeks of pregnancy [39].

Polysomnographic recordings in the third trimester confirm the presence of longer sleep latency, longer wake time after sleep onset, reduced sleep efficiency, and decreased deep sleep [40]. Patients complaining of insomnia during this period

should be carefully assessed for OSA and RLS, which can present as difficulty in initiating or maintaining the sleep.

The presence of insomnia has a significantly negative impact in terms of quality of life and daytime functioning and has been linked with reduced ability to tolerate labor pain [41]. Moreover, some studies reported that women whose average sleep lasts 6 h tend to have longer labors, higher chance of cesarean sections, and increased risk of preterm birth compared to women sleeping for more than 6 h per night [21, 42].

Finally, insomnia is strongly associated with both preexisting and de novo peripartum depression [43, 44]. In case of pregnancy-related insomnia, the first recommendation is to rule out other sleep disorders, such as RLS or BRSD, or underlying depression. Therapeutic opportunities include nonpharmacological interventions based on sleep hygiene measures, dietary modifications, and sleep positioning adjustments. Some researchers reported efficacy of acupuncture, massages, yoga, and physical exercise [45]. Among nonpharmacological interventions, cognitive–behavioral therapy (CBT) is often effective and durable [46].

The use of sedative and hypnotic medications should be limited during pregnancy due to their potential for adverse effects on the developing fetus. Benzodiazepines (BDZ) and hypnotic benzodiazepine receptor agonist drugs (HBRA) may increase the risk of preterm birth, low birth weight, and/or small-for-gestational-age infants. However, lack of association between medication exposure and birth weight relative to gestational age and gender in a recent cohort of 82,038 pregnancies suggests the previously observed association with birth weight could be explained by earlier delivery rather than impaired intrauterine growth. These compounds are also generally not recommended in the third trimester to avoid neonatal withdrawal issues. Antihistamines are a possible alternative when medication is considered necessary, although the evidence for efficacy and safety is limited to very few studies.

Pharmacological treatment should be used for the shortest possible period, although, the benefits of these medications may outweigh the risks in particular cases [47].

18.3.4 Circadian Rhythm Sleep Disorders During Pregnancy

In physiological gestations, the normal circadian rhythm of melatonin secretion seems to be preserved, with the period of secretion proportional to the duration of darkness. The amplitude of the nocturnal increase of melatonin secretion tends to raise in the third trimester [48]. The literature concerning circadian rhythm disorders during pregnancy is scarce and essentially relies on studies of pregnant women working on rotating shifts and night-work. Circadian disruptions seem to have a negative impact during pregnancy; however, most of the evidence comes from animal studies [49]. Human studies on women exposed to shift work provided evidence of detrimental effects on pregnancy outcomes. An increased risk of fetal loss was confirmed among women working fixed night shifts, along with increased

likelihood of delivering small-for-gestational-age babies, and a mean lower birthweight [48, 50, 51]. Of note, an association between circadian rhythm alterations and preeclampsia has also been reported [52].

The circadian system appears to play a role in term of labor as well. Specifically, spontaneous rupture of membranes mostly occurs during the night (12 am–4 am), and the onset of labor tends to peak around dawn and dusk, with lower rates during the day [53, 54]. In conclusion, although disruption of circadian rhythms during pregnancy appears to reflect both external (e.g. shift work) and endogenous (e.g. sleep disturbances) factors, the mechanisms leading to negative pregnancy outcomes are still unclear.

18.4 The Relationship Between Sleep Disturbances and Perinatal Depression

Karacan and colleagues were the first to hypothesize a link between sleep disturbances and postpartum depressed mood [55]. Empirical evidence accumulated over the following 40 years confirmed this strong relationship, with effect sizes ranging between 0.4 and 1.7 across studies [56]. Indeed, sleep disturbances have been reported to be more frequent in depressed than nondepressed pregnant women [57, 58]. During regular pregnancy, sleep can change due to physical factors (i.e., enlargement of fetus), hormonal abnormalities, or random sleep-wake patterns of the newborn.

Circadian rhythm dysregulation is a common feature among patients with mood disorders [59, 60]. However, studies on circadian rhythms during pregnancy and the postpartum remain scarce. Gonadal steroids (estrogen and progesterone) are endogenous modulators of circadian rhythm amplitude that undergo relevant modifications throughout the perinatal period. The relationship between mood and melatonin secretion, a typical marker of circadian rhythms, remains unclear. Plasma nocturnal melatonin concentrations, especially in the morning hours, were lower in depressed pregnant, but elevated in depressed postpartum women, compared with healthy controls of same gender. Melatonin timing measures were advanced in pregnant women with a personal or family history of depression. These findings implicate disturbances in the regulation of the melatonin-generating system in pregnancy and postpartum depression and suggest that abnormalities in melatonin timing parameters may be markers of vulnerability to depressive illness during pregnancy [61].

These preliminary data support circadian intervention (i.e., bright light therapy, BLT) as prevention measures in those women showing circadian vulnerability [62–64]. Sleep patterns during pregnancy have been studied with subjective (self-report questionnaires, rating scales, and sleep diaries) and objective sleep assessment tools such as polysomnography (PSG) and actigraphy [65–67]. Studies have generally shown a stronger correlation between self-perception of sleep quality and the development of depressive symptoms [68, 69]. The majority of longitudinal studies show that worsening in subjective sleep increases the likelihood of negative mood

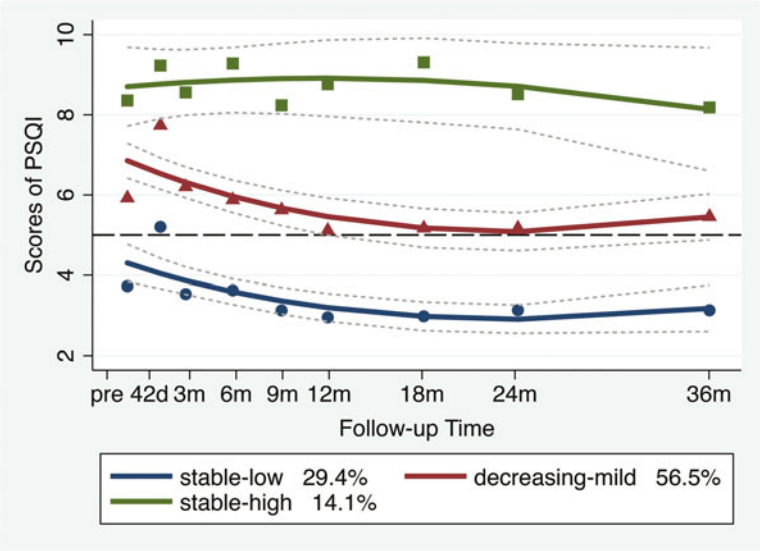

Fig. 18.3 Three distinct trajectories of subjective sleep quality in a cohort of 262 nonclinical pregnant women. The poorer sleep quality group demonstrated increased mood disturbances at 36 months postpartum [72]

symptoms across the perinatal period [70]. Although most women report mild sleep disruption throughout the perinatal period, increased risk of depressive symptoms in the postpartum has been reported among those with a significant decline in sleep quality from early to late pregnancy and those who report poor subjective sleep quality throughout [71].

Subjective sleep quality and mood disturbances were recently assessed in 262 Chinese women from late pregnancy to 3 years after delivery with nine fixed time points of data collection [72]. This large, longitudinal study confirmed that women are vulnerable to poor sleep quality from late pregnancy onward, with disturbances persisting over time. The authors were able to distinguish three distinct trajectories that are shown in Fig. 18.3. Poor sleep quality, depression, and anxiety scores during late pregnancy appeared to anticipate the sleep trajectories. In particular, worse sleep quality predicted mood disturbances at 36 months postpartum.

Poor sleep quality during early stages of pregnancy may contribute to the development of higher levels of depressive symptoms close to delivery [73]. Similarly, sleep disruption in late pregnancy has been associated with more depressive symptoms in the first few weeks after childbirth [69, 74]. Even the time of delivery has been associated with emotional disturbances, that is, sleep loss due to labor and nocturnal delivery has been linked with more emotional distress in the early postpartum, when "baby blues" in most commonly experienced [74]. Some studies have shown a higher frequency of sleep-wake disturbances (poor sleep quality, daytime sleepiness, poor daytime function) in depressed compared to nondepressed pregnant

women [56]. Furthermore, major depressive disorder has been associated with RLS, a typical cause of sleep disruption during pregnancy, especially in the third trimester [31, 75].

Krawczak et al. [76] compared sleep, daily activity rhythms, and mood during the third trimester and at 6–12 weeks postpartum between pregnant women with ("high-risk") and without ("low-risk") a history of mood disorder. By combining subjective (Edinburgh Postnatal Depression Scale, Pittsburgh Sleep Quality Index) and objective measures (actigraphy), they found that women with a history of depression reported worse mood, sleep, and daily rhythms during pregnancy; however, the only objective measure that significantly differed between the two groups was sleep efficiency (SE) in the postpartum period, suggesting a discrepancy between self-reported and objectively measured outcomes in their population. Variations of the interdaily stability, a measure of day-to-day stability of circadian rhythms, were found to correlate with day-to-day mood variation [77, 78]. High-risk women had lower variation amplitudes in pregnancy but not in the postpartum, when circadian rhythms are significantly influenced by the newborn. Sleep disturbances are reported in up to 90% of depressive episodes, but macro- and microstructural abnormalities often persist beyond the episode and have been proposed as markers which increase patients' vulnerability to relapse and recurrence and predictors of negative therapeutic outcome [79–84]. Likewise, sleep monitoring in pregnant women might be crucial to predict the likelihood of PND given the bidirectional link between sleep and depressive symptoms [65, 85]. Furthermore, abnormalities of macro-structural parameters and micro-architectural sleep features have recently been described in infants born to depressed mothers. These findings suggest that intrinsic features of sleep might contribute to the transmission of depression vulnerability from mothers to children [86].

18.5 Sleep Loss and Puerperal Psychosis

Puerperal psychosis (PP) is the most severe form of postnatal psychiatric disorder observed in mothers. It is estimated to occur in 1–2/1000 women in the first 6 weeks following delivery. A previous history of puerperal psychosis or bipolar mood disorder increases the risk dramatically, to over 30% [87]. The clinical onset is often abrupt and should be carefully distinguished from neurological causes such as autoimmune encephalopathies precipitated by immunological modifications that occur during the early postpartum [88]. Indeed, puerperal psychosis often presents as a full-blown manic psychosis with racing thoughts, distractibility, insomnia, and delusions but also delirium-like signs such as disorientation or acute dissociative experiences that are more typically observed in neurological conditions. Given that sleep loss is a widely recognized trigger for both manic episodes and psychotic symptoms, the abrupt peripartum modifications of sleep are likely to play a role in the pathogenesis of puerperal psychosis [89]. Although very few studies directly addressed this relationship, some evidence suggests individual differences in the

vulnerability to sleep-related mood regulation following sleep loss might explain the increased risk in women with bipolar disorder [90].

18.6 Routine Monitoring and Treatment

Monitoring sleep patterns during pregnancy appears to be a valuable preventive measure to detect the risk of PND. Polysomnography has provided the most objective evidence of a possible relationship between sleep disruption and depressive symptoms in the perinatal period. However, PSG should be reserved for severe or diagnostically uncertain cases. On the other hand, sleep actigraphy may be used extensively due to its minor cost and major comfort compared to PSG, especially during pregnancy. Preliminary findings from this growing field of research encourage the development of preventive interventions to ensure circadian rhythm and sleep stability throughout the perinatal period. These include clear communication of sleep hygiene to preserve positive sleep patterns, safe and effective chronotherapeutic measures such as BLT to target circadian rhythm disruption, and CBT to treat insomnia (iCBT) [91, 92]. Of note, a randomized controlled trial of almost 200 pregnant women without psychiatric morbidity confirmed that iCBT effectively reduces self-reported (but not objective) total wake time and might also have a positive impact on depressive symptoms [93].

In terms of pharmacological treatment, several available guidelines advise to continue antidepressants in women with a mood disorder who become pregnant, but clear evidence in support of this recommendation is lacking [94]. In the case of new episodes, most guidelines agree on psychosocial interventions for mild to moderate depression and pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs) for severe depression. Among these, sertraline is generally recommended as first line due to its relatively low teratogenic risk, whereas paroxetine is discouraged due to a slight increase of risk for congenital heart malformations. Antidepressant treatment can be safely continued during breastfeeding, although guidelines encourage close observation of the newborn. Reliable, evidence-based information on the use of sleep medications during pregnancy and breastfeeding is still very limited [95]. Whenever appropriate, the pharmacological treatment of sleep disturbances must include an individualized assessment and cautious examination of risks and benefits of maternal and fetal pharmacologic exposure [96]. In all cases, intrapartum and immediate postpartum monitoring should be guaranteed for the newborn exposed to psychotropic medication in utero.

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Sleep in Bipolar Disorders

19

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Abstract

Sleep disorders are ubiquitous across all phases of bipolar affective disorder (BPAD). Symptoms involving sleep are seen across all age group of patients presenting with BPAD. Sleep disorders are seen in manic, depressive as well as in the inter-episodic euthymic period. Sleep and affective symptoms show a bidirectional relationship; as sleep symptoms are often considered to be causative of affective dysregulation, leading to the warning signs of impending affective episodes. On the other hand, sleep symptoms are often among the most prominent initial symptoms in any affective symptoms. The management of sleep disorders in BPAD is riddled with unique challenges. Appropriate choice of investigations is very important for a precise diagnosis. The treatment involves both non-pharmacological and pharmacological approaches. Both the approaches are mostly used to complement each other.

Keywords

Sleep · Mania · Depression · Bipolar disorder · Chronotype

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19.1 Introduction

Bipolar affective disorder (BPAD) is an episodic disorder characterized by the presence of at least one manic or hypomanic episode with or without depressive episodes. It poses unique challenges to the clinicians owing to its variety in presentation. The disorder is quite common having a lifetime prevalence of 1% [1], though researchers are of the opinion that the more liberal threshold of bipolar spectrum disorder may inflate even further. Unsurprisingly, the concept of the disorder has been under constant evolution. The usual onset of the disorder is in the late teens to the late twenties. The prevalence does not show any gender disparity and equally involves males and females. The disorder is also life-threatening with high prevalence of completed suicide [2]. The disorder also has a devastating effect on the life of the patients with around one-fifth of the time following the first episode spent in illness [3]. Given this background, it comes as no surprise that BPAD is considered as one of the leading causes of disability.

The role of sleep in BPAD is very important. It forms one of the most important criteria in the diagnostic classificatory systems in most classificatory systems [4, 5]. It is well known that the criteria indicate that there can be a reduced need for sleep in manic or hypomanic episodes, whereas in depressive episodes the sleep may be either increased or decreased. Sleep disturbances can also be a troubling phenomenon in patients with BPAD in their euthymic phase. This chapter provides a comprehensive review of the sleep dysfunction in BPAD. Wherever possible the authors have employed systematic reviews and meta-analysis rather than individual studies to reach conclusions. However, when there has been a dearth of review, or to provide a historical context or to emphasize future trends, individual studies have also been quoted.

19.2 Sleep Disorders in BPAD

19.2.1 Sleep Disorders in Adults with BPAD

Sleep disorders in BPAD are quite pervasive, even more than the mood symptoms itself. In fact, it has been found that sleep disorders are present even in the euthymic states. Sleep disorders are characteristic of BPAD according to all the major diagnostic criteria. In a study on about 257 patients of BPAD [6] (including both BPAD-I and BPAD-II), it was found that all patients irrespective of their mood states had a delayed onset of sleep and increased midnight sleep breaks. Patients who were studied in mania showed higher prevalence of decreased need for sleep, whereas during depression, though insomnia was more common (up to 100%), hypersomnia was also highly prevalent (up to 75%) [6]. Studies done on patients who were in remission showed a sleep pattern akin to patients with insomnia, characterized by increased sleep fragmentation, and movement during sleep and higher activity levels during the least active hours of sleep [7].

Sleep duration is one entity that has been significantly associated with various mood states. Studies have shown that mood symptoms can emerge immediately after change in the total duration of sleep. The trend has been that a decrease in the total duration is usually followed by manic/hypomanic symptoms, whereas an increase in the total duration of sleep may precede a depressive episode [8, 9]. As a result, sleep symptoms are often pointed out when patients and attendants are made aware of emerging warning symptoms.

In manic episodes, patients usually present with a decreased need for sleep and also increase in the latency of sleep onset. Such disorders can be prevalent in up to 70–90% of the patients with mania [10]. Patients with mania can also present with shortened rapid eye movement (REM) latency and increased density. Decreased need for sleeping in mania has always been looked upon as a pathognomonic feature. Other studies have also shown that manic episodes present with decrease in total duration of sleep, decrease in REM latency, and increase in time spent without sleep after going to bed and REM density. These findings, along with the fact that decreased sleep can lead to precipitation of a new manic episode, have made sleep disorders a specific target for research in mania.

The research regarding sleep disorders in depressive phase appears to be more rigorous as compared to other mood states in BPAD. The rates of insomnia in depression across studies range between 78 and 100% [10]. In the depressive phase, other common sleep disorders include decreased sleep duration, delay in initiation, difficulty in sustaining the sleep, and early awakening [11]. The prevalence of hypersomnia, which is considered as an atypical feature, is also sizable at 75%. Not only the quality and quantity but macro-architecture of sleep is also altered during depression. There is a reduction of REM latency, increased REM density, and a trend of longer duration of REM sleep [12]. These symptoms often precede the onset of a clinical depressive episode, thus raising the possibility of allowing an early diagnosis of an impending episode. In probably the only study done on patient presenting with mixed episodes, the duration of sleep was found to be diminished [13]. In the various studies done on patients in remission, it was found that the patients tended to have an increased REM density, decreased REM latency, and less time spent in sleep as compared to healthy controls [14].

19.2.2 Sleep Disorders in Child and Adolescent with BPAD

The evidence regarding sleep in children and adolescents with BPAD appears to be less extensive as compared to the adults. However, it can be safely stated that the most common disorder that is seen in the adolescent age group is a decreased need for sleep [15]. The prevalence of parasomnias (e.g., nightmares, sleep paralysis) is also high in this age group as compared to the adults with BPAD [10]. Other common sleep disorders found in studies conducted in remitted bipolar pediatric patients included reduction of REM sleep and increase in non-REM sleep [16, 17]. When patients with pediatric BPAD were evaluated, sleep disorders were reported among the most common presenting complaints [18]. In another study done

on youths presenting with externalizing behavior, it was found that sleep disorders were one of the most common complaints in the subset who were finally diagnosed with BPAD [19]. The relation can be better explained with the help of another interesting study. In a study [20] on 28 adolescents with a then diagnosis of unipolar depression and 35 normal controls employing a prospective design, the diagnosis was revised after 7 years. The original polysomnography data at baseline were reviewed comparing patients who retained the diagnosis unipolar depression and those whose diagnosis changed to bipolar depression. It was found that patients who remained unipolar had decreased REM latency, increased REM density, and accentuated REM sleep duration. On the other hand, adolescents whose diagnosis changed had a shown a trend to spend more time in stage 1 sleep and less in stage 4. In conclusion, it may be said that sleep architecture can be an endo-phenotype for the subtype of mood disorder. This may be used for differentiating two states, wherever diagnosis is in question.

19.3 Pathophysiology

The pathophysiological basis of sleep disorders in bipolar disorders will require a brief recapitulation of various aspects of the circadian cycle. The circadian cycle consists of various cellular, neurobiochemical, and behavioral processes that are involved in informing our body about the phase of the day. Though essentially this is an endogenous process, in order to sync our circadian rhythm with the geophysical time (also called as entrainment), certain external cues are required. Such cues, also called *zeitgebers*, include activities like exposure to lights, meals, and ambient temperature. The central control of this process lies in the suprachiasmatic nuclei (SCN) located in the anterior hypothalamus. The information is transmitted throughout the body by another hormone called melatonin which is secreted from the pineal gland. Other than a diurnal variation in its levels (rises in darkness, peaks at midnight, and declines by dawn), melatonin also shows a circum-annual variation. It is postulated that this circum-annual variation controls the seasonal variation in behavior like sleep, appetite, and libido in animals. Melatonin also modulates the expression of clock genes, which are located in the *pars tuberalis* of the pituitary gland. This modulation leads to its action on the SCN through the melatonin receptors [21].

Melatonin also acts on the hypothalamo-pituitary axis (HPA) by stimulating the release of corticotrophin releasing hormone from the hypothalamus, which leads to the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland [22]. This leads to the diurnal variation in the release of various endogenous steroids. In addition, it also modulates the sensitivity of adrenal gland to ACTH. However, the endogenous steroids also exert their action on the other tissues of the body allowing the body to react to the stressful situations. It is postulated that the SCN is out of this control, which allows it to reset the circadian rhythm once the stressful situation is effectively dealt with.

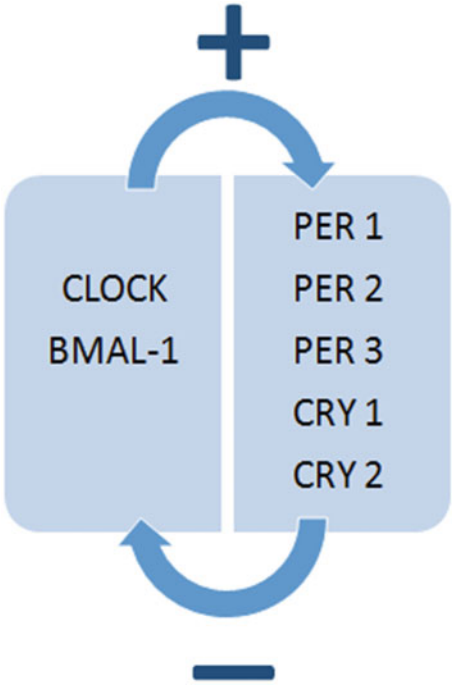

Fig. 19.1 Interaction of various genetic products in the modulation of sleep-wake cycle

The function of the SCN is also regulated by negative feedback from various genes (Fig. 19.1). Two important genes that should be named here are the circadian locomotor output cycles kaput (clock) and brain and muscle ARNT-like gene 1 (Bmal-1). The protein product formed from these genes forms a heterodimer that leads to the promotion of the period genes (per 1, per 2, and per 3) and cytochrome genes (cry1 and cry2). The protein products of period and cytochrome genes also form heteromers and get accumulated in the cytoplasm. When a critical level is reached, these heteromers interfere with the functioning of the CLOCK/BMAL complex and thus stops its promoting action on the PER/CRY complex. The proteins of PER/CRY complex are gradually degraded in the daytime finally leading to the removal of the negative feedback on the CLOCK/BMAL complex, usually over 24 h [23]. It is important to emphasize at this juncture that the sleep-wake cycle is not synonymous with the circadian rhythm, but rather the latter is one of the most important factors in modulating it. Other factors that play a role in modulating comprises various endogenous signals arising from other organs, like the gut, eyes, skin, etc.

19.3.1 Circadian Rhythm Dysfunctions

The dysfunction in circadian rhythm was one of the hypothesized reasons behind the various sleep disturbances in patients with BPAD, which has attracted significant

attention from the researchers. When compared with healthy controls, it was found that patients with BPAD in remission showed significant changes in their circadian rhythm. The changes included early phase shifting and increased time spent in sleep at night [24]. This findings were also supported by other studies that showed similar circadian dysfunction in recovered patients of BPAD [25]. The study also further goes on to endorse the fact that circadian disturbances could be the reason behind residual cognitive dysfunction in euthymic patients of BPAD [25].

Certain early studies found that patients with BPAD tend to have a shorter diurnal cycle as compared to controls [26]. It is postulated that in normal persons there are two sets of circadian rhythms. One is under the direct control of SCN and is related to propensity to fall asleep. The other is related to the total duration of sleep and is less connected to SCN. In patients with BPAD, there is dissociation between the two sets of circadian rhythm. This dissociation is related to loss of phase synchronicity in various presentation of the disorder [27].

Other than the circadian rhythm, studies have also intensively looked for the role of melatonin in BPAD. It has been found that patients with mania tended to show an early peaking of melatonin secretion and also higher levels than normal controls [28]. Whereas the melatonin peaking was found to be later than normal population in patients with BPAD in the euthymic phase [29]. In the depressive phase, it was found that the levels were lower for patients with bipolar depression [30]. However, there are certain authors who believe that the change in the levels of melatonin need not be state specific [31]. This is supported by the fact that the levels of melatonin in one study were found to be less than controls in all the phases, that is, manic, depressive, and euthymic [32]. It is worth discussing at this stage that patients with BPAD tended to show a higher suppression of melatonin levels in response to exposure to light as compared to normal controls. This suppression is blunted when the patient is treated with antipsychotics like sodium valproate or lithium. However, these findings are yet to be substantially replicated [33].

Attempts were also made to use serum cortisol for studying the dysfunction of the circadian rhythm. Past studies have shown that in the manic phase, the serum cortisol level tended to be higher at night and also reached the trough earlier as compared to controls [34]. During the depressive phase, it was found that the levels during the depressive phases may be elevated as well [35].

19.3.2 Role of CLOCK Genes

A brief introduction about the clock genes has already been provided in the initial part of this chapter. The role of clock genes in the sleep disorders in BPAD has been extensively studied. It has indeed been one of the rare successes in the field of genetics in psychiatry (Table 19.1). This enthusiasm was fueled by the animal studies showing that mutation of the clock gene showed behavior similar to mania and amelioration of those symptoms after being administered lithium [36]. A few studies effectively proved that single nucleotide polymorphism (SNP) at position 3111 of clock gene by substitution of thymine for cytosine was associated with

Table 19.1 Summary of evidence of relationships of genes related to sleep to clinical features of bipolar disorders

CLOCK gene	SNP at 3111 (T for C)—Delayed sleep latency
	Homozygous 3111C—Higher frequency of depressive episodes
BMAL-1	SNPs related to certain temperamental traits
PER 3	Differential response to treatment
	Evening chronotype
	Mood fluctuations
PER 2	Differential response to lithium
PER 1	Morning chronotype
CRY 2	Rapid cycling BPAD
CRY 1	Good response to lithium

delayed sleep latency and decrease in the total duration of sleep [37, 38]. It has also been seen that patients who have a homozygous 3111C setup tended to have a higher frequency of depressive episodes in BPAD, higher prevalence of insomnia, and lesser duration of sleep [38, 39].

However, the picture is not so rosy. A number of studies failed to find any relation with the various SNP of the clock genes and the various circadian phenotypes in BPAD [40]. However, it is now believed that the SNPs in clock genes may not be implicative in the causation of BPAD, a concurrent presence of multilocular interaction between the clock gene, BHLHB2, and the CSNK1E to increase the vulnerability of developing BPAD [40].

Another gene that has attracted interest is the Bmal1 gene. This gene is associated with various sleep disorders in BPAD like disorders in sleep-wake cycle and increased fragmentation of sleep [41]. A recent study has also tried to evaluate the putative relations between various SNPs of the clock genes and the temperament of the patients. Using the temperament evaluation of Memphis, Pisa, Paris, and San Diego-Auto questionnaire (TEMPS-A), it was found that certain SNPs of the Bmal1 gene were associated with certain temperamental traits [42]. For example, hyperthymic temperament was associated with three, anxious temperament with four, and cyclothymic personality was associated with two SNPs of the TIM gene.

Among the other genes, the per3 gene among the period genes has been shown to be associated with various symptoms of BPAD like mood fluctuations and differential response to treatment [42]. One of the most important mechanisms of action of lithium in BPAD was stabilizing the alteration of the circadian rhythm. It has been seen that patients who tend to respond well to lithium also tended to show expression of the per3 gene and *RORA* genotype.

Mutation in the period genes can also predict the various chronotypes in patients with BPAD. Polymorphism in the per1 gene is associated with the morning chronotype [43], whereas a polymorphism in the per3 gene is associated with the evening chronotype [44]. The cry2 gene (a cryptochrome gene) has been linked with the rapid cycling in BPAD [45], whereas the cry1 gene has been associated with a good response to lithium [46]. The GSK3β enzyme, which is associated with the

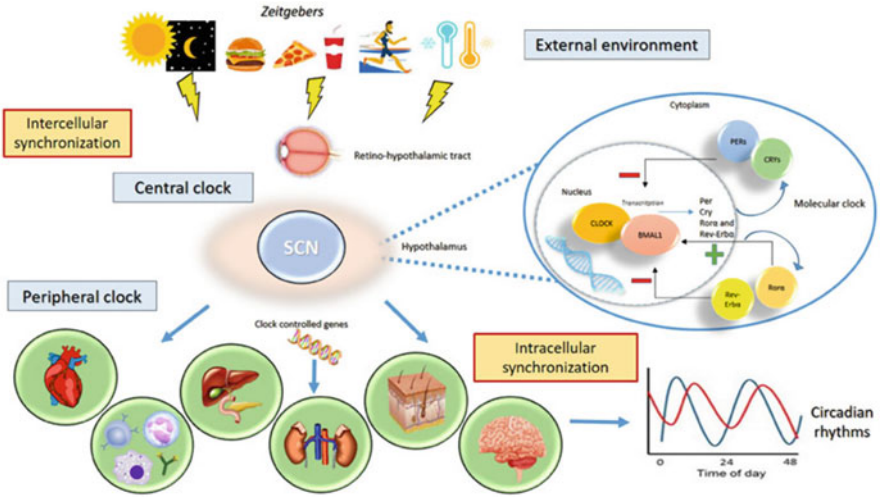

Fig. 19.2 Circadian rhythms. The clock system captures exogenous "zeitgebers" (light/dark cycle, temperature, exercise, food intake) and triggers the central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus through the retino-hypothalamic tract. The activity of the group of clock genes governs the generation of circadian rhythms. The genes CLOCK and ARNTL encode the transcription factors CLOCK and ARNTL, which together activate the transcription of Per, Cry, RORα, and REV-ERBα genes. The proteins PER1, PER2, PER3, CRY 1, and CRY 2 combine to inhibit their own transcription, whereas RORα and REV-ERBα act on ARNTL to activate and inhibit transcription, respectively. The processed information is transmitted to the peripheral clocks and to other clocks in the brain to stabilize 24-h periodicity. The stable relationship between internal rhythms and the external environment is needed to ensure the synchronization of individual endogenous rhythms. (Reproduced with permission from the authors of Steardo Jr L, De Filippis R, Carbone EA, Segura-Garcia C, Verkhratsky A, De Fazio P. Sleep disturbance in bipolar disorder: neuroglia and circadian rhythms. Frontiers in psychiatry. 2019 Jul 18;10:501)

regulation of the clock genes, has also been attributed as a potential mechanism of the therapeutic action of lithium [41, 47] (Fig. 19.2).

19.3.3 Chronotype

Another important aspect in the contribution of sleep in the pathophysiology of BPAD is the role of the chronotype of the patients. Chronotype is the inherent inclination of a person of preferring certain hours of the day to carry out certain actions. Grossly it is of two types. Persons who prefer carrying out activities in the morning hours are considered to have morning chronotype, whereas others who prefer the evening or the night hours are considered to have evening chronotypes. The circadian rhythm plays an important role in deciding the chronotypes. As already mentioned above, current evidence tells that polymorphisms in the cock gene and per3 predisposes toward evening chronotype, whereas mutations in the per1 gene is related to morning chronotype [23].

In a study comparing the chronotypes of patients with bipolar disorder type I (BPAD-I), schizophrenia, schizoaffective disorder, and controls, using the "Composite Scale of Morningness," it was found that the patients with BPAD-I typically had an evening orientation, a feature that was not shared by any of the three other groups [48]. This finding was further substantiated by another study done comparing patients with BPAD-I with a control group, which showed similar finding [49]. Studies that tried to compare the chronotypes among BPAD-I and BPAD-II showed no significant differences [50], though a trend toward more evening preference was observed in some studies in patients with BPAD-II [51].

19.4 Effects of Sleep Disorder in BPAD

Sleep disorders in BPAD can have a profound effect in the course and outcome of the disorder. The next section briefly highlights the various far-reaching effects of sleep dysfunction in BPAD.

19.4.1 Contribution to Relapse

There have been various theories postulated about how disordered sleep can lead to relapse in BPAD. One of the most common lines of thought have been the fact that sleep disturbances (delay in initiation, decrease in total duration, and poor quality) are one of the most consistent symptoms in the prodrome of both depression and mania in BPAD [52]. Secondly, various evidence points to the fact that induced sleep deprivation of any nature (e.g., sleep deprivation during family functions, long flights across time zones) can lead to appearance of manic symptoms [53]. In the same vein, another study provided evidence that prolonging the hours of sleep and exposure to darkness can lead to stabilization of the course of rapid-cycling BPAD [54].

Subsequent efforts were made to find the benefit of prospective monitoring of sleep in BPAD. Overall, the studies showed that a change in the pattern of sleep (e.g., delay in initiation and decreased duration) can predict onset of new mood episodes. However, the strength of this association with various mood episodes varied across studies [55, 56].

19.4.2 Role in Affective Regulation

There is a sizable volume of evidence that shows that sleep deprivation can lead to gradual negative affective state. Various studies done on non-diseased subjects showed that chronic sleep deprivation can lead to accentuation of negative emotions following a thwarting event and also attenuation of positive emotions to enhancing events [57]. An fMRI-based study [58] comparing the responses to images of emotional significance among sleep deprived patients and controls showed that

sleep deprived patients showed a higher activity (>60%) in the medial prefrontal cortex. The study speculated that sleep deprivation can lead to dysfunction in the medial prefrontal cortex, which is also related to affective regulation.

19.4.3 Role in Cognitive Functioning

There are also a number of studies that has shown that normal sleep is essential in effective cognitive functioning. Sleep deprivation adversely affected the vigilance, cognitive processing, and registration and consolidation of information [59]. This deficit is postulated in causing significant morbidity in patients with BPAD. This assumes even greater significance in younger patients or those involved in high functioning jobs, which makes it even more important that sleep disorders are properly evaluated in all patients with BPAD.

19.4.4 Role in Obesity

Obesity is one of the most notorious associations of BPAD. The current evidence safely concludes that obesity is more prevalent in both medicated and drug-naïve patients of BPAD as compared to controls [60]. A number of issues complicate this association. One of them is the propensity of various psychotropic drugs used in the management to increase body weight. Other factors include affective symptoms (both in mania or depression) that can lead to increased appetite and consequently weight gain. Sleep also plays an important role in causing obesity. In a meta-analysis conducted on this theme [61], it was seen that obese patients of BPAD tended to have a significantly shorter duration of sleep. The putative mechanism of this association is explained by the fact that sleep deprivation is often associated with increased appetite and insulin tolerance. Similarly, it has been found that sleep disorders in BPAD adversely affected the probability of patients exercising and having diets that could be considered weight-neutral [62]. These factors contribute to the fact that sleep disorders in BPAD can lead to obesity.

19.4.5 Substance Use Disorders

The complicated association of sleep in BPAD and substance use disorder is still a matter of speculation. Though research has substantially picked up in this aspect, a number of questions still remain unanswered. It has been proven beyond doubt that most of the substance use disorders are more prevalent among patients with BPAD [63]. The speculations range from the fact that substances have often been used for the purpose of self-medication to deal with troubling symptoms. The most commonly used substance for this purpose is alcohol, which at higher doses shows depressant effects [64]. Another substance that is often used is nicotine that helps

deal with the mood and cognitive symptoms arising out of the sleep deprived states in BPAD [65].

19.5 Effects of BPAD on Sleep Disorders

BPAD also plays a very important role in complicating the presentations of various comorbid sleep disorders. The following section highlights a few important sleep disorders that are often comorbid with BPAD.

19.5.1 Obstructive Sleep Apnea

Available evidence shows that obstructive sleep apnea (OSA) is highly prevalent in bipolar affective disorders. A meta-analysis of 12 studies, studying around 570,121 subjects with various severe mental illnesses, found that the prevalence of OSA in BPAD was around 24% which was more than schizophrenia but less than major depressive disorders [66]. Though depressive symptoms are highly prevalent in OSA, syndromal depressive episodes were found in around 22.4% of untreated patients of OSA [67]. The prevalence was almost comparable in studies using questionnaires and actigraphy. All of the studies were unanimous in finding that higher age and body mass index were associated with the development of OSA [66, 67]. Appropriate management of OSA with evidence-based treatments like continuous positive airway pressure therapy or mandibular advancement devices can also [68] improve the treatment outcome of comorbid BPAD [69].

19.5.2 Hypersomnia

Hypersomnia is another disorder that is often underdiagnosed in patients with BPAD. It has been estimated that the prevalence of hypersomnia in BPAD is around 29.9% [70]. A review on this topic opined that hypersomnia is a consistent state and trait domain of symptomatology of BPAD. However, it could not find out any relationship between hypersomnia and other clinical factors like polarity of the mood episode, type of pharmacotherapy offered, age, and type of BPAD.

19.5.3 Insomnia

Remitted patients with BPAD tended to report longer sleep latency, wake after sleep time, and total sleep time as compared to normal controls. These findings were replicated when manic patients were compared with normal controls. However, when patients of bipolar depression was compared to controls, they tended to show less daily activity and longer wake after sleep onset [71].

19.6 Bidirectionality in Relation Between Sleep Disorders and BPAD

Sleep is an important event of our daily life that is vital for normal functioning of our body. Disorders of sleep are often a symptom of BPAD. On the other hand, sleep in itself may also play a predisposing or precipitating factor in the course of BPAD. Thus, authors have always tried to conceptualize the relationship between sleep and BPAD as a bidirectional one. For example, unresolved sleep symptoms can lead to misinterpretation of the underlying psychiatric condition. For example, untreated insomnia can cause fatigue, impaired concentration, reduced efficiency at work which can mimic depressive symptoms. Insomnia is also a high risk for suicide, and the risk decreases with its successful treatment. Similarly, unaddressed insomnia in patients with affective symptoms may be responsible for treatment resistance. Thus, it becomes imperative that the proper evaluation of sleep is done before deciding the pharmacotherapy for the patient.

19.7 Approach to Assessing Sleep Disturbance in BPAD

The assessment of sleep in patients with sleep disorders should be detailed and tailored according to the presentation of the patient. At the onset of the assessment, a detailed analysis and goal-setting should be done. The guiding steps have been briefly illustrated in Table 19.2:

19.7.1 Investigations

The investigations for assessment of sleep disorders may include the following strategies.

19.7.1.1 Sleep Diary

Sleep diary is record of the events related to sleep that is maintained by the patients themselves. Important points that the patient has to maintain include:

(a) Time of going to bed
(b) Time taken for onset of sleep
(c) Time of leaving the bed
(d) No. of midnight awakenings
(e) Subjective assessment of freshness of sleep
(f) Causes of disruption if any
(g) No. of caffeinated drinks in 24 h
(h) No. of alcoholic drinks in 24 h
(i) Complete medical history
(j) Duration of exercises throughout the day

Table 19.2 Table highlighting approach to sleep disturbances in BPAD

Guiding principles	Suggested specific issues
To clarify type of sleep disturbance	Increase or decrease in duration, delay in phase, insomnia
To assess frequency, severity, and duration of sleep disturbance and factors leading to it	
Behaviors of the patient immediately contributing to sleep	Behaviors while going to bed (e.g., external temperature), while trying to fall asleep (e.g., using mobile phones), while waking up (e.g., sleepiness, lethargy)
An ABC (antecedent-behavior-cognition) charting is done in respect to the contributors of sleep	
Precise goals are recognized	Decreased in cell phone use
Motivational interviewing (MI)	The basic idea of these sessions is to facilitate the patient to generate potentially changeable behavior to derive better sleep and also analyzing its benefits and pitfall. The role of the interviewer is to be a facilitative one and not authoritative. Generally, the benefits are more pronounced when the suggestions are from the patients. The aims of the sessions should be periodically reviewed
Duke Structured Interview for Sleep Disorders (DSISD) scale can be used to characterize major sleep disorders	

19.7.1.2 Polysomnography

Polysomnography (PSG) is a multimodal investigation that provides us with a very detailed evaluation about various aspects of sleep. The current evidence shows that while the various parameters that are measured with PSG in patients with BPAD differ from normal control, the abnormalities may not be specific enough so as to differentiate between the various stages of BPAD or with other affective disorders [72, 73]. However, in spite of that, PSG remains the most preferred approach to study sleep disorders in patients with BPAD.

19.7.1.3 Actigraphy

Actigraphy is another tool that is used to study patients with BPAD for the sleep disorders. It is a relatively small instrument that can be worn on the wrist or other parts of the body and has the benefit of being noninvasive. As a result, the instrument is often used to obtain data over an extended period of time. Other than sleep, actigraphy has also been used to track the physical activity in patients with BPAD. Due to its ease of administration, studies using actigraphy far outnumbers that using PSG. A meta-analysis [74] conducted on this theme reported good concordance of findings with that of PSG, at least regarding parameters like sleep latency, sleep duration, fragmentation index, and sleep efficiency. The meta-analysis also pointed out that as compared to normal controls, euthymic patients with BPAD had an

increase in the sleep duration and decrease in the mean activity level throughout the day.

19.8 Management of Sleep Disorder in BPAD

Sleep disturbances are almost omnipresent among bipolar patients. Disturbances in sleep quantity and its architecture affect the course and prognosis of BPAD [14, 75, 76]. These disturbances are not only seen in the symptomatic phases but also in the asymptomatic or remission phases, and its adequate management becomes necessary for the overall treatment outcome [10, 14, 75, 76]. Hence, quite aptly sleep can be considered a likely biomarker of bipolar disorders.

It is only pertinent that sleep disorders are treated adequately and swiftly through combination of pharmacotherapy as well as non-pharmacological therapies, to manage symptoms of acute episode as well as prevent relapse and improves the overall quality of life.

19.8.1 Non-pharmacological Management

Pharmacological management of BPAD is so central to the overall management that it often becomes difficult to separate treatment of sleep disturbance from treatment of other disturbances. However, here we first focus on the non-pharmacologic methods, mainly because: (1) there are fewer side effects with virtually no interactions with other modes of management, pharmacological, as well as non-pharmacological; (2) though hypnotics are effective in some conditions (e.g., acute insomnia), there are risk of daytime residual effects, tolerance, dependence, and not to mention even rebound insomnia; (3) often in cases of BPAD, substance use disorders are found as comorbidity, and certain classes of insomnia medications—for example, benzodiazepine receptor agonists—pose a significant risk of use disorders [77].

Mood fluctuations in BPAD has been found to be associated with circadian rhythms [78]. This relationship is often bidirectional. *CLOCK* genes polymorphism has been found to be associated with circadian mood instability and relapses in BPAD [38]. There are several psychological interventions which are often done among patients with BPAD in the euthymic phase, namely interpersonal social rhythm therapy (IPSRT), family therapy, cognitive behavior therapy (CBT), and education about illness [79]. They have a role in management of sleep disturbance in both chronic insomnia (non-bipolar) and BPAD. Some of the common objectives of this approach have been depicted in Table 19.3.

Interpersonal and social rhythm therapy (IPSRT) is basically derived from the interpersonal psychotherapy. Originally designed for use in various affective disorders like depression, it focuses on problem-solving approach to various interpersonal problems. Important components of this approach are to adhere to specific sleep-wake rhythm and also maintain a closely monitored daily routine. It is designed to help people with bipolar disorder to improve their mood by

Table 19.3 Table showing common objectives of various non-pharmacological interventions for Bbipolar disorder

Common objectives of psychosocial interventions for bipolar disorder
• Educate patient and family leading to understanding and acceptance of illness • Identify early warning signs • Intervene immediately with emergence of warning signs • Improve compliance • Stabilize various biological and social rhythms (e.g., daily routines) • Improve coping skills • Improve communication both interpersonal and family • Re-engage various roles, like familial, social, occupational, etc. • Control substance use

understanding and stabilizing both biological and social rhythm. Additionally, there are sufficient evidences to suggest that insomnia that is comorbid with other psychiatric disorders can benefit from cognitive behavior therapy for insomnia (CBT-I).

Harvey et al. describe a treatment approach combining a modified CBT-I, some components of IPSRT (interpersonal social rhythm therapy), and motivational intervention (MI) [79]. Steps recommended by them are as follows:

19.8.1.1 Education for Sleep and Circadian Rhythm

Patients are educated first about the definition of circadian system and various factors influencing it, which are both personal as well as environmental. One of the most influential environmental factors influencing the circadian system is light and patients are taught about it. Patients are also educated about the importance of these rhythms, including circadian as well as the social one on their mental health. Patients are also warned about the usual inclination to often move toward a gradual delayed sleep phase. They are helped to identify any symptoms related to sleep as a common prodrome or warning sign of relapse. They are educated to see the link between sleep symptoms and fluctuations of mood and are educated about the mood regulatory function of sleep. Lastly, in the end, different behavioral strategies are highlighted and emphasized which are needed for treatment of both current and future sleep disturbances during the course of BPAD, which include hypersomnia, insomnia, decreased need for sleep, as well as phase delay in sleep. In subsequent sessions, various sleep principle are reiterated so that patients may have a basket of options for managing myriads of sleep disturbances and issues that they may face in future.

19.8.1.2 Components of Behavioral Modification

- Stimulus control [80] is one of the most important components of cognitive behavior therapy for insomnia (CBT-I) [81]. It pays attention primarily on two components:
  - Regularizing the sleep-wake cycle
  - Intensification of the bond between the bed and sleep [80]
- Restricting time in bed and avoiding bed completely for any activity apart from sleep is derived from various studies that concludes that disproportionate time

spent in bed leads to insomnia [82]. Initially time in bed is restricted to actual sleeping time only, and progressively the sleeping time is optimized keeping in view of the amount of sleep needed. It is important to maintain a minimum of 6.5 h of time in bed, to avoid mood symptoms resulting from sleep deprivation. The goal is to improve sleep efficiency to a minimum of >85–90%, ultimately leading to a more consolidated sleep which leads to a more fulfilling sleep and eventually leading to better mood stability.

- Regularizing sleep and wake times. Using the techniques of IPSRT patients is motivated to wake at the same time, even on weekends and holidays [83]. Day time naps are absolutely avoided which leads eventually to evening sleepiness. Gradually patients are able to move their bedtime forward by 20–30 min every week.
- Wind-down: In this, patients are gradually trained to indulge into a relaxing activity in dim to no light situation for half an hour to one hour prior to sleeping. This results in the circadian cycle to move ahead in patients who are evening-types and helps in entrainment [84]. In current times, one of the central issues are the use of various Internet-based media (social media, smart phones). In addition, patients are also encouraged to enforce a digital blockade and shunning electronic gadgets.
- Wake-up. It is important to bring about certain changes in habits and behaviors one immediately perform after waking up. Principle of IPSRT is used to entrain patients in making choices useful for wakefulness. Some of the examples are: getting up immediately as the alarm goes off and not hitting snooze. Also, they are trained to open the curtains to let the sunlight inside the bedroom, leave the bed immediately on waking up, make the bed tidy, and go out in the sun or somewhere bright. The bed should ideally be placed near the window. Patients are encouraged to indulge into morning chores and social contacts to counteract sleep inertia.

19.8.1.3 Cognitive Components

- It is important to challenge unhelpful beliefs about sleep [85]. Some of the common unhelpful believes are: “What is the point in going to bed early when I can’t fall asleep immediately,” playing games on cell phone helps me sleep, and “I can’t sleep without taking sleeping pills,” etc.
- Patients with BPAD are often concerned about their sleep, because they know that sleep symptoms can be warning signs. Some of the strategies are practiced to reduce rumination before sleep which includes cognitive therapy, diary writing, or scheduling a designated “worry period.”
- Monitoring: Patients of BPAD with sleep problems are extra vigilant and tend to look for signs of sleep deprivation like easy fatigability and cognitive symptoms during daytime. Using behavioral techniques, patients are counseled to accept the feeling of lethargy and drowsiness on waking up as normal “sleep inertia.”

19.8.1.4 Relapse Prevention

The relapse prevention is based on consolidating on gains and constantly working on behavioral strategies to achieve sleep hygiene. Important aspects that need more involvement are looked into one by one by making precise strategies and making plans for achieving each goal.

19.8.2 Other Non-pharmacological Methods

According to a meta-analysis on Internet-based CBT for insomnia, it was found that eCBT-I is useful in improving sleep latency, increasing total sleep time, and improving sleep efficiency [86]. An ECG-based home sleep monitoring device (M1) has been found to increase total sleep [87]. Only very recently, there are data to suggest that mindfulness-based therapy can improve overall sleep quality as well as other symptoms of bipolar [88].

19.8.3 Pharmacological Management of Sleep Disorders in BPAD

The empirical pharmacological treatment of insomnia in BPAD until now includes benzodiazepines, benzodiazepine receptor agonists, sedating antidepressants, anticonvulsants, sedating antipsychotics, and melatonin receptor agonists. There are many pros and cons of each molecule with the caveat that no medication has been till now specifically approved for management of insomnia in BPAD.

Benzodiazepines offer several benefits in the treatment of insomnia vis-à-vis known efficacy and a wide range of half-lives. However, there has not been a single study to directly prove that improving sleep by using benzodiazepines improves the overall mood. The current evidence also does not support any role of benzodiazepines in alleviating symptoms of the prodromal phase of mania or during the euthymic phase to prevent relapse. However, evidence from an uncontrolled retrospective chart review and a prospective open trial tells that clonazepam was effective as a substitute for antipsychotics used adjunctively with lithium in the maintenance treatment of BPAD. However, there are other trials available that could not replicate this success [89–92]. But benzodiazepines come with many side effects, like sedation, cognitive dulling, motor in coordination, risk of abuse, and withdrawal. Benzodiazepine receptor agonists, also called “Z” drugs like Zolpidem, Eszopiclone, etc., are another class of drugs used for sleep disturbances in bipolar. These molecules have usually shorter half-lives, so daytime sedation and carryover effects are minimal. Also they have minimal dependence potential when used on non-nightly basis [93, 94]. Although they are used as hypnotics to treat insomnia in BPAD, according to our review, there are no studies to date that have investigated their use as adjunctive medications in the management of BPAD. Thus, in one hand, Zolpidem has been commonly prescribed medication for insomnia in BPAD in atleast one chart review [95], use of benzodiazepines, on the other hand, for similar indications have not been encouraging [96, 97]. In fact, if we draw conclusions from

the large sample that participated in the Systematic Treatment Enhancement Program for Bipolar Disorder, benzodiazepines can be said to mostly be associated with worse outcome [98].

Low dose sedating antidepressants are often used to treat chronic insomnia [99]. Tricyclics and trazodone have been found to have a higher propensity to give manic switch in BPAD in comparison to SSRIs [100–103]. It can be concluded that the role of sedating antidepressants in the management of insomnia in bipolar should be taken with a pinch of salt.

Newer anticonvulsants like gabapentin, topiramate, and tiagabine are also sometimes used as an off-label agent as hypnotics in BPAD patients. There is some logic to it, as these agents are sedating and can have mood stabilizing properties as well. But there are only some suggestion that gabapentin can improve subjective quality of sleep, attenuate light sleep, accentuate REM sleep, and possibly amplify slow-wave sleep [103]. Similarly, tiagabine can lead to augmented slow-wave sleep, although its benefits as a hypnotic in primary insomnia is still debated [104]. As for gabapentin, the evidence is built on a few case reports [105] and on open trials against medications targeting circadian rhythms [106, 107]. The current evidence though appears promising is actually preliminary. Overall, these agents appear to be less useful as a hypnotic in BPAD than benzodiazepines and "Z" drugs.

Often atypical antipsychotics are used in treatment of BPAD, as first-line or as an adjunctive agent. Most have been found to have sedating properties. However, due to various side effects associated with these agents, like metabolic syndrome, lethargy, cardiovascular side effects, and above all the risk of extrapyramidal symptoms, their use as hypnotics are largely controversial. Low dose quitiapine has been found to be used most commonly as sedative-hypnotic agent in BPAD. It was found to improve sleep quality as well be useful in bipolar depression [108, 109]. However, these agents come with a catch as quite commonly they may cause restless leg syndrome and various sleep-related leg movement syndromes and paradoxically worsen the sleep quality [110, 111].

Due to no associated risk of abuse, potential melatonin receptor agonists like ramelteon and other drugs like exogenous melatonin can be useful in the treatment of BPAD-associated insomnia, especially in patients with comorbid substance use disorder [112, 113]. Some preliminary studies suggest that melatonin withdrawal in euthymic bipolar may delay sleep onset and also may have mild mood elevating effect [114]. Thus, we can say that the use of agents that target the melatonin receptor and exogenous melatonin in bipolar patients requires further investigation.

19.8.4 Other Novel or Miscellaneous Management Techniques

Light has been found to have therapeutic benefits in patients with BPAD, mostly during the euthymic phase. One putative mechanism of this benefit could be by regulation of mood by improving sleep homeostasis. A direct positive effect is seen on the EEG with increased delta sleep activity via the secretion of melanopsin, which is a photo pigment expressed in a subset of retinal ganglion cells that activates the

VLPO which in turn improves the sleep homeostasis [115]. Recent data also support an impact of BLT (bright light therapy) which by re-synchronizing the biological clock (circadian system), and/or enhancing alertness, and/or increasing sleep pressure (homeostatic system), consequently stabilizes the mood both in acute and remission phases [115]. Often combination of three different chronotherapeutics, such as sleep deprivation therapy, light therapy, and sleep phase advance, are all used to get the desired result. This sets the sleep clock and in turn treats the mood symptoms [116].

19.9 Conclusion

The relationship between sleep and affective symptoms in BPAD has been an important area of interest in the recent past. Though a lot of advances have been made, it is redundant to state that a lot of questions still remain unanswered. However, it is also important to state at this time that a better understanding in this area is important so that we can tailor our treatment approaches and achieve better outcome. The future approaches in this field involve upgradation of our knowledge regarding the genetics of sleep in BPAD and translation of that knowledge to pragmatic and appropriate treatment approaches. Our current understanding at various junctures is based on association, and we have failed to establish a causal relationship between various entities. But, further clarity in this relationship is required so that we can develop newer treatment approaches.

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Sleep in Schizophrenia

20

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Abstract

Sleep complaints in schizophrenia are fairly frequent. This chapter provides a comprehensive review of various aspects of sleep and schizophrenia. The initial section deals with characteristics of sleep disturbances in the form of subjective sleep complaints and macro- and microstructural sleep abnormalities. Epidemiology and characteristics of individual sleep disorders are also reviewed here. Structural, circuitry, and molecular pathophysiological correlates specific to the interface of sleep and schizophrenia are highlighted. Subsequent section focusses on the directionality of the association between sleep disturbances and schizophrenia; in this section, sleep disturbances across various stages of schizophrenia (from prodrome to residual) are reviewed along with a special emphasis on the mediating role of cognitive dysfunction. Later sections deal with various available treatment strategies and approach to a patient of schizophrenia with sleep complaints.

Keywords

Sleep architecture · Slow wave sleep · Sleep disorders · Psychosis

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20.1 Introduction

Schizophrenia is characterized by positive symptoms (delusions, hallucinations, passivity, etc.), negative symptoms (anhedonia, amotivation, apathy, etc.), catatonia, and cognitive symptoms (memory and attentional impairments, executive dysfunction, etc.). Principally, schizophrenia is defined by phenomena (or symptoms) that occur during awake state. However, up to 80% of patients with schizophrenia spectrum disorders have been found to show sleep disturbances, irrespective of the nature of symptoms [1, 2]. Disturbance of sleep in schizophrenia has been long known. Pioneers of modern psychiatry, Emil Kraepelin [3] and Eugen Bleuler [4], both have described sleep to be impaired in schizophrenia, a century years back. Sleep impairment has been understood as a "state" marker, with severity of clinical symptoms strongly correlating with degree of sleep disturbances in both chronic [5] and early phases of illness [6]. On the other hand, impairment of sleep has also been proposed as a "trait" marker. Disturbed sleep has been found to be prevalent during remission states as well; [7, 8] and both clinical [9] and genetic "at-risk" [10, 11] individuals have been reported to have sleep deficits. Moreover, many sleep disorders like obstructive sleep apnea (OSA), circadian rhythm disruption (CRD), restless leg syndrome (RLS), and periodic limb movement syndrome (PLMS) have been found to be comorbid with schizophrenia [2]. With both sleep rhythms and schizophrenia psychopathology being proposed to have common neurobiological underpinnings [12–14], study of sleep offers a window into greater understanding of etiopathogenesis, and hence, better management of schizophrenia. Moreover, several treatment options have been proposed with respect to the interface of sleep and schizophrenia [15]. In this chapter, characteristics of sleep disturbances in schizophrenia including various pathophysiological models, the bidirectional relationship between schizophrenia core psychopathology and sleep deficits, and treatment aspects are highlighted.

20.2 Characteristics of Sleep Disturbances in Schizophrenia

Most common sleep abnormality in schizophrenia patients is insomnia, that is, difficulty initiating and maintaining sleep [8]. Sleep in schizophrenia patients has been described in terms of subjective reports or objective assessments, mainly using polysomnography (PSG). While standard interpretation of PSG recordings describes their "macrostructure" in terms of sleep stages delineated according to Rechtschaffen and Kales [16] scoring criteria, sleep "microstructure" is described in terms of quantification of sleep spindles and slow wave activities, detection of arousals, etc. This subsection highlights impairments in each of these descriptors among schizophrenia patients.

20.2.1 Subjective Sleep

Subjective reports of sleep are generally assessed in terms of sleep quality. The Pittsburgh Sleep Quality Index [17] has been the most widely used tool. Subjective sleep disturbances have been reported to be present since early psychosis and to be associated with symptom severity [6]. Consistently studies have reported poor sleep quality in patients with schizophrenia [6, 18–22]. About half a proportion of patients with schizophrenia have been labeled as "poor sleepers." [21] Poor sleep quality also correlates with impaired overall quality of life [19, 21].

Subjective sleep estimation measures have been significantly correlated with objective sleep variables. Rotenberg et al. [22] found that subjective estimation of sleep onset latency, sleep depth, nighttime wakefulness, and dreams significantly correlated with polysomnographic (PSG) macrostructural measures such as sleep onset latency (SOL), percentage duration of slow wave sleep (SWS%), and eye movement density, respectively. Interestingly however, different treatment agents might have diverse effects on subjective versus objective measures. Kajimura et al. [20] reported that soundness of sleep in the subjective sleep assessment is better evaluated during treatment with zopiclone than with benzodiazepines. Baandrup et al. [18] found that melatonin significantly improved self-reported sleep quality, but had no effect on objective sleep efficiency.

Although less often reported, the frequency of subjective sleep disturbances in hospitalized schizophrenia patients has been reported to be statistically comparable to other psychiatric illnesses such as depression, anxiety, and substance use disorders [23].

20.2.2 Sleep Macrostructure

Generally, sleep macrostructure is classified in terms of sleep continuity (total sleep time, sleep onset latency, sleep efficiency, and wake time after sleep onset) and sleep architectural (percentage duration of each of the sleep stages, REM latency, and REM density) measures. To date, several PSG studies have compared sleep macrostructure between schizophrenia patients and healthy controls. A recent systematic review and meta-analysis by Chan et al. [24] evaluated 31 such studies that included a total of 574 patients and 515 healthy controls. This report concludes that schizophrenia patients have significant impairments in both sleep continuity and sleep architecture. They were found to have reductions in total sleep time, sleep efficiency, slow wave sleep (SWS), duration, and latency of rapid eye movement (REM) sleep and significantly increased sleep onset latency and wake time after sleep onset. A summary of this study's findings is depicted in Table 20.1.

Chan et al. [24] also highlight that factors like duration of illness, medication status, and duration of medication withdrawal influence these findings. While reduced duration of SWS and REM latency was seen in patients with duration of illness greater than 3 years, decreased REM latency was restricted to patients with short durations of illness. Medication-naïve patients were found to have impairments

Table 20.1 Sleep architectural measures in schizophrenia patients compared to healthy

Total sleep time (TST)	↓↓
Sleep onset latency (SOL)	↑↑↑
Sleep efficiency (SE)	↓↓↓
Wake time after sleep onset (WASO)	↑↑↑
Percentage duration of stage 1 sleep	↑
Percentage duration of stage 2 sleep	–
Percentage duration of stage 3 sleep	↓
Percentage duration of stage 4 sleep	↓
Percentage duration of slow wave sleep	↓
Percentage duration of REM	↓
Latency of REM	↓
REM density	↑
Duration of first REM	–

Number of arrows signify effect size (hedges g) of the difference between schizophrenia patients and healthy controls (one arrow = 0.2–0.5; two arrows = 0.5–0.8; three arrows >0.8); direction of arrows reflect direction of difference (upward = increased in patients; downward = decreased in patients)

restricted to sleep continuity measures only. Although sleep continuity measures were similar, schizophrenia patients with antipsychotic withdrawal for longer than 8 weeks were shown to have no significant deficits in any of the sleep architectural measures unlike those with shorter durations of withdrawal, who showed impairments in NREM stage 1 and 2 durations, and REM latency.

Studies have shown that while positive symptoms are associated with both sleep continuity and architectural impairments, deficits restricted to sleep architecture corelate with negative and cognitive symptoms. On one hand, reduced sleep efficiency, prolonged sleep latency, increased REM density, and shorter REM latency have been correlated with positive symptoms [5, 25–27]. While on the other hand, short REM latency and SWS deficits correlated with negative symptoms, [28–30] and cognitive symptoms correlated with SWS deficits [5, 27].

Longitudinal studies [31] report that in relation to phase of illness and treatment (i.e., during remission), REM parameters tend to normalize while SWS measures remain impaired.

Anecdotal studies have reported that both sleep continuity and architectural measures are useful in discriminating schizophrenia patients from other psychiatric disorders like depression [32]. Though impairments related to SWS have been suggested as being more specific to schizophrenia [33], in recent years, studying macrostructural abnormalities has gone out of favor mainly citing its lack of specificity to schizophrenia [33–35].

20.2.3 Sleep Microstructure

While macrostructure measures describe temporal organization of sleep, microstructure, which is analyzed by scoring phasic events, provides essential information

regarding dynamic characteristics of sleep processes that are responsible for the circadian alternation of wake and sleep [36]. Microstructure, most commonly, is described as under-arousals, awakenings, cyclic alternating pattern (CAP), sleep spindles, K-complexes and delta bursts (also called microarousals), rapid eye movements, body movements, atonia, nightmares, etc.

More recently, microstructure assessment has expanded to incorporate "dissociated stages of sleep (DSS)," which includes the phenomena of "intermediate sleep (IS)" [37]. Description of these phenomena involves analysis of electrophysiological sleep patterns that exhibit simultaneous occurrence or rapid oscillation between different sleep stages components. They include: NREM sleep with rapid eye movement (NRSWR), REM sleep without rapid eye movement (RSWR), REM sleep without atonia (RSWA), etc. This preliminary study by Guénolé et al. [37] found that RSWA was significantly increased in drug-naïve first-episode schizophrenia patients.

Although repeated awakenings (fragmented sleep) [38, 39], increased nightmares [40], and increased REM density [24] have been reported, microstructural assessment of sleep spindles and slow waves, which are the main brain oscillations during non-REM sleep, has received majority attention.

20.2.3.1 Reduced Sleep Spindles

Reductions in sleep spindles, principally examined during stage 2 NREM, have been repeatedly and consistently observed in schizophrenia patients, albeit in a few studies with very small sample sizes (for review see Manoach et al.) [41]. Measures used as descriptors of sleep spindle activity are spectral power and coherence in the sigma frequency (12–16 Hz) range, number, duration, density, amplitude, morphology of spindles, and integrated spindle activity. Consistent results have been found with respect to reduced number and density of sleep spindles and sigma power (see Table 20.2). Schilling et al. [42] report specific reduction in fast (12–15 Hz) spindle density. Fair consistency has also been seen on reduced spindle duration and amplitude in schizophrenia; Wamsley et al. [43] found these measures not to be significantly different compared to controls. Sigma frequency spectral coherence, spindle morphology, and integrated spindle activity have been reported/assessed only in small number of studies. Interestingly, the integrated spindle activity, a measure derived by dividing the sum of absolute amplitude of each detected spindle by total non-REM sleep duration, has been found to be significantly reduced in schizophrenia patients; and this difference has a very large effect size [44, 45].

These findings do not seem to be influenced by chronicity of illness/duration of illness as schizophrenia patients with both early and chronic stages of illness have shown similar findings [41]. Most of these studies (Table 20.2), with the exception of Manoach et al. [46] have been conducted in patients receiving antipsychotic medications. As of yet, it remains to be explored on how much of a confounding influence does use of long-term medications have on these findings. However, single-dose studies have demonstrated no effect of antipsychotic drugs on sleep spindles [47, 48].

Table 20.2 Findings on microstructural descriptors of spindle activity in schizophrenia patients

	Sigma power	Sigma coherence	Number	Duration	Density	Amplitude	Morphology	Integrated spindle activity
Ferrarelli et al. 2007	Reduced	NR	Reduced	Reduced	NR	Reduced	NR	Reduced
Ferrarelli et al. 2010	Reduced	NR	Reduced	Reduced	NR	Reduced	NR	Reduced
Manoach et al. 2010	Reduced	NR	NR	NR	Reduced	NR	NR	NR
Wamsley et al. 2012	***NS***	Reduced	Reduced	***NS***	Reduced	***NS***	***NS***	NR
Manoach et al. 2014	Reduced	NR	NR	Reduced	Reduced	Reduced	NR	NR
Göder et al. 2015	Reduced	NR	NR	NR	Reduced	NR	NR	NR
Tesler et al. 2015	NR	NR	NR	NR	Reduced	NR	NR	NR
Schilling et al. 2017	NR	NR	NR	NR	Reduced	NR	NR	NR

Compared to non-psychiatry controls; *NR* not reported (or assessed); *NS* not significant

Manoach et al. [41], in their review, also highlight that sleep spindles have significant correlation with cognitive (motor learning, declarative/visual memory, executive functions, intelligence quotient, etc.) and positive symptoms of schizophrenia. Studies have also attempted to address specificity of these findings to schizophrenia patients. Sleep microstructure measures of sleep spindles have been found to validly discriminate schizophrenia patients from depression [44] and non-schizophrenia psychosis [46].

20.2.3.2 Slow Wave Sleep (SWS) Deficits

A good number of studies have attempted to characterize microstructure of slow wave sleep in schizophrenia by comparing various descriptors in patients compared to non-psychiatry controls (see Table 20.3). Overall, we derived about nine descriptors from various studies—slow wave amplitude, delta wave count/density, wave slope (up/down), frequency of multipeak waves, slow frequency (i.e., delta/theta) spectral power, high frequency (beta and gamma) spectral power, altered distribution, accumulation/dissipation, and rapid eye movements (REMs). Highest evidence, in terms of most studies to show significant difference, is for reduced slow wave amplitude and delta wave count/density. Inconsistent results are seen on delta slow frequency (delta and theta) spectral power and altered distribution. Rest of the descriptors have been limited to a very few studies. Inconsistencies in results and in use of assessment methodology have led to limited attention to slow wave microstructural sleep deficits [10, 49]. Castelnovo et al. [50], in a recent review, emphasize upon use of uniform methodology. Another possible reason, for this lesser attention, has been quoted as the effect of medications. Antipsychotics have been found to induce electroencephalographic (EEG) slowing and reductions in slow frequency spectral power [51, 52].

Association of negative symptoms with reduced delta wave count [53, 54] and of positive symptoms with enhanced gamma power during slow wave sleep [55] has been reported. Recently, Kaskie et al. [56] found a significant negative correlation between slow wave density and positive symptoms. More studies, however, are required to strengthen these assertions.

A few studies have investigated the specificity of slow wave microstructural deficits to schizophrenia. Greater delta wave counts (Ganguly et al. 1987) [53], abnormal accumulation/dissipation of slow waves [57], and lower gamma power during SWS [55] were seen more in patients with depression compared to schizophrenia. However, amplitude of slow waves has been found to be comparable between schizophrenia and depression [57, 58].

20.2.4 Comorbid Sleep Disorders

Apart from sub-syndromal sleep disturbances and complaints, schizophrenia patients have been found to have many comorbid sleep disorders. It is common to have two or more sleep disorder comorbidities in schizophrenia patients

Table 20.3 Findings on microstructural descriptors of slow wave sleep in schizophrenia patients

	Amplitude	Delta/wave count/ density	Wave slopes	Multipeak waves	Delta power	High frequency power	Altered distribution	Accumulation/ dissipation	REMs
Hiatt et al. 1985	Reduced	NR	NR	NR	NR	NR	NR	NR	NR
Ganguly et al. 1987	NR	Reduced (total and frequency)	NR	NR	NR	NR	***NS***	NR	NR
Keshavan et al. 1998	Reduced	Reduced	NR	NR	Reduced (also theta)	NR	NR	NR	***NS***
Hoffmann et al. 2000	Reduced	NR	NR	NR	NR	NR	NR	***NS***	NR
Tekell et al. 2005	NR	NR	NR	NR	NR	Greater gamma power	NR	NR	NR
Göder et al. 2006	NR	NR	NR	NR	Reduced	NR	NR	NR	NR
Ferrarelli et al. 2007	NR	NR	NR	NR	***NS***	NR	NR	NR	NR
Sekimoto et al. 2007	NR	Reduced	NR	NR	NR	NR	Present (lack of laterality)	NR	NR
Ferrarelli et al. 2010	***NS***	***NS*** (large amplitude waves; total and frequency)	***NS***	***NS***	NR	NR	NR	NR	NR
Manoach et al. 2014	NR	NR	NR	NR	Reduced (also theta)[a]	NR	NR	NR	NR

Sekimoto et al. 2011	NR	Reduced	NR	NR	NR	NR	Present (lack of laterality)	NR	NR
Manoach et al. 2014 (analyzed stage 2 NREM)	NR	NR	NR	NR	Reduced (also theta power)	NR	NR	NR	NR
Kaskie et al. 2018	***NS***	Reduced	***NS***	NR	***NS***	NR	NR	NR	NR

Compared to Non-psychiatry controls; *REMs* rapid eye movements; *NR* not reported (or assessed); *NS* not significant
[a]Did not survive multiple comparison correction

[59, 60]. This subsection describes the characteristics of each of these comorbid sleep disorders.

20.2.4.1 Insomnia

Insomnia is commonly comorbid with schizophrenia [13]. Studies have reported prevalence rates of insomnia in schizophrenia patients to range from about one-fifths to one-half of the population [61–65]; with about an additional one-third population qualifying for subthreshold insomnia [61]. Moreover, disruption of several of the sleep continuity and architectural measures, especially reduced total sleep time and sleep onset latency (Sect. 20.2.2), implicate greater incidence of insomnia in schizophrenia patients. Among schizophrenia patients with comorbid insomnia, about 20% each have initial and middle insomnia and about 15% have late insomnia (early morning awakening) [62, 63]. About 50% of schizophrenia patients with comorbid insomnia have been found to suffer from severe insomnia [61]. Moreover, other sleep disorders like RLS, PLMS, narcolepsy, and parasomnias have been seen to be significantly associated with insomnia in schizophrenia [59].

There are inconsistencies in the reports showing association of insomnia with clinical symptoms of schizophrenia. Although studies suggest that insomnia is associated with an increase in paranoid thinking, even up to two to threefold [66], some studies on schizophrenia find no independent association of insomnia with positive and negative symptoms [62, 63]. However, recent studies have shown significant association of insomnia with positive symptom and general psychopathology [60, 67]. More significantly, and consistently as well, insomnia has been strongly correlated with suicide risk [64, 68].

20.2.4.2 Circadian Rhythm Disruption (CRD)

Although small in number, studies show strong evidence for CRD in schizophrenia patients [69–73]; strongly supported by results from animal models as well [74, 75]. The abnormalities range from mild to severely disturbed rhythms with fragmented sleep epochs. About half of the schizophrenia patients have been reported to have severe circadian disruption ranging from phase-advance or phase-delay to non-24-h sleep-wake cycles [73]. However, a recent study by Homabli et al. [59] report very low (i.e., 5%) rates of CRD in schizophrenia patients. Non-24-h melatonin cycles, manifold enhancement in sleep-related prolactin release, and non-inhibition of nocturnal cortisol secretion are some of the related abnormal endocrine rhythms (Van Cauter et al. 1991; Wulff et al. 2012) [72, 73]. The relation between positive and negative symptoms and CRD has been inconsistent and inconclusive. While Afonso et al. [69] found that schizophrenia patients with predominantly positive symptoms have a statistical trend for greater CRD, Bromundt et al. [70] failed to find a significant correlation between CRD and positive and negative symptoms. However, a strong association between CRD and cognitive symptoms has been elicited [70]. Speculations about the confounding role of antipsychotics are still inconclusive and studies addressing this relationship are sparse [13, 71].

Reviews focusing on CRD in schizophrenia suggest that interventions targeting resynchronization circadian rhythms may prove effective in the treatment of schizophrenia symptomatology [13, 76–78]. Perhaps, CRD has been found to be comorbid with other illnesses like bipolar disorder and major depressive disorder [76, 77].

20.2.4.3 Restless Legs Syndrome (RLS)

A series of papers by Kang and colleagues [79–86] report descriptive data on the proportion of schizophrenia patients having comorbid RLS. They report 21.4% of schizophrenia patients to have a comorbid RLS and up to half of them to have at least one RLS symptom, that is, sub-syndromal RLS. They report RLS to be significantly greater in schizophrenia patients compared to controls. Schizophrenia patients with RLS report significant association between psychopathology scores and insomnia [79]. Patients recruited in these studies were hospitalized and were on antipsychotic medications. As antipsychotics are known to cause RLS [87], confounding effects of medications cannot be ruled out. Perhaps, Kang and colleagues use the term antipsychotic-induced RLS in many of their reports.

Antipsychotic-induced akathisia, although a close differential for RLS and challenging to differentiate [13], should be cautiously ruled out before diagnosing comorbid RLS in schizophrenia patients. While, leg paresthesias characterize RLS, inner restlessness has been shown to be a hallmark to akathisia [88]. RLS and akathisia have also been differentiated based on periodic limb movements (PLMs) and long latency flexor reflex (LLFR); RLS has been reported to have greater PLMs and greater LLFR [88, 89].

20.2.4.4 Periodic Limb Movement Syndrome (PLMS)

Although PLMS is a most common associated feature of RLS and has been considered together with RLS by many authors, this subsection deals with PLMS separately. Reported rates of PLMS in schizophrenia are very inconsistent. While Staedt et al. [90] reported PLMS to be present in all schizophrenia patients, Ancoli-Israel et al. [91] showed PLMS rates to be 14%. Intriguingly, the former study emphasizes the chronicity of antipsychotic use and the latter study reports no significant correlation of PLMS with duration of neuroleptic use. Both these studies included patients in later ages and who were on chronic (mean duration: >25 years) antipsychotic treatment. A very recent study by Hombali et al. [59] reported a prevalence of 14.1% for combined RLS/PLMS symptoms in schizophrenia patients. This study, with a better sample size compared to the earlier two, reported RLS/PLMS to be significantly correlated with age; older aged patients being less likely to have this comorbidity.

20.2.4.5 Obstructive Sleep Apnea (OSA)

Several reviews and meta-analyses have suggested that OSA has been found to be a common sleep disorder comorbid with schizophrenia [13, 92–96]. The reported prevalence rates of OSA in schizophrenia range from 15 to 48%, with meta-analysis by Stubbs et al. [95] reporting a pooled mean of 15.4%. Increasing age and higher BMI have consistently been reported as significant predictors of OSA in

schizophrenia [94, 95]. While some report improvement in psychotic symptoms secondary to treatment of comorbid OSA, significant associations between antipsychotic dose and OSA measures have not been found [93, 94]. The comorbid rates, however, are found to be significantly less than those found in major depressive disorder and bipolar disorder [95].

20.2.4.6 Narcolepsy

Comorbid occurrence of narcolepsy and schizophrenia like psychosis, is not rare. Walterfang et al. [97] suggested that the association between narcolepsy and schizophrenia is a chance cooccurrence. They found no evidence for a common pathology and hence concluded that the association may be medication related. However, later studies suggested that patients with narcolepsy type 1 (i.e., NT1) present with psychotic symptoms along the course of their illness [98–102]. All these studies assessed for psychotic symptoms in diagnosed cases of narcolepsy. Studies describing narcolepsy among established cases of schizophrenia report prevalence rate of 5–10% [59, 103]. Hombali et al. [59] found these rates to be lower than those seen with depression and anxiety.

Although systematic investigations to delineate the two conditions as either cooccurring or related to a single disease process are required, a possible common autoimmune pathology has been suggested to underlie them [98, 104].

20.2.4.7 Parasomnias and Sleep State Misperception

Comorbid parasomnias such as sleepwalking, night terrors, nightmares, etc. in schizophrenia patients have been studied sparsely and have not been studied systematically. Hombali et al. [59] report that 9.1% of schizophrenia patients subjectively report parasomnias. Very recently, Reeve et al. [60] found nightmare disorder as a common comorbid sleep disorder in early non-affective psychosis patients, being second only to insomnia. Nightmares have been shown to be associated with an impending relapse, increased delusional severity, and risk of suicide [105]. Moreover, amelioration of nightmares and associated distress has been suggested to reduce psychotic symptoms as well [105].

Another important scenario is when subjective sleep complaints are present but objective measures including PSG do not reveal any abnormalities. This condition, regarded as "sleep state misperception (SSM)" or "paradoxical insomnia," has been found to be fairly common and has been shown to be associated with severity of negative symptoms [106]. Disturbances in memory and reasoning, core psychopathological elements of schizophrenia, have been attributed to SSM [107].

20.3 Pathophysiology

While sleep macrostructure provides us with a gross overview of the sleep architecture, microstructural abnormalities help us understand the pathophysiology of sleep dysfunction in schizophrenia better. As described in earlier sections, predominant and consistent dysfunction among various microstructural abnormalities has been

sleep spindle deficits and to some extent deficits in slow wave sleep. Therefore, pathophysiology of sleep dysfunction in schizophrenia has mostly been derived and understood based on specific abnormalities in sleep spindles. Moreover, as the basic deficit in sleep spindles has been their reduction in number/density, conceptualization of pathophysiology focusses on generation of sleep spindles specifically.

20.3.1 Structural Correlates

Thalamus has been primarily implicated in the pathophysiology of sleep spindles. Principally, the thalamic reticular nucleus (TRN), termed as "pacemaker," has been recognized as the most important structure associated with generation of sleep spindles [12]. Structurally, TRN is a shell-like wrap around the dorsal thalamus. Apart from TRN, the medial dorsal nucleus (MDN) and the lateral geniculate nucleus (LGN) have also been implicated [12] (see Fig. 20.1).

Structural changes in all the three regions—TRN [108–110], MDN [111] and LGN [112]—have been found to be implicated in schizophrenia, albeit inconsistently reported in postmortem studies [113]. Combining data from postmortem and animal studies, Steullet et al. [109] showed profound abnormalities in parvalbumin (PV) expressing neurons of the TRN in schizophrenia. Volume of

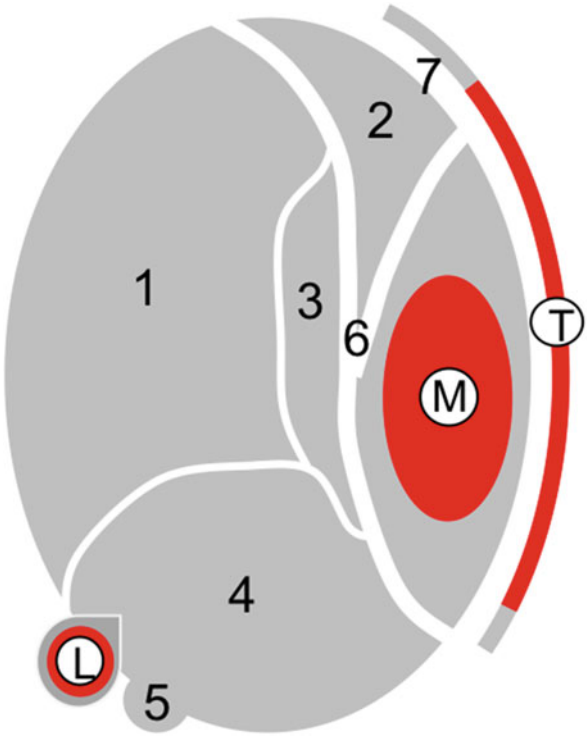

Fig. 20.1 Thalamic nuclei. Nuclei implicated in the pathophysiology of sleep are colored in red. *T* thalamic reticular nucleus (TRN); *M* medial dorsal nucleus (MDN); *L* lateral geniculate nucleus (LGN); (1) ventricular nuclei; (2) anterior nuclei; (3) lateral nuclei; (4) pulvinar nuclei; (5) medial geniculate nucleus; (6) internal medullary lamina; (7) external medullary lamina

MDN, especially the left MDN, has been shown to be reduced in schizophrenia patients. Converging evidence suggests that sensory gating and attentional and emotion processing deficits found in schizophrenia stem from deficits in TRN [12]; deficits in sleep spindles have been suggested to have a mediating influence [108–110].

Apart from thalamus, prefrontal cortex (PFC), especially cortical layer VI neurons, has been implicated in the initiation and maintenance of sleep spindles [114]. Specifically, pyramidal cells of the medial PFC have been shown to have a significant role in initiating as well as terminating sleep spindles [115]. Perhaps, PFC is one of the most significant neural areas implicated to be abnormal in schizophrenia; and cognitive dysfunction has been consistently associated with PFC deficits [116, 117]. Intriguingly, deficits in both TRN and PFC have been shown to be developmentally linked [109, 118].

Although not specifically investigated in schizophrenia, dopamine-related areas—ventral tegmental area (VTA), substantia nigra (SN), and ventral periaqueductal gray matter and their projections onto basal forebrain, midbrain, brainstem, and hypothalamus—have been implicated in CRD or sleep-wake cycle disturbances [119]. Dopamine-containing pineal gland, which regulates sleep-wake rhythms through the circadian release of melatonin, also has been implicated [119].

20.3.2 Circuitry Correlates

TRN, with its distinct structural organization, is the principal modulator of information flow between thalamus and cortex [110]. Specifically, thalamo-cortical (TC) and the cortico-thalamic (CT) circuitry neurons are implicated in the physiology of sleep spindles [114] (see Fig. 20.2).

In line with the hypothesis that dysconnectivity is the core underlying feature of schizophrenia [120], white matter connectivity abnormalities in TC networks, including the thalamic radiation that carries fibers from the thalamus to prefrontal areas, have been reported consistently in schizophrenia. Several lines of evidence, both from functional magnetic resonance imaging (fMRI) and source localizing EEG, suggest reduced thalamus-PFC connectivity [12, 119, 121].

Moreover, MDN and LGN have been showed to serve as “higher-order” and “first-order” relay nuclei, respectively [12, 121]. “High” and “first” in order refer to afferent projections from cortex, specifically layer V, and subcortical structures, respectively. Very recently, Parnaudeau et al. [122] emphasized MDN-PFC connectivity and its role in higher-order cognitive functions. With the focus distinctly falling on MDN, TRN-MDN-PFC circuit dysfunction has been suggested to underlie sleep spindle deficits in schizophrenia in recent studies [122].

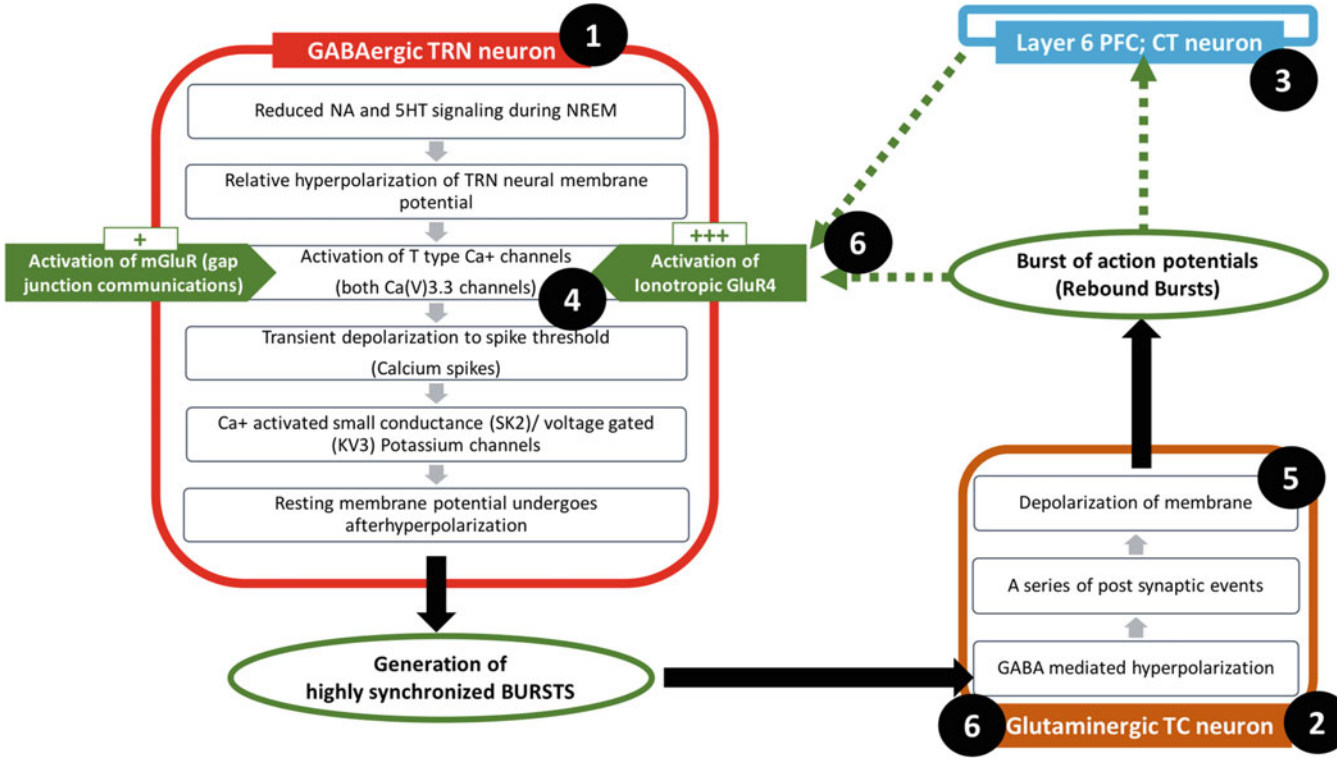

Fig. 20.2 Flowchart showing the basic physiological model of generation of sleep spindles through the thalamus-cortex-thalamus (TCT) circuit. (Adapted from Clawson et al. (2016)). Digits inside black colored circles depict proposed deficits in schizophrenia patients—structural abnormalities in TRN (1), TC projections (2), and the PFC (3); deficits in Ca+ channel activity in TRN (4); defective depolarization due to reduced GABA activity in TC neurons (5); reduced glutaminergic activity in the TCT circuit (6). *TRN* thalamic reticular nucleus; *GABA* gamma-aminobutyric acid; *mGluR* metabotropic glutamate receptor; *NA* noradrenergic; *5HT* serotonergic; *Ca* calcium; *V* voltage; *TC* thalamo-cortical; *CT* cortico-thalamic

20.3.3 Molecular Correlates

20.3.3.1 Neurotransmitters

The molecular mechanisms underlying sleep spindles have been shown in Fig. 20.1. A brief summary is given here: The GABAergic neurons in the TRN, which is the 'pacemaker' for sleep spindles, are the primary underlying structures. A reduced baseline noradrenergic and serotonergic signaling during NREM maintains a relative hyperpolarized state. Excitatory (glutaminergic) stimulus, predominantly from activation of ionotropic (or activation of gap junction communications from metabotropic receptors in its absence), activates the T type calcium (Ca+) channels. Their subsequent activation of voltage-gated potassium channels leads to membrane afterhyperpolarization and subsequent generation of highly synchronized bursts, that is, spindles. Consequently, "rebound bursts" are then generated by glutaminergic TC neurons after TRN-led GABAergic innervation mediates a series of postsynaptic events and subsequent depolarization. These rebound bursts send excitatory efferents to TRN as well as cortical neurons, which in turn excite TRN through CT neurons; excitatory effects being predominantly glutaminergic [114].

Reduction in the levels of intracellular Ca+ in the TRN, which otherwise has a high content in healthy individuals, has been hypothesized as one of the pathophysiological factors responsible for sleep spindle deficits in schizophrenia. Reduced GABA synthesis, secondary to reduction in glutamate decarboxylase enzyme activity and in GABA membrane transporter density, and therefore impaired GABA mediated depolarization and rebound bursts in the TC neurons, has also been suggested to underpin these deficits. One another molecular mechanism that is implicated to underlie these deficits in the TCT circuit is reduced glutaminergic activity that stems from reduced N-methyl-D-aspartate (NMDA) glutamate receptor activity in TC neurons, MDN, and PFC (for review see Ferrarelli [15]) (see Fig. 20.2). In a gist, this TRN model, with regards to neurotransmitter systems involved, implicates GABA and glutamine dysfunction.

In addition to GABA and glutaminergic neurotransmission, dopaminergic and cholinergic systems have also been implicated. GABA deficits in the TCT, specifically in the TRN, have also been shown to be caused secondary to activation of the dopamine-4 (D4) receptors; they are found presynaptically on GABA-containing projections from the globus pallidus to the TRN. Implying a role in insomnia among schizophrenia patients, abnormal dopaminergic D1 and D2 transmission has been hypothesized in SWS and REM stage impairments as well [13, 56]. Moreover, dopaminergic dysfunction has also been implicated in the CRD comorbid with schizophrenia. Dopamine has been known to promote wake and suppress REM and non-REM (NREM) sleep, and dysfunctional DR4 in the pineal gland leads to impaired melatonin release and subsequent CRD [119]. Recently, Yates [123] suggests a mutual, two-way relationship between dopamine and sleep in schizophrenia—elevated dopamine levels causing CRD and in turn CRD increasing dopamine release and sensitivity. He suggests that interplay between sleep and dopamine is vital to onset and course of schizophrenia. Reduced striatal dopaminergic neurotransmission has been hypothesized in RLS/PLMS. Understandably, RLS/PLMS

seen in schizophrenia has been attributed to the effects of anti-dopaminergic agents [81].

With respect to cholinergic neurotransmission, which initiates and coordinates REM sleep, cholinergic super-sensitivity has been suggested as an underlying mechanism for REM-related abnormalities in schizophrenia [119]. Specifically, negative correlation between REM latency and plasma cholinesterase isozyme activity has been demonstrated in schizophrenia [124]. Role of serotonergic neurotransmission in the pathophysiology of sleep deficits in schizophrenia, although suggested anecdotally in SWS deficits [56], is by and large understudied.

20.3.3.2 Genes

Several genes implicated in spindle physiology have been found to be impaired in schizophrenia patients. As discussed earlier, T type Ca+ channels in the TRN neurons are crucial for generation of sleep spindles. Two genes encode these channels—CaV3.2 (CACNA1H) and the CaV3.3 (CACNA1I). CACNA1I, whose genetic deletion leads to reduction in spindle generation, has been found to be significantly associated with schizophrenia [12, 41]. Excess dopaminergic transmission leading to abnormal activation of D4 receptors, be it in the TRN or in the pineal gland, has been proposed to be caused by impaired degradation of dopamine. The catechol-o-methyl transferase (COMT) gene and its encoding enzyme COMT are responsible for this process and have been implicated in sleep-wake regulation. Polymorphisms in the COMT gene have been consistently found in schizophrenia and implicated in comorbid CRD in these patients [119]. Val81Met polymorphism in the tyrosine hydroxylase (TH) gene, which is also involved in the dopaminergic neurotransmission, has also been found to be associated with RLS in female patients with schizophrenia [86].

Strong evidence for sleep-wake or circadian rhythm disturbances and their association with various endocrine rhythms in schizophrenia (discussed in Sect. 20.2.4.2) has prompted investigations to study molecular rhythmicity (or molecular oscillatory systems) in this disorder. These studies, although preliminary, suggest a role (decreased or loss of rhythmic expression) of several clock genes in schizophrenia [125–127]. They are the Circadian Locomotor Output Cycles Kaput (CLOCK), PERIOD (PER) 1, 2 and 3, TIMELESS (TIM), and the Cryptochrome (CRY)-1 genes. Particularly, the CLOCK gene has been suggested to be related with dopaminergic neurotransmission [125]. Interestingly, schizophrenia patients with CLOCK polymorphisms have been suggested to be at a higher risk of RLS as well [128].

Other genes that have been suggested to be associated with RLS in schizophrenia are BTBD9 and GNB3 [129]; their exact role in the pathophysiology of sleep in schizophrenia is yet to be clearly determined.

20.4 Bidirectional Relationship

Unlike conditions like depression, mania, anxiety, etc., where sleep disturbances are considered primary symptoms of the illness, sleep impairments in schizophrenia are traditionally considered to arise secondary to other core symptoms [130]. Over the course of this chapter, so far, we gather enough evidence to suggest a significant relationship between schizophrenia and sleep disturbances. Understanding the direction of this relationship is also crucial, especially from a treatment point of view. Both directions, schizophrenia psychopathology leading to sleep deficits and vice versa, have been postulated (for understanding sake, these will be referred in this chapter ahead to as "forward" and "backward" directional hypothesis, respectively). In addition, existence of a common pathway that explains or binds the two of them has also been suggested. This subsection describes evidence available on each of these three hypotheses. While reports of schizophrenia like psychotic symptoms in established cases of primary sleep disorders is an area to probe, studies on sleep disturbances across various stages in the schizophrenia illness course also are relevant in this regard. Studies assessing cognition in the context of sleep and schizophrenia are also described here. Endorsing a need to highlight the context of backward hypothesis, initially we discuss occurrence of psychotic symptoms secondary to sleep deprivation in healthy individuals.

20.4.1 Psychotic Symptoms in Sleep Deprived Healthy Population

Studying psychiatric sequalae of sleep deprivation in healthy individuals is an area that received fair attention in the recent past. The World Health Organization's World Health Survey (WHS), a 70 country, population-based survey, found a strong association between sleep problems and psychotic symptoms in general population, globally [131]. Two very recent papers [132, 133] systematically reviewed various experimental and observational studies with an aim to assess causal association between sleep disturbances and psychotic and related phenomena. Barton et al. [132] report that insomnia is associated with psychotic-like, dissociative, and hypomanic experiences. They also report an association between hypomanic experiences and evening-ness chronotype and circadian dysrhythmia; evening-ness chronotype, that is, working more efficiently in the evenings, going to sleep late at night, and waking-up late in the morning, was linked to dissociative experiences as well. Experimental sleep-manipulation studies consistently show a potential causal link between sleep loss and psychotic-like phenomena [132, 133]. While complex hallucinations and disordered thinking start to occur by 48 h of sleep deprivation, delusions, hallucinations in all sensory modalities, and a picture resembling acute psychosis occur by the third day without sleep [133]. Very recently, Reeve et al. [134] compared sleep loss condition (restricted to 4 h sleep for 3 nights for 2 consecutive weeks) with standard sleep condition and found that sleep loss is significantly associated with paranoia, hallucinations, and cognitive disorganization, apart from impaired emotional valence and working memory.

20.4.2 Psychotic (Schizophrenia) Symptoms in Sleep Disorders

Section 20.2 of this chapter describes various sleep disorders encountered in patients with schizophrenia. Various studies described in that section, by and large, report sleep comorbidities in established cases of schizophrenia (forward hypothesis). In this subsection, we attempt to focus on occurrence of schizophrenia/psychotic symptoms in cases of sleep disorders.

Most evidence for a backward directional relationship is available for narcolepsy. Specifically, narcolepsy type 1, that is, NT1, has been consistently found to present with psychotic symptoms along the course of its illness [98–102]. Data on schizophrenia/psychotic symptoms in established cases of insomnia are very sparse. However, very recently Cosgrave et al. [135] found psychotic-like experiences to be significantly greater in persons with insomnia compared to the control group. Although a bidirectional cause-to-effect relationship between RLS and schizophrenia has been suggested by Mackie and Winkelman [136], data to test this hypothesis are largely insufficient.

20.4.3 Sleep Disturbances Across Various Stages of Schizophrenia

20.4.3.1 Prior to Illness Onset/Prodromal States/Clinical (or Ultra)-High-Risk (CHR/UHR)

Two sets of studies, that is, those assessing sleep disturbances prior to illness onset retrospectively and those assessing them in CHR/UHR subjects, have been found. Some studies including CHR/UHR assessed the validity of sleep disturbances in predicting psychosis onset as well.

Abnormalities in sleep disturbance (in general), sleep duration (i.e., insomnia), and sleep continuity have been reported prior to illness onset in schizophrenia patients, consistently; some in fact date back sleep disturbances to early childhood (for review, see Davies et al. [6]; Lunsford-Avery and Mittal) [137]. These reports are predominantly retrospective chart reviews or family/parent/self-interviews. Sleep disturbance during remission has also been suggested as an important predictor of relapse in schizophrenia [8, 138].

Studies conducted on CHR/UHR individuals also report disturbances in sleep continuity and architectural measures. While reduced subjective sleep quality, reduced sleep efficiency, increased sleep onset latency, and increased wake time after sleep onset are the sleep continuity disturbances, increased slow wave sleep, greater PLMs, increased REM onset latency, and reduced REM% are the impaired sleep architecture measures (for reviews, see Davies et al. [6]; Lunsford-Avery and Mittal [137]; Zanini et al. [139]). Recently, Poe et al. [140] assessed sleep disturbances in 194 CHR individuals and found that they are significantly greater in this group compared to healthy controls, and that these sleep disturbances were significantly correlated with greater positive and negative symptoms and impaired overall functioning. While most of these studies are either polysomnographic or actigraphic, very recently, Waite et al. [141], using qualitative thematic analysis,

found disrupted sleep timing as the characteristic hallmark of sleep problems in UHR individuals.

Interestingly, longitudinal studies assessing onset of psychosis in UHR individuals consistently have found sleep disturbances at recruitment to predict not only transition to psychosis but also increased positive symptom severity [142, 143]. A mediating role of depression and anxiety, however, has been found [138]. While these studies assessed sleep disturbance in general or sleep continuity measures, Lunsford-Avery et al. [144] assessed CRD in UHR individuals and found them to be a possible vulnerability marker for emergence of psychosis. This study findings support the "two-way relationship between dopamine and sleep in schizophrenia" hypothesis by Yates et al. [123], which was based on a moderating role of CRD. A study by Alderman et al. [145], however, did not find sleep disturbances in UHR individuals to be significant predictors of transition to psychosis.

Of note, a few studies that assessed sleep profiles in genetic-high-risk, that is, unaffected first-degree relatives, have shown sleep architectural abnormalities in slow wave sleep [11, 146], REM sleep [146], and integrated spindle activity [10]. These reports suggest that these measures might be trait/endophenotype markers for schizophrenia. Interestingly, across all these studies, it has been seen that sleep continuity measures are unaltered in relatives.

20.4.3.2 Early/First-Episode Versus Chronic Schizophrenia

Impaired sleep macro- and microstructure (as discussed in Sects. 20.2.1 through 20.2.3) are well documented in early/first-episode schizophrenia patients, [6] therefore suggesting that duration of illness and hence chronicity of symptoms do not necessarily lead to these impairments. In fact, studies comparing sleep profiles across various phases of illness report no substantial difference [27, 147]. Anecdotal evidence, albeit inconsistently, however report poorer sleep quality in chronic schizophrenia cases compared to recent onset cases [148].

A meta-analysis by Chouinard et al. [149] on drug-naïve/untreated patients rules out significant confounding, moderating effect of medications on sleep impairments in schizophrenia. Rather, a clinical review by Monti and Monti [27] report counteracting effects of antipsychotics on sleep impairments in schizophrenia patients, across various phases of illness.

Although significantly impaired sleep profile in schizophrenia patients across various phases of established illness and significant association between impaired sleep measures and various symptom complexes have been demonstrated (also discussed in Sect. 20.2), surprisingly sparsely has there been an attempt to understand the directionality of relationship between sleep and schizophrenia symptomatology. Perhaps only very recently, Reeve et al. [150] using mixed effect models showed that insomnia predicted hallucinations later on than vice versa, and that the association between insomnia and paranoia was bidirectional.

20.4.3.3 Relapse

Reeve et al. [138], in their systematic review, identified three studies that assessed sleep disruption as a predictor of relapse in schizophrenia. They suggest that sleep

disruptions allow us to detect an impending relapse, with acceptable sensitivity and specificity.

20.4.3.4 Moderating Role of Cognitive Dysfunction

Increasingly, schizophrenia is being conceptualized and treated as a neurocognitive disorder [151], more so with its core symptoms and outcome being understood based on cognitive impairments [152–154].

With evolving evidence from neurosciences, the role of sleep in cognitive functions, specifically learning and memory, has changed from being passive to more active. While focus of earlier research was REM sleep, more recently the highlight has been on SWS and sleep spindles. In short, sleep spindles/SWS and REM sleep have been shown to be involved with consolidation of memories and executive functioning, respectively [155–157]. As sleep macro- and microstructural abnormalities related to these stages of sleep have been found in schizophrenia patients (Sects. 20.2.2 and 20.2.3), a causal association between sleep and cognitive deficits has been hypothesized [130]. Correspondingly, experimental studies have found associations between sleep spindle deficits and impaired sleep-related memory consolidation [158] and between reduced REM latency and impairment in executive functions [159]. However, some negative results in this regard have also surfaced recently [160]. Moreover, the TRN, the TCT networks, and clock genes implicated in core sleep deficits, that is, sleep spindles and SWS, in schizophrenia have been implicated in memory-related plasticity [41, 119].

Nevertheless, studies assessing the longitudinal course of sleep deficits, cognitive impairments, and other psychotic symptoms are necessary to objectively test the hypotheses proposed.

20.5 Treatment

Sleep disturbances needs to be treated due to its impact on core psychotic phenomena, quality of life, and social functioning in schizophrenia. Various strategies have been proposed.

20.5.1 Deep Sleep Therapy

Deep sleep therapy, though only of historical importance, marks an important landmark in the biological therapies for schizophrenia. Zurich-Burghölzli psychiatrist Jakob Klaesi (1883–1980) used a combination of two barbiturates for deep sleep therapy (putting patients into a therapeutic stupor) in 1920. The idea was previously attempted with other barbiturates and with bromine. This therapy was occasionally used as a remedy for psychotic illness in the 1930s and 1940s. Deep sleep therapy lists as one of the early somatic therapies along with insulin coma therapy and electro- and chemical convulsive therapy. Its use ceased, rather completely, after the introduction of chlorpromazine in the early 1950s [161].

20.5.2 Pharmacological Strategies (I): Insomnia

Currently, there are no clear recommendations regarding the most effective pharmacological treatment approach for insomnia in patients with schizophrenia [162]. Sleep-inducing effects of antipsychotics are largely utilized in clinical settings. Barring eszopiclone, most of the recommended treatments for primary insomnia, such as zaleplon, zolpidem, ramelteon, doxepin, and suvorexant, have not been studied adequately in schizophrenia probands [163]. Interestingly, diazepam, a classical benzodiazepine hypnotic, has been found to be effective in halting psychotic progression in those with early signs of exacerbation in a randomized controlled trial (RCT) by Carpenter et al. [164] Among the off-label options, only melatonin, paliperidone, and sodium oxybate have been systematically studied and are described briefly in this section (for detailed review, please see Stummer et al. [15]).

20.5.2.1 Antipsychotics

Antipsychotics improve overall quality and efficiency of sleep by reducing psychotic hypervigilance; mostly explained by its anti-dopaminergic actions. Moreover, GABAergic deficits secondary to activation of dopaminergic neurotransmission (discussed in Sect. 20.3.3.1) have been suggested to be undone by dopaminergic antagonism, primarily. Antagonistic effects at histaminergic and alpha-1 adrenergic receptors help enhance sleep, more directly. Anticholinergic effects have been shown to decrease the intensity of REM sleep and lengthen REM latency. Serotonin receptor antagonism has been shown to promote sedation and slow wave sleep as well [15]. A summary of effects on various sleep parameters (continuity and architectural) is provided in Table 20.4 (for review, see Stummer et al. [15] and Katshu et al. [165]). Antipsychotic effects on sleep are discussed in detail in Chap. 41).

Limited but available data on head-to-head comparisons show risperidone to be better than haloperidol, chlorpromazine, and flupentixol and, olanzapine to be better than clozapine (especially with respect to SWS) [15]. However, as a norm, more

Table 20.4 Effects of various antipsychotics on sleep parameters

	SE	TST	SOL	NREM1	NREM2	SWS	REM	WASO
Haloperidol	+	+	+					
Thiothixene	+	+	+					
Flupentixol	+	+	+					
Clozapine	+	+	+		+			
Risperidone	+				+	+		
Olanzapine	+	+		+	+	+	+	+
Paliperidone	+	+	+					

Adapted from Stummer et al. [15], Katshu et al. [165], and Oliveira et al. [167]; *SE* sleep efficiency; *TST* total sleep time; *SOL* sleep onset latency; *NREM1* non-rapid eye movement-stage 1; *NREM2* non-rapid eye movement-stage 2; *SWS* slow wave sleep; *REM* rapid eye movement; *WASO* wake time after sleep onset

sedating second-generation antipsychotics such as quetiapine, olanzapine, or risperidone have been utilized for treating insomnia in schizophrenia [166]. Moreover, a switch to second-generation antipsychotic from a first-generation antipsychotic has been shown to improve subjective sleep quality, which also correlates with improvement in negative symptoms [15]. Although investigation into improvement in sleep profile with quetiapine is carried out less systematically, its use in low dosages (25–75 mg) as an augmentation is largely evidenced from practice-based data [15]. Paliperidone has been the only systematically (i.e., randomized, placebo-controlled trial designs) studied antipsychotic for the treatment of insomnia in patients with schizophrenia. Paliperidone (3–12 mg) has been shown to increase increased total sleep time, decreased latency to sleep onset, improved sleep quality, and decreased daytime drowsiness [15, 167].

20.5.2.2 Melatonin

Ever since Ferrier et al. [168] in 1982 showed that schizophrenia probands with insomnia to have disturbed patterns of melatonin secretion (to the order of 2:3), use of melatonin in this regard has gained attention. Moreover, recent studies also suggest its role in reducing brain oxidative stress [169] and in the neurodevelopmental etiology of schizophrenia [170]. While Stummer et al. [15] in a very recent review identified three trials using melatonin in the treatment of sleep in schizophrenia, Oliveira et al. [167] in their systematic review include two trials using melatonin alongside one each for eszopiclone and paliperidone for treating insomnia in schizophrenia. Both report good tolerability and improvement with melatonin (average dosage 2–3 mg) in sleep efficiency and additional therapeutic benefits in attenuating metabolic adverse effects of second-generation antipsychotics.

20.5.2.3 Zopiclone/Eszopiclone

Non-benzodiazepine sedatives have been shown to accentuate slow wave sleep with minimal effects on REM sleep in contrast to benzodiazepines. Eszopiclone has been shown to increase sleep spindles during NREM stage 2 in schizophrenia patients, even in those without insomnia, [171] hence holding up promise in improving neuronal plasticity. A recent meta-analysis by Kishi et al. [172], which included three trials that studied the use of eszopiclone for insomnia in schizophrenia, concluded the molecule might be helpful in improving severity of insomnia. This meta-analysis also reports alpidem, another related "Z" drug, to have shown superiority in improving the overall schizophrenia symptoms, compared to placebo. Very recently, Mehta et al. [173] showed that eszopiclone is helpful in ameliorating persistent negative symptoms.

20.5.2.4 Sodium Oxybate

Sodium oxybate is routinely recommended in the treatment of cataplexy and narcolepsy [174]. Way back in the early 1980s, Levy et al. [175] reported a negative trial on the use of sodium oxybate in the treatment of schizophrenia. However, on a background of a hypothesis that GABA-B receptor agonists increase slow wave sleep, a systematic 4-week open-label trial by Kantrowitz et al. [176] showed that

sodium oxybate (4.5 g/night titrated up to 9 g/night) improved subjective sleep quality, slow wave sleep, and total PANSS scores, with no additional benefits in cognition. Potential risk of abuse with this molecule, however, remains a concern over the therapeutic benefits [15]. Also there are anecdotal reports of sodium oxybate inducing or exacerbating psychotic symptoms [177] and cause sleep apnea [178].

20.5.3 Pharmacological Strategies (II): Other Comorbid Sleep Disorders

Strategies for treatment of comorbid disorders like OSA, narcolepsy, CRD, nightmares, and RLS/PLMS are described in detail elsewhere (Chaps. 16, 17, 18, 19, 20, respectively). Consultation liaison between a psychiatrist and sleep physicians is suggested while managing these comorbid disorders, especially when having to treat with drugs that are routinely not used in psychiatric settings. In the context of schizophrenia, there are certain points that need to be specified for each of these disorders.

- RLS/PLMS: It is important to understand the role of antipsychotics in the causation of RLS/PLMS and also essential to differentiate it from antipsychotic-induced akathisia (described in Sect. 20.2.4.3). First-generation antipsychotics (FGAs) are less often reported to induce RLS than second-generation antipsychotics (SGAs), especially those with lower dopamine receptor occupancy, [179] an exception being aripiprazole. Aripiprazole not only seems to be less likely among all antipsychotics to cause RLS, but also has been used in the treatment of RLS [180–183]. However, an anecdotal case of aripiprazole-induced RLS also has been reported [184]. Gabapentin has been successfully used in the treatment of antipsychotic-induced RLS [179]. Caution should always be noted before initiating treatment of RLS with dopamine agonists like ropinirole and pramipexole, as these drugs are known to precipitate psychosis [185, 186].
- OSA: While on one hand psychotic symptoms have been reported to improve when comorbid sleep apnea is successfully treated; [93] on the other hand, antipsychotics (especially SGAs), mediated with their association with impaired metabolic profile, precipitate OSA [187]. Continuous positive airway pressure (CPAP) therapy remains the mainstay [92].
- Narcolepsy: Modafinil/armodafinil and sodium oxybate are the mainstay treatment for excessive daytime sleep and cataplexy in narcolepsy [188]. As discussed earlier in the previous section, sodium oxybate is also being used as an adjunct for treating insomnia in schizophrenia. Modafinil/armodafinil, although not successfully, have been studied as adjuncts in the management of cognitive and negative symptoms [189].
- Nightmares: Prazosin has been suggested for nightmares in patients with schizophrenia [105].

- Sleep state misperception (SSM): Although some benzodiazepines and Z-drugs have been shown to improve sleep perception in cases of primary insomnia by improving sleep itself [107], no data are available on schizophrenia patients.

20.5.4 Non-pharmacological Strategies

Waters et al. [162] found that cognitive behavior therapy (CBT) was the most preferred option (even preferred over pharmacotherapy) for treatment of insomnia among schizophrenia patients. While patients perceived pharmacological treatment as a short-term solution only, they saw CBT to have a potential to support and empower them in taking responsibility for their own recovery. Moreover, CBT for insomnia (CBT-I) is considered as a first-line recommended treatment for insomnia, generally [190]. Initially, Myers et al. [191] in a case series demonstrated feasibility and benefits of using CBT-I in schizophrenia with persecutory delusions. A subsequent pilot RCT demonstrated a significant reduction in insomnia (with a large effect size; $d = 1.9$) among patients with persistent delusions and hallucinations [192]. In a recent open-label trial, Chiu et al. [193] emphasized on the effectiveness of CBT-I for insomnia in schizophrenia; they emphasize that CBT-I ought to be tailored to the person and their insomnia presentation. Waite et al. [194] recommend adaptations in several factors specific to the context of sleep problems in schizophrenia for CBT. These include delusions and hallucinations interfering with sleep, attempts to use sleep as an escape from voices, circadian rhythm disruption, insufficient daytime activity, and fear of the bed based upon past adverse experiences.

Psychological treatment may also be essential for management of nightmares, which have been found to be the second most reported sleep complaint in schizophrenia [60]. Image rehearsal therapy (IRT), apart from prazosin, has been found to be helpful in these patients, especially in the early phases itself as an adjunct to standard treatment [105]. Behavioral approaches, primarily involving corrective feedbacks, have been used in "reversing" misperception of sleep in SSM [107]. While the long-term utility of these techniques are yet to be investigated, no study so far has specifically studied schizophrenia patients.

Brain stimulation therapies also have a role in improving sleep in schizophrenia. Limited but available literature on utility of electroconvulsive therapy (ECT) on sleep in schizophrenia suggests that it improves sleep efficiency, REM latency, and REM density [195]. Interestingly, Kim et al. [196] in an animal model reported electroconvulsive seizure to alter expression and daily oscillation of circadian genes that are implicated in sleep deficits in schizophrenia. Göder et al. [197] investigated the use of transcranial direct current stimulation applied during night in schizophrenia patients. Although they did not report any significant differences in sleep parameters compared to sham condition, they found improvements in certain cognitive variables. While use of transcranial magnetic stimulation in improving sleep profiles has been considered in psychiatric disorders such as depression [198], its use in schizophrenia is sparse.

Among complementary and alternative treatments, acupuncture has shown to improve several impaired sleep parameters in schizophrenia patients—SOL, SE, and WASO [199].

20.6 Approach to a Patient

As per the literature reviewed over the course of this chapter, we present an algorithm on how to approach a patient of schizophrenia with sleep disturbances (see Fig. 20.3). This algorithm does not represent strict guidelines (which are nonexistent due to limited data) but provides a rough guide in approaching this subset of patients.

This self-explanatory algorithm is divided into various phases, which define such an approach. They begin with clinical history and assessment, moving on to laboratory assessments (primarily polysomnography) and review of existing treatments corresponding to various phases of illness. Emphasis on reviewing sleep symptoms on each visit has been made, especially where clinical history does not reveal either subjective or objective sleep complaints. The algorithm culminates in management phase, which is classified into those treated on traditional-psychiatry lines and those requiring consultation liaison with sleep physicians.

20.7 Conclusion

Although sleep and its disturbances do not form a necessary domain in diagnosing schizophrenia according to existing classificatory systems, they are worth evaluating in each case. Sleep disturbances and disorders are commonly comorbid with schizophrenia. Most consistent evidence is in the form of insomnia and specifically sleep spindle and slow wave sleep deficits, apart from macrostructural abnormalities like reduced total sleep time and efficiency, increased sleep onset latency, and nighttime wakefulness. Preliminary data from both animal and human studies point to the thalamic reticular nucleus and abnormalities in the thalamo-cortical-thalamic network as the basic pathophysiological unit for sleep disturbances in schizophrenia. Although traditionally sleep disturbances were thought to be secondary to schizophrenia symptoms, the relationship between the two is bidirectional and rather intricate. Although limited number of studies are available on specific treatment strategies for sleep disturbances/disorders in schizophrenia probands, an accountable guidance for treatment approach could be put forth. Proper attention to assessment of sleep in schizophrenia and treatment of its disturbances can be the key in improving overall prognosis of this disorder. Certainly, data from high quality research (both experimental and clinical) studies are needed for improving the management guidelines.

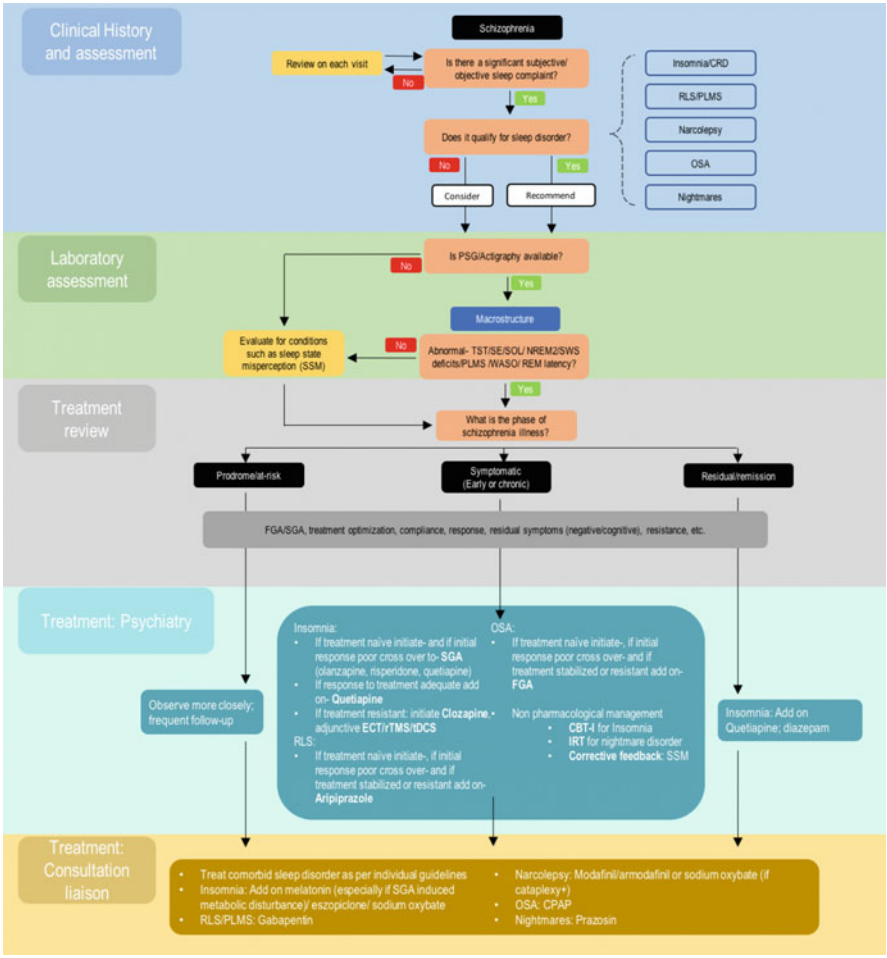

Fig. 20.3 Algorithm for approach to assess and manage sleep disturbances in patients of schizophrenia. *CRD* circadian rhythm disruption; *RLS* restless leg syndrome; *PLMS* periodic limb movement syndrome; *OSA* obstructive sleep apnea; *PSG* polysomnography; *SSM* sleep state misperception; *TST* total sleep time; *SE* sleep efficiency; *SOL* sleep onset latency; *NREM1* non-rapid eye movement-stage 1; *NREM2* non-rapid eye movement-stage 2; *SWS* slow wave sleep; *REM* rapid eye movement; *WASO* wake time after sleep onset; *FGA* first-generation antipsychotic; *SGA* second-generation antipsychotic; *ECT* electro-convulsive therapy; *rTMS* repetitive transcranial magnetic stimulation; *tDCS* transcranial direct current stimulation; *CPAP* continuous positive airway pressure; *CBT-I* cognitive behavioral therapy for insomnia; *IRT* image rehearsal therapy

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Sleep and Substance-Use Disorder

21

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Abstract

Sleep problems are ubiquitous in substance-use disorders (SUDs) ranging up to 90% in some individuals. For most substance-use disorders sleep problems are responsible for the initiation, persistence, relapse, comorbidities, complications, and poor quality of life. Neurobiologically, the different neurochemicals and neurocircuitry involving orexins, melatonin, acetylcholine, GABA, glutamate, dopamine, and adenosine influence the reward and sleep pathways. Different genes discovered in the last decade [e.g., period genes Per1 and 3, cryptochrome genes Cry1–2, circadian locomotor cycle kaput (CLOCK), neuronal PAS domain protein 2(NPAS2), brain and muscle ARNT-like protein 1 (Arntl1), and D-box-binding protein (Dbp) genes], morning and evening chronotypes, different cytokines and neuroendocrine mediators (e.g., melatonin), and emotional (mood symptoms like depression) and neurocognitive markers like impulsivity are involved in the bidirectional relationship between substance use and sleep. Due to such close relationship between sleep and addiction both demand equal attention by the treating clinician particularly because of the fact that currently insomnia disorder is considered to be comorbid with substance-use disorder (SUD) rather than just being induced. However, in spite of the high comorbidity between SUD and sleep disorders like insomnia, circadian rhythm disorders, and other sleep disorders, only some interventions like CBT-I have shown evidence for treatment. Most of the pharmacotherapies (e.g., gabapentin for comorbid insomnia and alcohol-use disorder) have shown initial promise but none have

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been approved. Similarly there is lack of any definite policy to address this public health concern at sleep-addiction interface. Hence technological advances in the form of optogenetics and chemogenetic techniques, newer Web-based psychosocial interventions, and newer drugs like dual-orexin antagonist along with wise policy decisions are required to understand and solve the crisis at the sleep-addiction interface.

Keywords

Addiction · Alcohol · Opioids · Sleep apnea · Insomnia

21.1 Introduction

"*Drink sir, is a great provoker of three things . . . nose-painting, sleep and urine.*
William Shakespeare

These lines by William Shakespeare illustrate the relationship between sleep and alcohol [1]. Much prior to Shakespeare, the intimate relationship between sleep and alcohol had been illustrated by the stories of Greek mythology where "Hypnos," the Greek god, had been lured by "Ambrosia" [2]. This not only is limited to literary and mythological worlds but also has firm corroboration from modern scientific literature—chronic alcohol use has been associated with many behavioral concerns including complaints with sleep in as many as 36–91% of patients [3]. Understanding the alcohol-sleep interface is relevant because increasing alcohol consumption is being considered as one of the most important public health problems—global per capita alcohol consumption increased from 5.9 L in 1990 to 6.5 L in 2017. In 2016, the harmful use of alcohol resulted in some three million deaths (5.3% of all deaths) worldwide and 132.6 million disability-adjusted life years (DALYs), that is, 5.1% of all DALYs in that year [4].

Apart from alcohol, other common substances that have an impact on sleep include tobacco, cannabis, opioids, and stimulants. Tobacco is responsible for eight million deaths yearly, mostly in low- and middle-income countries [5]. Cannabis is the most commonly used illicit substance across the world—in 2017 the total number of cannabis users was 188 million corresponding to 3.8% of the global population aged 15–64 years though the highest prevalence was in the population aged 15–25 years. Other substances having widespread use as per the World Drug Report, 2019, are opioids and stimulants [6]. Common among stimulants to be researched for sleep effects is cocaine. Hence this chapter tries to examine the relationship between "sleep problems" and common substances like tobacco, alcohol, cannabis, opioids, cocaine, and others starting from their epidemiology and pathophysiology and finally leading to their management. Hypnotics and sedatives will be covered separately.

21.2 Extent of Problem

The effect of each individual substance on sleep is unique based upon its distinct pharmacological profile:

Tobacco: Smokers are in general more dissatisfied with their sleep quality than nonsmokers and have more than double the risk of presenting complaints related to sleep like difficulty in initiating and maintaining, early awakenings, and increased daytime somnolence [7]. Insomnia is reported in up to 42% of abstinent smokers, while up to 80% of the smokers experience sleep disturbance which is exacerbated following cessation and this is a robust predictor of relapse [8, 9].

Alcohol: Sleep problems in persons with alcohol dependence have been reported consistently. A review of 13 studies reported that during the acute withdrawal stage from alcohol averagely 58.4% of patients experience insomnia [10]. However, prevalence varies between 36 and 91% due to differences in sample characteristics like demographics, drinking severity, duration of abstinence, and comorbidity across studies [10]. This appears to be a significant problem warranting clinical attention considering the prevalence of insomnia in general population which has been reported to range between 10 and 15% [11]. The problem persists for weeks to months after being abstinent from alcohol. Alcohol may induce or facilitate a number of sleep disorders, e.g., insufficient sleep duration, insomnia disorder, circadian rhythm abnormalities like circadian rhythm disorder, social jet lag, or delayed sleep wake phase disorder, and sleep-related breathing disorders [12].

Cannabis: Cannabis by its impact on the endocannabinoid system may improve sleep problems initially. Thereafter, with chronic usage sleep problems develop which have been found in 32% to 76% of persons experiencing withdrawal [13]. In a study among recent treatment-seeking adult chronic cannabis users ($n = 87$), 77% had >5 scores on Pittsburgh Sleep Quality Index (PSQI) and 55% had sleep efficiency scores less than 85% [14].

Opioids: The acute effects of opioids are sedation and daytime drowsiness which progressively increase with a higher dosage unless tolerance sets in. Within 2–3 days tolerance develops to these effects and once withdrawal sets in, insomnia is very common. In fact, insomnia is one of the defining features of opioid withdrawal as per the Diagnostic and Statistical Manual—DSM-5 Edition [15]. The one-month prevalence of poor sleep quality (defined as PSQI >5) was 76.3% among 513 heroin-dependent subjects [16]. Similarly, poor sleep quality has been reported among 80.6% of the patients taking "prescription opioid" compared to 8.8% of the control group in another study [17]. Hypoxemia and sleep-related breathing disorder are also common and up to 40–70% of patients on opioid substitution experience it [18, 19]. Paradoxically, opioids are also the treatment for some of the sleep disorders—improvement in sleep by opioids has also been reported in periodic limb movements and restless legs syndrome [20].

Cocaine: Unlike alcohol, cannabis, and opioids, acute intake of cocaine has improved sleep parameters during the initial weeks as per subjective reports [21]. However, quasi-quantitative measures like PSQI and objective parameters report contrary viewpoints suggesting paradoxical insomnia characterized by increased

sleep latency, reduced total sleep time, and slow-wave sleep during the early abstinence period [22].

From the above narrative, it is clear that sleep problems and substance use have bidirectional relationships. Furthermore, the presence of one may worsen each other as illustrated by the poor response to obstructive sleep apnea in patients with comorbid medication/drug usage [23]. It is also that with comorbid sleep and SUD, there is impaired quality of life, increased suicidality, and psychosocial problems [24]. A review of recent studies about the proportion of people having sleep and substance-use problems is shown in Table 21.1.

Nosology: The International Classification of Sleep Disorders (ICSD) 3rd Edition [25] has classified sleep disorders under seven broad sections like insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders. Traditionally, most of the major conditions have a category "induced due to a medication or a substance" except the circadian sleep-wake disorders. For the "induced" category, "the sleep disturbance is explained by another current sleep disorder, mental disorder, medication use, or SUD." However, one of the characteristics of ICSD-3 has been to discard the conceptualization of insomnia due to substance use as a mere secondary condition and to reclassify it as a subtype of chronic insomnia disorder [26]. Similarly, DSM-5 has also emphasized the diagnosis of "substance-medication-induced sleep disorder" when the symptoms of the sleep disorder predominate and they are sufficiently severe to warrant clinical attention and not merely substance intoxication or withdrawal-related symptoms of sleep disorder [15]. In the International Classification of Diseases-11 (ICD-11), sleep-wake disorders are outside the ambit of mental behavioral and neurodevelopmental disorders [27]. Considering their importance and the fact that more than one specialty is required to manage them, they have been recognized as a separate specialty in ICD-11 [27]. Otherwise, the structure is very similar to that of ICSD-3 and DSM-5 and shows an advancement from ICD-10 where they were mostly considered as nonorganic sleep disorders and were classified among various medical specialties [28].

The implications of such nosological changes are huge—acknowledgement of sleep problems as a comorbidity rather than a consequence of SUDs, thereby requiring to manage sleep problems side by side with the management of substance-use problems. At this juncture we need to understand the effects of individual substances on sleep and the underlying relationship between sleep and addiction.

21.3 Individual Substances

Studying the effects of individual substances on different sleep parameters is important because no two substances are alike and different substances affect sleep differently as shown in Table 21.2. Among the common substances alcohol is discussed in detail because it has the most extensive literature.

Table 21.1 Relationship between sleep and substance use in different studies across the world in the last 5 years

Author/ year	Sample/methodology	Results
Sivertsen et al., 2015	Population-based study among Norwegian adolescents aged 16–19 years	Short sleep duration, sleep deficit, large bedtime differences, and insomnia were associated with higher odds of all alcohol and drug use, misuse measures
Tang et al., 2015	Cross-sectional study exploring sleep quality in illicit drug users ($n = 2178$) in China than among nondrug users ($n = 2236$)	Prevalence of sleep disturbance was much higher in drug users (68.5%) than nondrug users (26.4%)
Skarupke et al., 2017	Cross-sectional study within German Health Interview ($n = 7698$)	Coffee, alcohol, and smoking contributed to the prediction of insomnia complaints in adolescents (11–17 years)
Terry McElrath et al., 2016	Nationally representative monitoring the future study—8th-, 10th-, and 12th-grade students in the USA	As 7 plus hours' sleep frequency increased, substance-use frequency significantly decreased, and vice versa. Controlling for deviance and psychosocial and general health covariates significantly decreased strength
Serdarevic et al., 2017	Cross-sectional study in a community outreach program in north-west Florida in the USA	Insomnia was 42% more likely among those who reported using prescription opioids than those who did not use it
Manzar et al., 2018	Community-dwelling Ethiopian adults ($n = 339$)	The poorest sleep quality was found among concurrent users of alcohol, khat, and tobacco smoking followed by concurrent users of tobacco and khat
Nguyen-Louie et al., 2018	Path-analytic models in a longitudinal study in the USA to examine whether the effects of risk factors were modeled by sleep chronotype, daytime sleepiness, and sleep-wake behaviors	Early-mid adolescent psychiatric health and sleep behaviors prior to drinking onset predicted greater substance use 5 years later
Lyngdoh et al., 2019	Cross-sectional study conducted among 739 students by a pretested, structured questionnaire in Manipur in India	Around two-fifths of the adolescents were not getting enough sleep. However, no such significant association was found with sleep pattern
Winiger et al., 2019	1656 adult twins in Colorado, USA	Earlier age of onset for regular cannabis usage was significantly associated with shorter sleep duration on both weekdays and weekends

USA—United States of America
This is not an exhaustive list and includes only prominent studies from different areas across the world

Table 21.2 Relationship between individual substance use and sleep problems

Substance	TST	SOL	SWS	REM latency	REM	WASO	States
Alcohol	↑	↓	↑	↑	↓	↓	Intoxication
	↓	↑	↓	↓	↑	↑	Withdrawal
	↓	↑	↑	↑	↓	–	Chronic use
Opioids	↓	–	↓	↑	↓	↑	Intoxication
	–	–	–	–	↓	↑	Withdrawal
	–	–	–	–	–	–	Chronic use
Cannabis	↑	↓	↑/↓	–	↓	↑	Intoxication
	↓	↑	↓	↓	↑	–	Withdrawal
	–	–	↓	–	–	–	Chronic use
Cocaine	↓	↑	–	↑	↓	–	Intoxication
	↑	↓	↑	↓	↑	–	Withdrawal
	↓	↑	–	↑	↓	–	Chronic use
Nicotine	↓	↑	↓	↑	↓	–	Intoxication
	↑	↓	–	↑	↑	↑	Withdrawal
	↓	↑	↓	↑	–	–	Chronic use

TST total sleep time; *SOL* sleep-onset latency; *SWS* slow-wave sleep; *REM* rapid eye movement sleep; *WASO* wake after sleep onset; ↓ decreased; ↑ increased; – not available; and ↑/↓ varies with the dose of the substance

Adapted from Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: a focused review. The American Journal on Addictions. 2015 Oct;24(7):590–8

21.3.1 Tobacco

For the current users, nicotine increases both overall sleep-onset latency (more studies) and REM-onset latency. However, it reduces the sleep efficiency, percent of slow-wave sleep, and overall total sleep time while findings regarding the percentage of REM sleep are inconsistent [29]. For tobacco users in withdrawal or those who are abstinent, it decreases common sleep parameters like total sleep time, sleep and REM latency, increased daytime sleepiness and sleep efficiency except an increase in the percentage of REM sleep [30]. Overall, polysomnographic (PSG) studies suggest that smokers have less deep sleep than nonsmokers [31]. Recent studies have shown that even among e-cigarette users there was more impact that is less sleep duration than among otherwise healthy individuals [32]. Tobacco use and sleep interact through cognition, affective, and emotional mediators.

21.3.2 Alcohol

Acute alcohol intake and sleep changes in healthy individuals: Multiple studies have extensively investigated the acute effects of pre-bedtime dosage of alcohol. As the blood alcohol levels continue to rise in the initial part of the night, the sedative effects of alcohol come into play. A shortened sleep-onset latency and increased

slow-wave sleep are the commonest features during the first part of the night. REM sleep, in turn, is suppressed and REM-onset latency increases, with decreased REM sleep in this early part of the night. Some studies have shown these REM findings to persist throughout the entire night [33]. The second half of the night is characterized by increment in stage 1 sleep and periods of wakefulness. The initial augmentation and later poor sleep quality often herald the beginning of a downward spiral of insomnia and increasing amounts of alcohol use as a form of self-medication leading to a vicious cycle [34].

21.3.2.1 Alcohol and Its Effects on Sleep in Patients with Alcohol Dependence

As a person continues with alcohol intake, with time as alcohol is metabolized and blood alcohol levels fall, there is an increase in stage 1 and 2 non-REM sleep (N1 and N2 sleep), and REM sleep, with multiple awakenings and reduction in sleep efficiency. These sleep disturbances may persist even after the acute effects of alcohol have abated [35].

The duration for which the sleep disturbances persist varies considerably among different studies. Around 91% of individuals with alcohol dependence experience sleep disturbances after about a week of abstinence [36]. Research shows that sleep disturbances improve over the first 2–4 weeks of abstinence. Sleep disturbance is very common in early alcohol recovery (2–8-week period following detoxification). Studies report that up to 65% of patients in early recovery experience sleep disturbances. However, these may persist even at 27 months of abstinence [37].

21.3.2.2 Sleep Disturbances and Relapse to Alcohol

Research over the past three decades has given rise to considerable evidence that sleep disturbances can possibly predict relapse to drinking. Among alcohol-dependent persons presenting for treatment, baseline sleep problems upon entering treatment may be predictive of subsequent relapse. Individuals who report insomnia within 6 months before quitting are more likely to relapse even after 5 months of abstinence [38]. Among the earliest PSG studies it was found that certain measures at the baseline (that is, at the time of admission) such as short rapid eye movement (REM) latency, percentage of REM sleep, and increased REM density possibly predict relapse to alcohol [39]. Brower et al. [40] studied sleep among abstinent patients using objective (PSG) as well as subjective measures (Sleep Disorders Questionnaire). Those who relapsed had longer sleep latencies, shorter rapid eye movement sleep latencies, and less stage 4 sleep percentage than abstinent patients [40]. Conroy et al. [41] found that greater subjective accuracy in the estimation of "wakefulness at night" predicted relapse. This study also showed that the results may differ based on how drinking outcomes are defined such as frequency of drinking days, heavy drinking days, and point of time when outcomes are assessed (6 weeks vs. 12 weeks) [41].

However, some recent studies did not show the association between subjectively assessed sleep disturbances and relapse to alcohol use [42]. In a study which utilized PSQI, a well-validated scale to measure sleep quality, no difference in PSQI scores

was noted between patients who relapsed and those who were abstinent at 3 months [34]. Another study measuring insomnia subjectively by Athens Insomnia Scale did not show association between relapse and insomnia over 12 months [43]. Hence the interaction between alcohol and sleep is far from being settled.

Periodic limb movements and its association with relapse have been found in one study. It showed that periodic limb movements are more commonly seen in those who subsequently relapse after detoxification [44]. A few of the recent studies have assessed sleep disturbances objectively by the use of actigraphy in conjunction with subjective sleep assessments. Also, alcohol can impair normal breathing by impairing normal arousal response, relaxing upper airway, leading to snoring and sleep disturbances—hence the association of alcohol and snoring [45].

21.3.3 Opioids

Sleep is affected in all opioid-use phases including acute and chronic usage, withdrawal symptoms, and while on agonist maintenance therapy. Acute usage leads to a decrease in slow-wave and REM sleep while an increased stage 2 NREM sleep [46]. For chronic users morphine produces signs of persistent sleep disturbance like shifting of deep sleep towards later in night, increased waking state during middle of night, and bursts of delta activity thereby indicating normalization [47]. For patients with opioid dependence, PSQI-based study reported poor sleep quality in four out of five of the group compared to less than 10% of the control group [17]. The domains affected in actigraphy were total time asleep, sleep efficiency, latency of onset of sleep, and total time awake and time mobile. During opioid withdrawal, the REM sleep was more disrupted than NREM sleep [48].

Patients on long-term opioid substitution (buprenorphine and methadone) also have prominent sleep issues. Among patients with methadone maintenance, 60–70% reported poor sleep quality [49]. Nordmann et al. [50] in a longitudinal study on patients with methadone maintenance mentioned that 60.5% reported medium-to-severe sleep disturbance which was aggravated by younger age, pain, and severe nicotine dependence. Sixty-three percent of patients on buprenorphine were found to have PSQI scores more than 5, suggesting poor sleep quality [51]. Dunn et al. [52], in a cross-sectional study on 185 opioid-dependent patients who were receiving buprenorphine and methadone, showed that there was no significant difference with respect to the different sleep parameters. Recent research has shown that 70–85% of patients on opioids have sleep-disordered breathing (SDB) [53]. Chronic opioid use decreases respiratory drive by weakening both central and peripheral responses, i.e., disables the normal protective responses to hypoxemia during sleep [54]. However, other studies have reported that buprenorphine improved sleep quality also [55].

21.3.4 Cannabis

Though cannabis has several psychoactive constituents, the most significant appears to be tetrahydrocannabinol (THC) which acts on the cannabinoid receptors like CB1 and influences REM sleep. Studies are equivocal about whether it increases or decreases [56]. Effect of cannabis on sleep has been studied in three different phases of its use—acute intake, chronic intake, and withdrawal. However, the most important issue to be considered is the concentration and potency of THC which primarily influences the effects. Acute intake is associated with shortened latency to sleep onset, reduction of REM sleep, and increase in slow-wave sleep. However, with chronic intake the endocannabinoids are affected, thereby leading to tolerance, and opposite effects are seen, though REM sleep is less affected [22]. During withdrawal, sleep disturbance persists for about 2 weeks but in case of marijuana, it may persist for more than 45 days [57]. A characteristic of sleep problems in cannabis is the vivid, strange dreams that have been reported to last for about 6 weeks. During cannabis abstinence sleep problems are considered an important risk factor for relapse [58].

21.3.5 Stimulants Like Cocaine

Acute subjective effects of cocaine usage are increased alertness and resemble other stimulants like amphetamine. PSG studies have shown longer sleep latency, reduced total sleep time, and suppression of REM sleep [22]. About six studies have investigated the effects of chronic cocaine use on sleep—increased slow-wave sleep and sleep-onset latency, along with reduction of REM sleep, total sleep time, and sleep efficiency [22]. Withdrawal on the other hand showed two types of responses—acute and delayed. While initially there is decreased REM latency and REM rebound later there is decrease in the absolute amount of REM. After 2.5 weeks of abstinence there is an increased sleep latency, slow-wave sleep, decreased sleep efficiency, and decreased REM and total sleep time similar to chronic cocaine use [59]. This is similar to persons with chronic insomnia but there are no apparent complaints. One of the possible explanations of this discrepancy is that there is a dysregulation of the homeostatic sleep and wakefulness drive. It thus distorts cocaine users' ability to recognize the need for sleep. Hence they have occult insomnia and this may explain the sleep-related cognitive, attention, and learning deficits observed in such patients [60].

21.4 Pathophysiological Aspects of the Relationship Between Sleep and Addiction

Sleep is regulated by two prominent drives—namely homeostatic and circadian [61]. In the homeostatic drive the body is in a state of equilibrium balanced by wake-promoting and sleep-promoting mechanisms. For example, the orexin works as a

modulator and tries to keep one of either ventro-lateral pre-optic area or reticular activating system in sustained activation [62]. On the other hand, sleep is also mediated by circadian rhythm which is preset by the action of zeitgebers prominent among them being light, food, reward, punishment, sex, and use of addictive substances. The chief regulator of the circadian rhythm is the suprachiasmatic nucleus (SCN) regulator located in the hypothalamus [63]. To fall asleep it is important that both of the homeostatic (also known as "S") and circadian processes (process "C") overlap (please see Chaps. 1 and 3 for details).

Relationship between sleep and addiction has been robustly studied in validated animal models followed by human studies. Animal models are helpful in assessing the effect of a single variable by either overexpressing or underexpressing a trait under study using different technological advances. For example a specific gene related to circadian rhythm may be overexpressed or deleted in transgenic mice with the help of transfecting viruses or through optogenetic and chemogenetic modalities [64]. These models have been used to answer two very important questions—first, underlying or preexisting differences in sleep characteristics that can predispose some individuals to SUDs and second, to study the proneness to relapse. With the help of animal models it has been shown that the rewarding effect of addictive substances varies with the circadian rhythm. For example, cocaine is more reinforcing at 1 am and 1 pm than at 7 am and 7 pm in rats. However, this circadian pattern is lost at high doses (>2.5 mg/kg). Mice also show higher sensitization for cocaine during daytime compared to night [65]. The findings of the animal models that reward value of drugs change with circadian rhythm have been studied first in healthy volunteers and then clinical samples for better bench-to-bedside understanding of translational research at the sleep-addiction interface. This is highlighted in terms of neurotransmitters, neurocircuitry, genetics, neuroendocrine, neurocognitive, and other mediators and finally replicated in longitudinal community-based epidemiological studies to understand the relationship between sleep and addiction.

21.4.1 Neurotransmitters and Neurocircuitry

The interactions between sleep and neurotransmitters can be better understood by studying the relationship between sleep, neural pathways, and neurochemicals (see Fig. 21.1). The four group of neurons, namely the monoaminergic neurons (serotonergic-raphe nuclei, noradrenergic-locus ceruleus, histaminergic tuberomammillary nucleus) and cholinergic neurons (in the laterodorsal tegmental nucleus and pedunculopontine nucleus), were traditionally considered to be wake promoting. Median ventrolateral preoptic (VLPO) nuclei which provide GABA-ergic innervation of the entire wake-promoting system inhibit arousal during sleep [66]. The same along with contiguous limbic regions play an important role in both reward and sleep. Even a minor influence on one affects the other—it has been shown that even a night of sleep loss can lead to decrease in D2/D3 dopamine receptor availability in ventral striatum [67]. The similarity between substance use

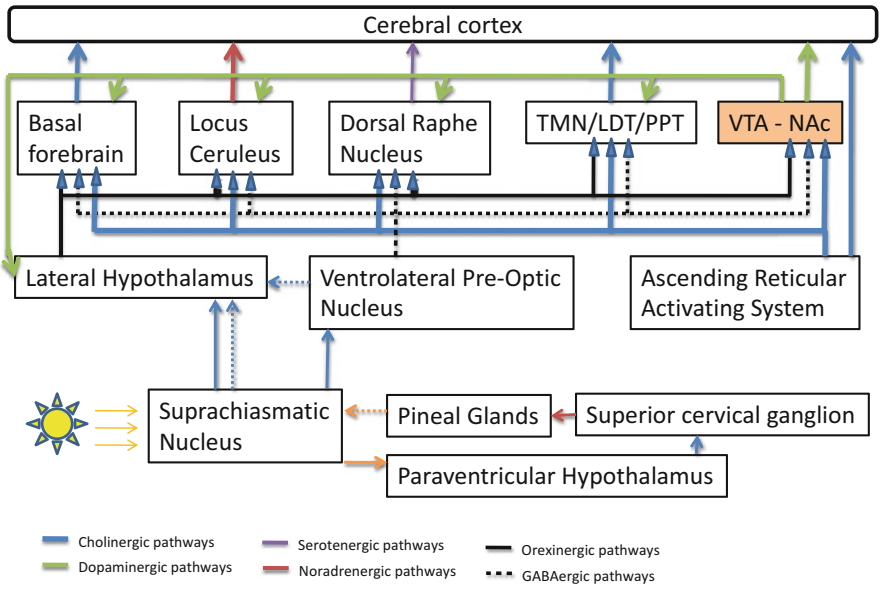

Fig. 21.1 Brain neurocircuitry related to sleep

and sleep neurobiology is understood by the fact that subjects with substance-use disorders, compared to control subjects, have a decrease in D_2 receptors in the striatum on the order of about 20% [68].

With the development of newer techniques the "paradigm" is gradually shifting from monoamine, acetylcholine, and peptide neurotransmitter to fast neurotransmitters like glutamate and GABA. Recent research has shown that the specific synaptic vesicles and GABA, glutamate, orexin, adenosine, and melanin-concentrating hormone (MCH) play a pivotal role in the regulation of sleep and reward [69].

Orexinergic pathways emerging from posterior lateral hypothalamus appear to control both sleep-promoting and wakefulness-promoting regions as a common substrate in sleep and substance-use disorders [70]. While the orexins promote wakefulness and maintain arousal, the stimulation of ventrolateral preoptic nucleus decreases the orexinergic tone, reducing arousal centers, and induces NREM sleep. The chronic loss of orexin-producing neurons, as in the case of narcolepsy, results in chronic sleepiness manifested as intrusion of REM sleep into the wakefulness. The same orexinergic pathways are also implicated in the behaviors driven by reward pathways. The orexin pathway is interconnected with the wider motivation and reward circuits involving glutaminergic and dopaminergic pathways [71]. Evidence from self-administration and drug reinstatement models has clearly delineated that orexins primarily coordinate motivational activation thereby having a wider role in substance use disorder rather than having primary reinforcing effects [71].

Adenosine is an endogenous sleep-promoting neurochemical. Microdialysis experiments in the brain of cats have shown that adenosine levels increase twofold in the basal forebrain during 6-h period of wakefulness [72]. Depletion of adenosine triphosphate (ATP) leads to rise of adenosine which exerts its hypnotic activity via A1 and A2A receptors to promote prostaglandin-D2-induced sleep. A2A receptor antagonism is known to potentiate the acute effects of psychostimulants [73]. A2A receptor active neurons related to sleep in the ventrolateral preoptic and basal forebrain area send inhibitory signals to suppress the histaminergic neurons in the tuberomamillary nucleus which contributes to arousal through histamine H1 receptors. A2A receptor antagonism counteracts dopamine-2 receptor inactivation. The antagonistic pair of D2 and A2A receptors appear to predominate in GABA-enkephalinergic neurons of ventral striatum, a site for goal-directed behaviors like substance-seeking behavior these interactions highlight the close relationship between the sleep and reward pathways in the brain [74]. The above interactions highlight the close interactions between the sleep and reward pathways in the brain.

21.4.2 Genetics

In the last decade there has been discoveries about a new family of genes which explain the relationship between sleep and substance use like period genes (Per1, 3), cryptochrome genes (Cry1–2), circadian locomotor cycle kaput (CLOCK), neuronal PAS domain protein 2 (NPAS2), brain and muscle ARNT-like protein 1 (Arntl1), and D-box-binding protein (Dbp) genes that are molecular components of the circadian clockwork (see Table 21.3) [75]. These genes are present in different tissues and peripheral organs of the body and express the circadian rhythm of their own under the circadian regulation of master organ which is the suprachiasmatic nucleus (SCN). The SCN serves as the master clock, which is the source of rhythmicity for circadian functioning [76]. With inputs from retina, the activity-rest cycle is synchronized with day-night changes. The SCN is complemented by multiple other peripheral clocks throughout the tissues of the body which are all inherently rhythmic but together orchestrate a single rhythm and maintain the appropriate synchrony.

The human CLOCK gene placed at chromosome 4q12 is one of the most important genes of the endogenous master clock system. The CLOCK-BMAL1 complex influences the function of the own by forming a set of transcription factors which bind to E-box enhancer elements upstream of period (Per) and cryptochrome (Cry) genes activating their transcription [77]. The genes producing proteins related to circadian timings interact with each other at different levels like translational-transcriptional and posttranslational feedback loops, thereby self-sustaining diurnal oscillations. Dyssynchrony between the central and peripheral oscillators is responsible for the development of different mental and substance-use disorders [78].

In animal models, period gene mutations have been demonstrated to have changes in sensitization of drug-induced motor movements following exposure of stimulants like cocaine [79]. Similar changes in sensitization were also found in

Table 21.3 Genes and their effect on the neurocircuitry

Genes	Effects
CLOCK	Influences dopamine tone in the ventral tegmental area and also striatal glutamate
PER1, PER2, PER3	
ARNTL, ARNTL2, NPAS2	These genes play an important role in maintaining the effective synchrony in normal light/dark and feeding conditions
CSNK1E	NPAS2 is similar to CLOCK in its structure and function and is able to induce transcription of Cry and PER genes in environments where CLOCK is nonfunctional
REV-ERBalpha	It phosphorylates the PER and Cry protein products which are fed back into the nucleus to inhibit the expression of the CLOCK-BMALI complex, thereby continuing the negative feedback loop

CLOCK gene mutant mice. PER1 and CLOCK gene expression has opposite effects on the free-running circadian period. While PER1 shortens the circadian period, CLOCK protein lengthens the circadian cycle. Apart from lengthening the cycle, the CLOCK gene also influences the dopaminergic reward pathways. For example, polymorphisms in the CLOCK genes have been shown to lead to a hyperdopaminergic state with elevated dopamine transmission in the ventral tegmental area and nucleus accumbens, thereby leading to increased substance use [80].

Also the psychoactive substances, e.g., chronic opioid and psychostimulants, influence CLOCK gene expression [81]. On the contrary, genetic variation in the human dopamine transporter (DAT) gene has been shown to influence neural responses to sleep loss. Individuals with a copy of the nine-repeat DAT allele that is linked to higher phasic dopamine activity demonstrate greater striatal responses to monetary reward after sleep deprivation. This mutual influence of CLOCK genes and psychoactive substances also implies a bidirectional relationship between them which will be discussed later.

21.4.3 Neuroendocrine, Neurocognitive, and Other Mediators

Stress response is mainly mediated by the hypothalamo-pituitary adrenal (HPA) axis. The HPA axis is under circadian regulation, that is, the corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone, and glucocorticoid hormone, and related receptors are discharged rhythmically varying between light and dark phases [82]. The interaction between the CLOCK genes and glucocorticoid activity is done via the CLOCK-BMAL1 complex and through acetylation and epigenetic regulation.

Substance use has enormous influence on our body clock as most or all of the known zeitgebers (time givers) for the master clock like the timing of light exposure, food intake, timings of sleep, outdoor activities, and social activities are likely to be impacted by short-term or long-term substance use. Measurements in the peripheral mononuclear blood cells (PMBCs), cortisol, and several peptides reveal disruptions in the rhythms of circadian gene expression (PER1 and PER2). Specifically, PER1

and PER2, as well as adrenocorticotropic hormone (ACTH), β-endorphin, and interleukin-2 (IL-2), all showed normal daily rhythms in healthy controls but not in patients with substance-use disorder during early abstinence period [83].

Sleep loss causes major impairments in hippocampus-dependent memory—sleep deprivation before and after learning prevents the formation or consolidation of new memories. Such impairment in prefrontal and hippocampus contributes to reduced prefrontal inhibition, increase in impulsive responding, and reward sensitivity [84]. In case of patients with chronic alcohol use, the circadian rhythm disturbances and cognitive deficits like response inhibition and impulsivity noted in acute discontinuation period improved very slowly after quitting and continuing abstinence [85].

Sleep loss or deprivation affects reward pathways and enhances the brain reactivity to positive experiences. Thus as a result of sleep deprivation, while the ventrostriatal, mesolimbic reward pathway activity increases, medial prefrontal cortical response for executive functioning reduces and a dyssynergy of "top-down" or "bottom-up" control appears [64]. A multitude of factors including the endogenous and exogenous factors, viz., phase delay in the circadian rhythms, a decreased homeostatic sleep drive, and the resulting eveningness, are associated with high novelty seeking, lower harm avoidance, higher risk-taking, and lower medial prefrontal cortical response to reward [65]. Thus neurobiological studies strongly point to a bidirectional relationship which needs to be further studied in the community-based longitudinal studies.

21.4.4 Relationship: Who Came First—Chicken or Egg?

An epidemiologically relevant way to establish the relationship between sleep problems and later alcohol usage is to longitudinally follow up individuals in the community among youths who are yet to develop substance-use problems. Wong et al. [86] in 2004 conducted the first longitudinal study to examine the temporal relationship between sleep and substance use. Hasler et al. [87] in a series of studies established the relation between late chronotype, circadian misalignment, reward dysfunction, and alcohol involvement. Later studies by Pasch et al. [88] used cross-lagged structural equation models to examine the relationship between sleep and substance use adjusting for sociodemographic data, body mass index, pubertal status, and depressive symptoms. Weekend sleep and cigarette use were bidirectionally related as were cannabis use and total sleep. In another longitudinal study Nguyen-Louie et al. [89] studied the relationship between chronotype, daytime sleepiness, erratic sleep-wake behaviors, and lifetime cigarette, cannabis, and alcohol usage. Important covariates were age, pubertal development, hours playing video games, and sociodemographic status in this study. The study found that sleep was an important mediator of the relationship between mental health and sleep.

The fact that unhealthy sleeping leads to worsening of the substance-use profile was illustrated by the study by Patterson et al. [90] where it was shown that short sleepers are at risk of progressing to more severe substance-use disorder. The authors hypothesized that cognitive impairments, anxiety, and depressive symptoms could

be the bridge between unhealthy sleep and substance use. Some studies have shown that earlier age of onset for regular cannabis use may have a negative impact on adult sleep duration making it shorter—however, the age of cannabis usage in such studies has been assessed retrospectively [91]. A study designed to examine the associations between trajectories of early cigarette smoking and insomnia found that insomnia was associated with higher probability for the chronic smoking at age 36 compared with no or low smoking [30].

Conroy [26] reviewed these studies and mentioned that the lack of well-conducted specific longitudinal studies, heterogeneity of substances, variation in sleep parameters, lack of community-based studies, and objective validation of sleep and multiple confounders have made a conclusion rather unlikely other than a "superficial" bidirectional relationship. In spite of such inadequacies, both biological and epidemiological studies have made huge progress in unravelling the important relationship between addiction and sleep. Hence, it can be concluded with a fair degree of confidence that there are underlying preexisting differences in sleep characteristics that can predispose some individuals to develop substance-use problems and relapse and secondly, there are individual differences in how the consumption of individual substances interacts with neural architecture to influence the sleep patterns as amply demonstrated in Table 21.2. This bidirectional relationship can be easily understood with the example of adolescent substance use and sleep and the specific example of tobacco and sleep.

21.4.5 Adolescent Substance Use and Sleep

Adolescent brain is in a critical period of development having increased firing rates of dopamine of the ventral tegmental area with peak in dopamine receptor expression. Delays in sleep, circadian preference, and chronotype begin around puberty and reach their maximum at around age 20. This, along with social pressures, excessive involvement in electronic devices, and decreasing parental control, leads to a vicious cycle of sleep disturbance, circadian misalignment, and sleep loss. Due to synaptic pruning in adolescents, slow-wave sleep decreases by 60% across adolescence [92]. As already discussed, sleep and circadian misalignment are associated with substance use and affective disorders. Cross-sectional studies report that eveningness is one of the important predictors of increase in substance use. A large population-based study from Norway assessed the sleep behavior and population variables in relation to substance use. In this study 9328 adolescents aged 16–19 years were surveyed [93]. Insomnia, sleep deficit, and short sleep duration were significantly associated with higher odds of alcohol and drug use/misuse measures. The associations were modified by sociodemographic factors and coexisting symptoms of depression and ADHD which are not explained by staying up late because they are independently involved in substance use as is illustrated in longitudinal studies.

Pasch et al. in 2012 observed in longitudinal follow-up studies of adolescent subjects lower likelihood of use of cigarettes and marijuana in persons with good

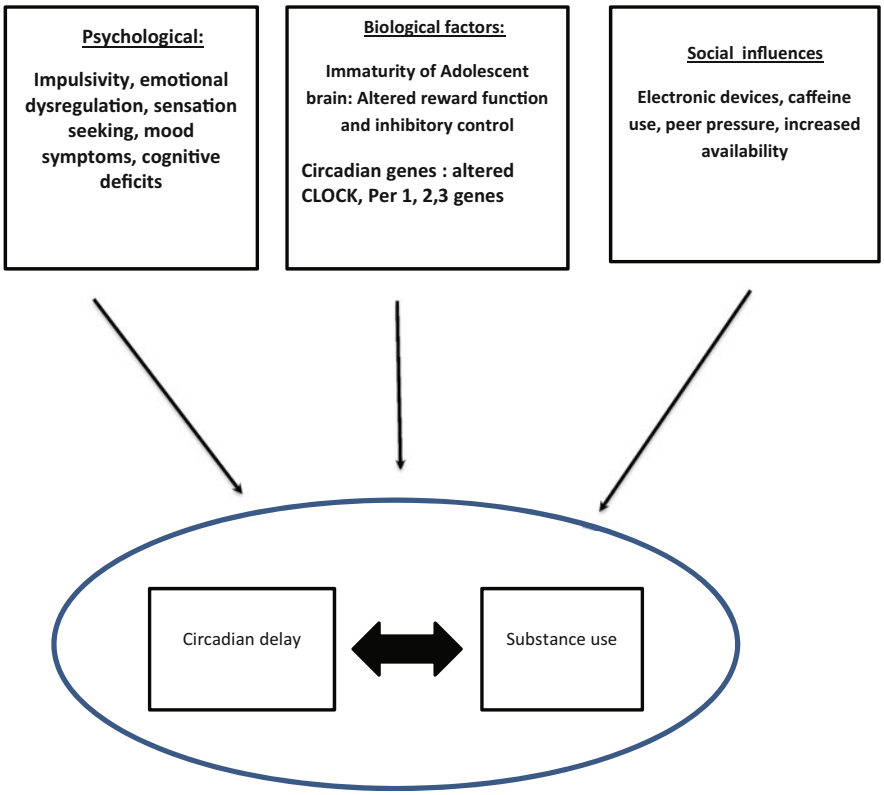

Fig. 21.2 Relationship between adolescent substance use and sleep problems

baseline sleep durations [88]. The subjects with lesser total sleep time in the weekdays and delay in going into sleep during the weekends had increased likelihood for the use of alcohol than their normal counterparts. The patients using alcohol and cigarettes had reduced total sleep; however in the persons using marijuana oversleeping and increased total sleep time were noted. The poor sleep durations were also associated with lowered inhibition, poor emotional regulation, and reduced capacity to refuse substances from peers. The relationship between sleep and substance usage is illustrated in Fig. 21.2.

21.4.6 Relationship between Sleep and Tobacco

The mechanisms underlying the common comorbidity between substance usage and sleep problems need to be substance specific based upon the pharmacological effect of the substances.

21.4.6.1 Tobacco/Nicotine Affecting Sleep

For nicotine in tobacco, there is stimulation of the nicotinic acetylcholine receptors located on the hypothalamus and reticular formation leading to release of acetylcholine, serotonin, dopamine, and gamma-aminobutyric acid that affects the sleep-wake cycle [94]. Apart from this for nicotine for those who are heavy smokers the acute drop in blood nicotine levels may lead to stronger craving and sleep disruption [31]. Also the associated medical comorbidities may play a role in sleep architecture—for example, chronic obstructive pulmonary disease in smokers may impair sleep architecture [95].

21.4.6.2 Sleep and Chronotype Predicting Tobacco/Nicotine Use

Poor sleep and tobacco use have robust association. In adolescents, the general unhealthy behaviors and sleep pattern are often seen in cigarette smokers [96]. What leads to what is an arguable, but bilateral, relationship likely exists. Chronotype has also been related to smoking habits. The morning-type persons are at lesser risk of tobacco use than the evening types [87]. The hypothesis entertained here is that the sleep pattern is more regular and sleep deficits are lesser in the former chronotype. The persons smoking cigarettes often have difficulty in falling asleep and maintaining sleep, daytime sleepiness, and associated dysfunctions, necessitating high caffeine intake and depressive symptoms when compared to nonsmokers. This has been reflected in longitudinal studies like that by Patterson et al., where a large cohort of 600 smokers were followed over a 5-year period. It showed that transitioning from 7–8 h to less than 6 h of sleep per day was a risk factor for developing more severe smoking behaviors [90]. Hence sleep and substance use affect each other bidirectionally.

21.5 Management

21.5.1 Assessment

Sleep disorders in the context of substance use require a careful assessment followed by management plan (see Box 1). It needs to be assessed whether the sleep problems are there at the time of initiation or maintenance, early morning awakening, impaired daytime functioning, or dyssynchronous circadian rhythm [97]. For this purpose a detailed sleep history of each individual patient needs to be taken. The common sleep-related disorders in the context of substance use include insomnia, circadian rhythm disorder, delayed sleep phase type, sleep-related breathing disorder, and periodic limb movement problems in sleep [98]. Sleep problems are commonly assessed with sleep diaries and actigraphy. Both DSM-5 and ICSD-3 specify criteria that insomnia symptoms should occur at least three nights per week for at least 3 months for a diagnosis of chronic insomnia (ICSD-3) or persistent insomnia (DSM-5) [15]. As discussed previously, insomnia disorder is currently considered a comorbidity and hence needs to be treated simultaneously with other SUDs. However, a challenge remains during assessment because sleep disorder and

SUDs influence each other—to disentangle the influence of each other. This can only be done when the person is away from substances for a considerable amount of time—at least few months or if the sleep history is obtained reliably before substance use. However, in practice both are not available most of the times leading to a clinical dilemma. It needs to be remembered that insomnia is a multifactorial condition and commonly there are other associated comorbidities like common medical disorders, mental disorders (most commonly mood disorders), other sleep disorders, and psychosocial stressors like marital conflicts [10].

Box 1 Stepwise Management Plan of Substance Use and Comorbid Sleep Problems

1. Diagnosis of substance-use disorder
2. Evaluate sleep abnormality
3. Rule out physical and psychiatric causes
4. Assess for:
   (a) Circadian rhythm disturbance
   (b) Sleep-related breathing disorder
   (c) Insomnia
   (d) Other sleep disorders
5. Assess the timing of symptoms
   (a) During continued use
   (b) During the withdrawal state
   (c) As part of abstinence syndrome
6. Use structured assessments like Pittsburgh Sleep Quality Index (PSQI) and investigations like polysomnography if required
7. Plan a bio-psycho-social assessment of the sleep and substance-related problems
8. Proper sleep education and sleep hygiene practice training are the first step
9. Plan psychological interventions based upon cognitive behavioral model for insomnia
10. Plan a pharmacotherapy based upon the medications with available efficacy

Apart from subjective assessment, objective assessment can be done with the help of questionnaires and investigations like Sleep Problems Questionnaire, Athens Insomnia Scale, Insomnia Severity Index, and PSQI to screen for sleep disturbance [99]. Also there are sleep diaries which are helpful in recording subjective sleep pattern over a stipulated time period. Polysomnography is an objective method to assess physiological parameters during sleep, and is indicated when there is a suspicion of comorbid sleep disorders like sleep apnea, periodic limb movement disorder (PMLD), or difficult-to-treat insomnia.

All patients and their caregivers should be educated about the basic principles of sleep hygiene. Thereafter, specific treatments with respect to different substances are hereby described.

21.5.2 Tobacco

As in insomnia, the standard treatment is cognitive behavior therapy-insomnia (CBT-I). In an RCT comparing CBT-I with standard treatment versus standard treatment alone, it has been shown that the time to relapse to insomnia was longer among participants receiving the CBT-I [100]. Among pharmacological treatments, though benzodiazepines and melatonin receptor agonists are not contraindicated for the management of sleep disturbances associated with smoking cessation, they have not been evaluated systematically [31]. Comparison of the effect of "24-h nicotine patch" versus the "16-h nicotine patch" on sleep showed that the former improved sleep better than the latter with particular improvements on slow-wave sleep among smokers. However, the nicotine patch disrupted sleep in nonsmokers [101].

21.5.3 Alcohol

The first step is to encourage the patient to be abstinent and practice the basic sleep hygiene practices. The CBT-I is the frontline treatment and is endorsed by the American and European guidelines [102]. CBT-I targets the dysfunctional beliefs, emotional aspects, and unhealthy behaviors related to sleep. Apart from CBT-I, studies have also shown the efficacy of progressive muscle relaxation on sleep quality [103]. It has been shown to be efficacious in different randomized controlled trials (RCTs); for example, in an outpatient-based study having weekly CBT-I sessions, it has been shown to decrease insomnia but at the same time there has been no effect on drinking [104, 105].

Among pharmacological studies, there are a number of RCTs that have assessed the effect of gabapentin, trazodone, mirtazapine, amitriptyline, quetiapine, acamprosate, and topiramate on insomnia associated with alcohol withdrawal. The greatest number of studies have been with gabapentin (used up to 1500 mg for up to 12 weeks) and some of the studies have shown a significant decrease in insomnia and drinking—particular efficacy was shown in decreasing withdrawal symptoms and craving [106, 107]. In cases of comorbid alcohol, depression, and insomnia three medications have been studied, namely trazodone, mirtazapine, and amitriptyline, as they have sedative histaminergic properties [108]. However, after stoppage of such medications particularly trazodone, a RCT has shown that there is worsening of drinking outcomes [109]. For others namely mirtazapine and amitriptyline there was, however, not much effect on craving and drinking though there was improvement in depressive symptoms and sleep [108]. In a double-blind randomized controlled trial, among patients with comorbid mood and psychotic disorders up to 400 mg of

quetiapine had a significant effect on insomnia though there was no improvement in drinking outcomes [110, 111].

A placebo-controlled trial of acamprosate 666 mg for 15 days improved wake after sleep onset and stage 3 sleep—however drinking outcomes and their relation to sleep were not reported in this study [112]. In a meta-analysis of nine studies in insomnia in the context of alcohol-use disorder, participants reported significantly greater improvements in sleep quality and depressive symptoms with behavioral in comparison to pharmacological interventions. However the interventions did not improve rates of alcohol abstinence. There are several methodological issues related to substance use [113]. It needs to be reiterated to the treating clinician that in the absence of effective medications for comorbid insomnia and substance use, they should not resort to starting benzodiazepines beyond the stipulated withdrawal period as this may lead to increased chances of developing dependence in this vulnerable group. Also though melatonin receptor agonists like agomelatine and ramelteon have been touted as effective treatments in view of the sleep-phase disturbances which are important risk factors of substance use, in practice they did not show any evidence of efficacy [114].

Hence it may be summarized that though medications like gabapentin are promising candidates for the treatment of alcohol dependence and insomnia symptoms, CBT-I is the first line of treatment (for brief summary see Table 21.4).

21.5.4 Cannabis

It has been previously discussed that cannabis affects both subjective and objective sleep which remain even several months after abstinence. Persistent sleep problems also influence relapse and comorbid substance use. Preliminary studies have also shown both pharmacological and psychosocial interventions that improve sleep and also improve cannabis-use outcomes [115]. Medicinal use of cannabis due to pain and spasticity often improves sleep—however sleep should not be the only indication for medicinal usage of cannabis. So, currently no medication is specifically approved for the treatment by any guidelines. Hence in order to circumvent this problem the efficacy of fatty acid amide hydrolase (FAAH) agonist was studied in the treatment of cannabis withdrawal and dependence in men [116]. In this study there has been a significant improvement in the cannabis usage both self-reported and objective—which was the primary outcome measure. As a secondary outcome measure there was improvement in overall sleep with significantly more time in N3 sleep and longer latency to REM sleep.

21.5.5 Opioids

Insomnia and SRBD are the primary sleep disorders reported in those using opioids. Factors related to maintenance of sleep problems are benzodiazepine usage, pain, depression, and cigarette usage [24]. CBT-I has shown evidence for insomnia in

Table 21.4 Evidence for the treatment of insomnia and comorbid alcohol-use disorder

Intervention	Effect on sleep	Effect on drinking outcome	Remarks	Level of evidence
Cognitive behavioral therapy	Improved sleep quality, efficiency, awakenings, and time to fall asleep	No effects on alcohol outcome	Accepted as first-line treatment	High
Mirtazapine (15-45 mg bedtime)	Improved insomnia symptoms	Improvement in craving and other studies	Useful for patients with comorbid depression	Moderate
Gabapentin (600 mg or 1200 mg at bedside)	Efficacy in insomnia symptoms	Improved craving	Most promising medication for the purpose of sleep and substance use	Moderate
Quetiapine XR (25-200 mg at bedtime)	Subjectively improved sleep outcome	Improvement in craving inconclusive	Should be considered with coexisting mood and psychotic disorders	Moderate
Melatonin	Improves sleep and circadian rhythm	No particular efficacy in reducing alcohol use	May be useful with comorbid circadian abnormalities	Low
Topiramate	Decreased sleep disturbances	Decreased alcohol craving	Preliminary evidence only needs further study	Low
Trazodone	Improved	Worsened alcohol intake	Improved sleep quality but deteriorated substance use	Low
Acamprosate	Improves craving	Improves sleep disturbance during alcohol withdrawal	Most evidence is for improvement in sleep architecture during withdrawal but not beyond	Low
Amitriptyline and doxepin	Improved sleep	Improved craving	Side effect is a concern—used in cases with comorbid depression	Low

opioid dependence. Among drugs, trazodone was not found to have efficacy in a trial and no data exists for other medications. Similar to insomnia, little research exists for sleep-disordered breathing. A risk-benefit analysis needs to be done between opioid usage with risk of SRBD versus risk of relapse on tapering of opioids. Shifting to long-acting depot naltrexone is a viable alternate. Otherwise standard treatment options include CPAP, adaptive servo-ventilation (ASV), and bi-level spontaneous timed (ST) therapy [117].

21.5.6 Cocaine

Persons with cocaine-related problems rarely seek treatment for sleep disturbances though polysomnographic disturbances are quite evident. In one study though modafinil 400 mg was tried and it improved the sleep latency, relapse outcomes were not measured [118]. Other medications tried are lorazepam, tiagabine, and mirtazapine [119]. The latter improved sleep-onset latency in depressed patients with cocaine usage but did not reduce cocaine consumption [120].

In a preliminary study there was significant improvement in PSQI scores along with the primary outcome measure being cocaine usage with repetitive transcranial magnetic stimulation (rTMS) in patients with cocaine-use disorder [121]. However, there was no control used and the study was done on a retrospective group. Hence like all substances, comorbid cocaine-use problems and sleep disorder do not have any specific treatment.

21.6 RLS and Substance Use

Restless legs syndrome (RLS) is a common sleep disorder affecting about 5–10% of the population [122]. It is a movement disorder characterized by an irresistible urge to move the legs, precipitated by rest and relieved by movement and most prominent in the evening or at night. It is highly comorbid with substance use disorders. The most important challenge is to differentiate between substance withdrawal and sleep disorders. Important clues are an exacerbation of restlessness only during night and the persistence of restlessness even after abstinence from substances [123]. Initial studies have shown that RLS happens in a percentage of patients undergoing detoxification—51% of those detoxifying from opioids and 22% undergoing detoxification from alcohol [124]. The relationship further needs to be explored as opioids are also a treatment for RLS.

21.7 Sleep-Related Breathing Disorders and Substance Use

A history of alcohol use is common among patients with obstructive sleep apnea (OSA). A meta-analysis combining all available worldwide literature showed that alcohol users are about 25% more likely to have OSA. The relationship may be mediated by reduction of genioglossal muscle tone predisposing patients to upper airway resistance and collapse. Also obesity may be another mediator of the relationship between alcohol usage and OSA [125]. Similar to alcohol there is a dose-dependent relationship between opioids and sleep disorder [126]. Chronic opioid use reduces respiratory drive, destabilizes pacemaker neurons, and disables the normal protective responses during sleep leading to fatal overdosage. 70–85% of patients on opioids have sleep-disordered breathing [127]. Patients on methadone are more prone to sleep-disordered breathing than buprenorphine. Hence sleep disorders are

important issues which require proper assessment in persons with substance use disorder [128].

21.8 Policy

An important application of this sleep-addiction interface is that related to road traffic accidents. It is well known that alcohol and other substances are directly related to fatal road traffic accidents [129]. In many countries chronic alcohol drinking status is routinely checked during renewal of driving licenses [130]. Similar reservations exist for most patients with untreated OSA, narcolepsy, and insomnia regarding their fitness to drive unless they receive treatment [131]. It has already been discussed that this group with combined sleep and addictive disorders have higher comorbidities which may have significant public health implications. For the adolescent group, the American Academy of Pediatrics has recognized that early school start time (i.e., before 8:30 am) is a key modifiable contributor to insufficient sleep in the vulnerable group of adolescents. However, for formulating specific interventions in the vulnerable individuals, further research at the sleep-addiction interface is required.

21.9 Conclusion and Future Aspects

Research in the last decade has tried to unravel the biological underpinnings between comorbid sleep disorders and SUDs in terms of genetics, neurochemicals, neurocircuitry, neurogenetics, neurocognitive, and neuroendocrine domains. However, this is far from enough as newer research like optogenetics and chemogenetics is further required to explore the bidirectional relationship currently inferred between SUD and sleep disorders. This relationship needs to be further explored in methodologically robust longitudinal epidemiologic studies. The comorbidity between sleep and SUD has been placed on firm grounds by current nosological systems which consider both to be simultaneously present, thereby necessitating careful assessment of both conditions. Among non-pharmacological interventions Web-based cognitive behavioral interventions appear to be the way ahead. Among current medications for comorbid alcohol-use and insomnia disorder, gabapentin has good evidence though it is still not an effective treatment. Though at present there is a lack of effective treatment for such comorbidities, newer drugs like dual-orexin receptor antagonist like suvorexant can be a game-changer in the future [132]. Overall, sleep-addiction interface is an important area which is certain to draw interest of basic science researchers, epidemiologists, clinicians, and policy makers in the near future.

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Sleep in Posttraumatic Stress Disorder

22

Katherine E. Miller, Janeese A. Brownlow, Richard J. Ross, and Philip Gehrman

Abstract

Sleep disturbances, insomnia and recurrent nightmares, frequently occur following trauma exposure and are core features of posttraumatic stress disorder (PTSD). This chapter describes these disturbances, highlights theoretical frameworks for the relationship between trauma exposure and these sleep problems, and discusses empirically supported treatments for insomnia and recurrent nightmares in PTSD. Although interventions targeting these sleep disturbances show promise in reducing symptoms, more rigorous controlled trials are needed in different populations to identify the factors associated with treatment responsiveness.

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Keywords

Sleep disorders · Insomnia · Nightmares · Posttraumatic stress disorder · Trauma

Reports of disturbed sleep are highly prevalent in trauma-exposed populations. Specifically, these populations endorse recurrent nightmares [1], difficulty initiating and maintaining sleep, that is, insomnia [2–4], and sleep-disruptive behaviors (e.g., simple and complex motor behaviors or vocalizations) [5]. Indeed sleep disturbances have been considered hallmark symptoms of posttraumatic stress disorder (PTSD) [6] and are codified in the diagnostic criteria: nightmares and other distressing dreams among the intrusion symptoms, and difficulty falling or staying asleep among the hyperarousal symptoms [7]. PTSD-related sleep disturbances are now recognized as problems requiring targeted intervention as they can contribute to both the development and maintenance of the disorder [8, 9], and can be resistant to treatment, often persisting following evidence-based trauma-focused interventions [10–12]. This chapter presents an overview of sleep disturbances in PTSD, discusses theoretical frameworks for the relationship between trauma exposure and these sleep problems, and summarizes the current evidence for empirically supported psychotherapeutic and pharmacological interventions for PTSD-related insomnia and recurrent nightmares.

22.1 Overview of Sleep Disturbances Associated with PTSD

Across diverse trauma-exposed populations, sleep disturbances are reported both in the acute aftermath of the traumatic event [13] and chronically for years afterwards [14]. In daily sleep diaries, individuals with PTSD report less total sleep time, lower sleep efficiency (i.e., percentage of total time spent in sleep versus total time in bed with intention to stay asleep), longer sleep onset latency (i.e., time to fall asleep), and more time awake after sleep onset [15–17]. In a retrospective report, individuals with PTSD compared to the general population are more likely to report recurrent nightmares and other forms of disturbed dreaming (OR = 5.3) [2]. Not only does the duration and pattern of sleep become altered in PTSD, but also the macroarchitecture. Polysomnographic (PSG) findings in PTSD are mixed, with some studies finding no significant differences in sleep architecture compared to individuals without PTSD (e.g., [18–20]). Sleep-state misperception is one hypothesis for the discrepancy between the objective and subjective sleep measures. For instance, on subjective measures, individuals with PTSD tend to underestimate their total sleep time and overestimate their sleep onset latency when compared to objective data [21, 22]. However, a meta-analysis of PSG data has provided evidence for more stage N1 sleep, less stage N3 sleep (i.e., slow wave sleep), and greater rapid eye movement (REM) density (i.e., number of REMs/REM sleep time) in individuals with PTSD than controls [23]. Another meta-analysis found that

PTSD was linked to poorer sleep continuity, lower sleep depth (as defined by more N1 sleep), and greater REM sleep pressure (as defined by shorter REM latency, greater REM density, and longer average REM sleep episode duration) [24]. The following section describes additional details about the specific sleep symptoms linked to PTSD.

Insomnia. Difficulty initiating and/or maintaining sleep is the most common sleep complaint following trauma exposure. In the PTSD literature the use of the term "insomnia" generally refers to hyperarousal-related sleep difficulties or excessive sleep reactivity [25], and may or may not indicate insomnia disorder (see the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5 [7]) and International Classification of Sleep Disorders (ICSD-3 [26]) for definitions of insomnia disorder), specifically regarding the latter's frequency and duration of symptoms [7, 26]. Approximately 70% of individuals diagnosed with PTSD report insomnia symptoms [2]. In comparison to individuals with insomnia disorder alone, Veterans with insomnia disorder comorbid with PTSD had more severe sleep complaints, worse subjective sleep quality, greater sleep fragmentation, and more variable night-to-night sleep [15]. Although transient insomnia is part of the normal immediate stress response, greater insomnia severity in this acute phase has been associated with the subsequent development of PTSD [27, 28]. Therefore, insomnia symptoms in the aftermath of trauma are likely a significant risk factor for a poorer trauma response trajectory. Other longitudinal research also shows that insomnia may be an antecedent, as well as a consequence, of PTSD. Soldiers with pre-deployment insomnia symptoms, insomnia disorder, or other daytime sleep complaints were significantly more likely to develop PTSD following deployment [29–31]. Bryant and colleagues [32] found that sleep disturbance in the 2 weeks prior to a traumatic event predicted the development of subsequent psychiatric symptoms, including major depression, substance use, anxiety symptoms, and of PTSD. This influence was independent of prior psychiatric disorders and the severity and type of trauma experience, suggesting that sleep contributes to the effective use of emotional and physical resources in response to stressors.

Nightmares. Whereas insomnia symptoms occur in several psychiatric disorders (e.g., depressive disorders, anxiety spectrum disorders, substance use disorders), recurrent trauma-related nightmares and disturbing dreams are specific to PTSD [7]. The prevalence of recurrent nightmares varies considerably across studies, ranging from 19 to 96% [33]. The frequency also varies, with reports of nightmares occurring up to six nights a week [34]. This variability in prevalence may be due, in part, to the reliance on retrospective reports, which are susceptible to memory biases, differing definitions and measurement tools used across studies, the PTSD diagnostic status of samples, and the population of interest (e.g., civilian versus military) [35].

Trauma-related nightmares are best understood as story-like sequences of dream imagery, with accompanying dysphoric emotions. They culminate in awakening, often accompanied by physiological arousal (e.g., heart palpitations, perspiration), with recall of nightmare content, which can sometimes be described in detail. Nightmare content may closely resemble, or include themes related to, the

individual's traumatic experience. These dreams are infrequently reported in the sleep laboratory [36], hindering the identification of key physiological correlates. However, they have been observed in both REM and non-REM sleep [37], and are associated with a longer time in wakefulness after sleep onset, poorer sleep efficiency, increased heart rate upon awakening, and elevated motor activity during sleep [38]. Higher nightmare frequency and nightmare-associated distress predict poorer psychological functioning [39]. After controlling for other PTSD symptoms, nightmares have been directly related to a greater risk of suicide attempts [40] and deaths by suicide [41], highlighting the importance of nightmare assessment and treatment in individuals with PTSD.

22.2 Other Sleep Disorders and PTSD

In addition to the sleep disturbances specified in the PTSD diagnostic criteria, several sleep disorders frequently co-occur with PTSD. In addition to insomnia disorder, these include obstructive sleep apnea (OSA), rapid eye movement sleep behavior disorder (RBD), and periodic limb movement disorder (PLMD).

Obstructive sleep apnea. OSA is characterized by repeated upper airway obstruction during sleep, leading to arousals and sleep fragmentation [42]. Left untreated, OSA increases the risk of cardiovascular conditions, obesity, and motor vehicle accidents [43]. Additionally, comorbid OSA and PTSD may worsen sleepiness, fatigue, and sleep-related quality of life [44] and compromise the efficacy of PTSD treatments [45, 46]. The prevalence of OSA in trauma-exposed populations varies considerably (0.7–83%) based on the sample examined and differing diagnostic criteria, with relaxed apnea-hypopnea index criteria (AHI $\geq$ 5 compared to $\geq$10) increasing the prevalence of OSA [47]. Studies have included primarily males, and are of uncertain applicability to female trauma survivors [48], and Veterans with PTSD tend to have higher prevalence of OSA than nonveteran or mixed groups [47]. While it has been postulated based on animal data that trauma, frequent awakenings from sleep, and OSA are related, this remains to be validated in humans [49]. The primary measure of OSA severity is the apnea-hypopnea index (AHI), defined as the number of complete (apnea) or partial (hypopnea) blocks to airflow per hour of sleep. There is evidence that AHI predicts the number of nightmare reports [50], and that treating comorbid PTSD-OSA can reduce nightmare occurrence [51]. Thus, when OSA is suspected, a sleep study should be included in the clinical evaluation of PTSD patients. Central sleep apnea, a reduction in central respiratory drive, is less common than OSA and has not been investigated in the context of PTSD.

Rapid eye movement sleep behavior disorder. RBD is characterized by REM sleep without atonia on PSG and dream enactment behaviors [42]. Individuals with PTSD often report large body movements during sleep [2], and there is substantial evidence for REM sleep abnormalities among trauma-exposed groups. However, a hallmark of RBD, REM sleep without atonia, has not been identified in individuals with PTSD studied in the laboratory. Mysliwiec and colleagues [5] proposed a novel

diagnosis-trauma-associated sleep disorder (TSD)-incorporating trauma-related nightmare enactment associated with specific PSG features (altered REM latency, REM sleep without atonia) and disruptive nocturnal behaviors (e.g., vocalizations). These authors distinguish TSD, which is not codified in the DSM-5, the International Classification of Diseases, 10th revision (ICD-10), or the ICSD-3, from RBD by its frequent occurrence in young patients, with an onset near the time of a trauma exposure, and the presence of sympathetic activation in REM sleep. Also, TSD is distinguished from nightmare disorder by excessive motor activity, and by nightmares that may not be recalled upon awakening and that can occur in non-REM as well as REM sleep. The use of serotonin selective reuptake inhibitors (SSRI) may increase the frequency of RWA in PTSD samples; however, participants taking SSRIs in the TSD investigations reported dream enactment behaviors prior to psychotropic use [5].

Periodic limb movement disorder. PLMD is a sleep-related movement disorder characterized by repetitive leg movements during N1 and N2 sleep, and during periods of quiet wakefulness, which is associated with daytime dysfunction [52]. There is some evidence of a higher prevalence of PLMD in individuals with PTSD compared to control populations. A study assessing PLMD in combat-exposed Veterans reported a prevalence of 33% compared to 0% of the control group [53]. Another study found 76% of a sample of Veterans with PTSD had period leg movements [54], which is greater than the approximately 28% observed in the general population; however, these rates tend to increase with aging [55]. Both increased phasic leg muscle activity during REM sleep and higher PLM activity during non-REM sleep were observed in a Veteran population with PTSD compared to age-matched healthy controls [56].

22.3 Explanations for the Relationship Between Sleep Disturbances and PTSD

Advances in biological and psychological theories are elucidating the mechanisms underlying relationships between trauma exposure and sleep disturbances (see Fig. 22.1 for illustration of these factors). It has been postulated that transient sleep changes immediately following trauma exposure may be adaptive, promoting arousal and decreasing vulnerability to threat [57, 58]. Studies using an experimental trauma in an animal model [59] and exposure to a film with traumatic content in humans [60, 61] found that sleep deprivation during the sleep period following trauma exposure led to a reduction in PTSD-like symptoms and intrusive memories, respectively, presumably because of reduced consolidation of memory for the traumatic experience. Contrasting results from a different study showed that sleep following an experimental laboratory trauma reduced the development of intrusive memories [62]. These authors proposed that sleep following trauma may promote the adaptive consolidation and integration of memories. Similarly, others have suggested that nightmares in the early aftermath of trauma may indicate an attempt

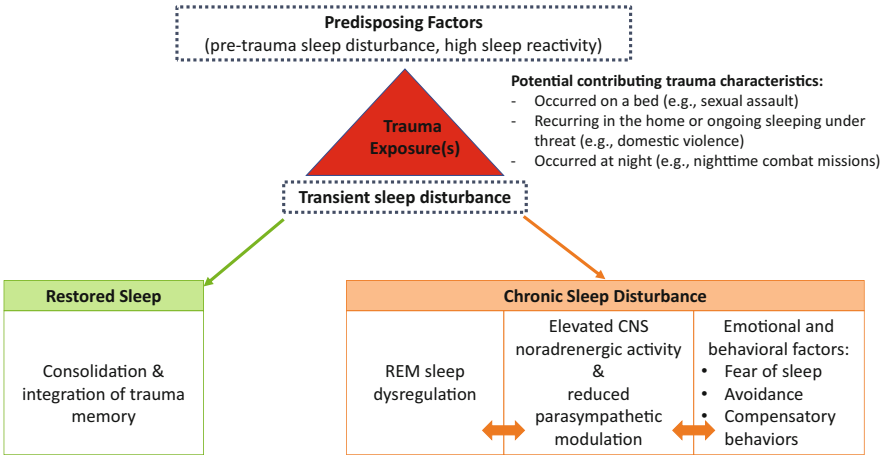

Fig. 22.1 The possible interacting biological, emotional, and behavioral variables underlying chronic sleep disturbance seen in PTSD. Some individuals may be more vulnerable to chronic sleep disturbance due to predisposing sleep disorders or symptoms and nighttime trauma-related cues (e.g., darkness, bed). *REM* rapid eye movement; *CNS* central nervous system

to assimilate the traumatic event into an individual's experiential history [63]; chronic nightmares, on the other hand, may indicate a failure of this process [64].

Disruptions of the physiological and neural mechanisms of sleep in the aftermath of trauma may be particularly important in understanding the role of sleep in the pathophysiology of PTSD. REM sleep disturbances have been viewed as the hallmark of PTSD [6, 65]. However, there is no consensus regarding the precise nature of these REM sleep abnormalities. The variability across studies has been attributed, in part, to the assessment of sleep at a range of times following the traumatic event [64, 66]. When examined within a month of the traumatic occurrence, individuals who later developed PTSD had shorter duration, and more, REM sleep periods [13]. REM sleep percentage and REM sleep segment length have been positively correlated with the duration of PTSD [66]; the authors suggested that these findings could indicate REM sleep's role in promoting recovery from trauma [66]. However, others have argued that the reconstitution of REM sleep, with its link to the chronicity of PTSD, could be interpreted as pathological [64].

As noted above, a meta-analysis of PSG data in PTSD studies, with a varying length of time elapsed since trauma exposure, found a large effect for increased REM density in PTSD compared to control samples [23]. Rapid eye movements are the prototypical REM sleep phasic event, and work in animals has linked REM sleep phasic activity to the processing of fearful stimuli [67]. One of the authors (RJR) has suggested that severe psychological stress can initiate processes in REM sleep phasic event generation that promote successful adaptation to trauma or, alternatively, the development of PTSD [64].

Disturbances of autonomic nervous system regulation have been observed during sleep in individuals with PTSD. An elevated heart rate upon or after awakening from

both REM and non-REM sleep nightmares has been described [37, 68]. Elevated central nervous system noradrenergic activity has been postulated to contribute to PTSD symptomatology [69]. Combat soldiers diagnosed with PTSD who had elevated baseline standing systolic blood pressure (a hypothesized proxy of brain alpha-1 adrenoceptor activation) were more responsive to treatment with prazosin, an alpha-1 adrenergic antagonist, than those with lower blood pressure, suggesting the presence of a "noradrenergic" PTSD subtype [70]. It will be important to clarify how autonomic control varies with sleep stage, and participates in the production of sleep symptoms, in PTSD. Reduced parasympathetic function across the sleep period also has been described in PTSD [71]. Nightmare reports in a sample of Veterans with PTSD were related to attenuated sleep period respiratory sinus arrhythmia (RSA), a putative index of parasympathetic tone [50]. Recently, Ulmer and colleagues found blunted parasympathetic modulation during non-REM sleep in a sample of Veterans and servicemembers with PTSD compared to controls [72]. Given the relation between reduced parasympathetic modulation and increased risk of cardiovascular events, this finding could have significant implications for the physical health of populations with PTSD [73].

Emotional and behavioral, including sleep-related fear, feeling of loss of control, and avoidance behaviors, play an important role in sleep disturbance in PTSD. Fear of sleep, which can become a conditioned response, is associated with recurrent nightmares and may contribute to insomnia [3]. It has been postulated that the awakening from a nightmare, as a form of escape behavior, may further reinforce this fear [34]. Trauma exposure typically involves elements outside a person's real or perceived control, resulting in a sense of helplessness [74]. As reminders of the traumatic event and the associated emotions, chronic nightmares may perpetuate this helplessness. Consequently, individuals may engage in avoidance behaviors, including substance use, sleeping during daylight hours, avoiding sleep until it is obligate, or, at the extreme, engaging in suicidal behavior [75].

22.4 Clinical Treatment Options

Disturbed sleep can persist following trauma-focused treatment of PTSD, even when waking symptoms have improved. This highlights the need for targeted sleep interventions. Recent American Psychological Association [76] and Department of Veterans Affairs/Department of Defense [77] clinical practice guidelines for PTSD recommend cognitive-behavioral therapy for insomnia (CBT-I) as the treatment for insomnia in patients with PTSD. Citing inconsistent and low-quality evidence, they make no recommendation for treating posttraumatic nightmares. In contrast, a recent American Academy of Sleep Medicine (AASM) position paper recommended imagery rehearsal therapy (IRT, see below) for treating PTSD-associated nightmares as well as nightmare disorder [78].

Psychotherapeutic interventions. CBT-I, a brief intervention aimed at enhancing overall sleep quality [79], includes instruction in stimulus control and sleep restriction, cognitive restructuring, sleep hygiene education, and relaxation training.

In a pilot study of CBT-I in patients with PTSD and self-reported chronic insomnia symptoms, Gellis and Gehrman [80] found significant improvements in self-reported sleep quality and insomnia severity. Talbot and colleagues [81] conducted the first randomized clinical trial (RCT) of CBT-I in a community sample with PTSD and comorbid insomnia disorder. Compared to waitlist controls, the CBT-I group had superior responses on all sleep diary measures, improved sleep quality, and increased PSG-derived sleep time; these effects remained significant at 6-month follow-up. Insomnia symptoms assessed by self-report remitted in 41% of the CBT-I group (versus 0%). Both the control and CBT-I groups reported reductions in PTSD severity and posttraumatic nightmares [82]. More recently, results from a chart review for Veterans in a residential PTSD treatment program indicated that group-delivered CBT-I significantly improved sleep efficiency, time awake after sleep onset, and self-reported insomnia severity [83]. RCTs with an active treatment control group are required to establish the relation of these responses to the therapeutic elements of CBT-I specifically. Although CBT-I is the recommended treatment for individuals meeting criteria for PTSD and comorbid insomnia disorder [77], it is unclear when it might be an appropriate option for managing insomnia symptoms that do not warrant a separate insomnia disorder diagnosis.

As noted previously, IRT, a cognitive-behavioral therapy for nightmares [84], is the only recommended treatment for nightmares associated with PTSD. It uses rehearsal or imagery exercises, in which individuals choose a nightmare, typically one of lesser intensity, and construct a revised, non-distressing version of this dream. IRT protocols vary in the type of nightmare targeted for treatment, the extent of exposure to nightmare content, the guidance provided by the therapist in nightmare rescripting, and the method of delivery (i.e., individual or group) [85]. Among trauma-exposed civilian populations, IRT compared to waitlist control significantly reduced nightmare frequency [84, 86], while improving sleep quality and the waking symptoms of PTSD. Among Veteran populations, outcomes are mixed. In a study in Vietnam War Veterans comparing IRT to an active control condition [87], neither group showed a significant change in nightmare frequency; however, the IRT group had significantly greater decreases in nightmare intensity and distress, but not sleep quality and total PTSD severity. Different study designs (e.g., waitlist vs. active control) and participant populations (e.g., civilian vs. Veteran; with or without a requirement for a PTSD diagnosis) and the lack of standardization in treatment protocols (e.g., number of sessions, amount of exposure) may explain discrepant results in IRT studies [88].

Exposure, Relaxation, and Rescripting Therapy (ERRT) is another therapeutic intervention specifically for trauma-related nightmares [89]. ERRT, although originally based in part on IRT, is unique in its focus on written and oral exposure to the most distressing nightmare and trauma-related thematic rescripting (i.e., changing the dream content based on identified trauma-related themes). ERRT also addresses negative thoughts and worries related to sleep and nightmares, offering strategies for stress management and relaxation. Time is spent discussing stimulus control, a set of strategies aimed at addressing conditioned arousal, and the development of a regular sleep/wake schedule. As with IRT, the findings of efficacy trials are mixed

[76, 77]. In primarily civilian trauma-exposed populations, RCTs comparing ERRT to a wait-list control have demonstrated efficacy for ERRT in decreasing nightmare frequency and severity, fear of sleep, and symptoms of PTSD and depression, while improving sleep quality and quantity [90, 91]. ERRT also has been shown to reduce physiological indices of fear associated with nightmare content (i.e., heart rate reactivity, skin conductance, and corrugators and frontalis electromyography) [92]. Pruiksma and colleagues [93] compared a full ERRT protocol (i.e., with exposure and rescripting) to a modified version excluding the latter treatment components. There were no statistically significant differences between groups at any time point, with both conditions exhibiting improvements in nightmare measures and daytime depression and PTSD symptoms. The authors suggested that a single session of exposure may have been too brief to show a benefit and recommended further investigation. Among Veterans, only outcomes from uncontrolled trials or case reports investigating ERRT variants are available [94–96]. Although these studies show promise, controlled trials of ERRT in military populations are necessary.

There presently is no clear understanding of why CBT benefits some individuals with trauma-related sleep disturbances, and not others. A recent study in Veterans of the Afghanistan and Iraq conflicts found that individuals with lower baseline verbal memory performance were less likely to respond to treatment with IRT or IRT + CBT-I [97], suggesting the importance of optimal neurocognitive functioning in treatment. The neural mechanisms of CBT-associated sleep changes remain to be identified. Germain and Nielsen [86] used PSG to study IRT and found no significant pre-to post-treatment differences in objective sleep measures, even when a reduction in nightmare frequency was observed. Similarly, PSG changes were not observed in a study comparing the efficacy of a behavioral sleep intervention to prazosin, a medication commonly prescribed for treating recurrent nightmares [98] (see pharmacological treatment section below). The methods for analyzing the PSG in these studies may be relatively insensitive, and future studies may need to supplement standard analysis with measures of REM sleep microarchitecture and possibly spectral analysis of the sleep EEG.

Combined CBT-I and IRT treatment approaches. As many trauma-exposed individuals present with both recurrent nightmares and insomnia, integrated protocols for both conditions have been explored. In an uncontrolled pilot study of a one-session protocol combining components of CBT-I and IRT, survivors of violent crime reported clinically significant improvement in sleep quality, nightmare frequency, and waking PTSD symptoms [99]. Three additional uncontrolled trials of combined treatment approaches in Veteran populations found improvements in nightmare frequency and sleep quality [100–102], with two of the studies also reporting significant improvements in PTSD symptoms [100, 102]. Ulmer and colleagues [103] compared a combined CBT-I/IRT protocol to treatment as usual in a Veteran population and found significant improvements in insomnia severity, sleep quality, and nightmare frequency, as well as PTSD symptoms. An RCT in Veterans comparing pharmacotherapy with prazosin (see pharmacological treatment section below) to an integrated CBT-I/IRT protocol and to a placebo control found

that both active treatment groups produced greater improvements in insomnia, nightmare frequency, and PTSD severity [98]. A four-session RCT in OEF/OIF Veterans with PTSD comparing a combined protocol to a waitlist control reported greater improvements in both self-report and actigraphic sleep measures, as well as PTSD and depression symptom severity, in the treatment group [104]. More work is needed to identify the benefit of each component of a combined treatment protocol.

Sequential PTSD and sleep treatment approaches. Given that sleep complaints often persist following a course of PTSD-focused interventions [105, 106] and that successful nightmare and insomnia treatments may improve daytime PTSD symptoms, it is important to understand the potential benefit of sequential sleep- and PTSD-targeted interventions. A case series assessing the effect of CBT-I on residual insomnia symptoms following PTSD treatment showed significant improvement in subjective sleep measures [107]. Preliminary findings suggest that treating sleep disturbances may facilitate the introduction of subsequent exposure-based interventions for PTSD [108]. A recent trial examining the efficacy of IRT prior to CBT for PTSD compared to CBT alone found no superiority of the sequential treatment protocol on PTSD symptoms [109]. However, the group that received supplemental IRT showed greater improvements in sleep symptoms, including nightmare frequency, nightmare-associated distress, and sleep quality. Additional studies are required to determine when sleep-focused treatment should be introduced during PTSD treatment.

Pharmacological treatment. Several classes of medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), typical/atypical antipsychotics, tricyclic and other antidepressants, alpha-2 adrenergic receptor agonists, and alpha-1 adrenergic receptor antagonists, have been evaluated for reducing posttraumatic insomnia and nightmares [110, 111]. With regard to insomnia, there are few studies [112], and no specific pharmacotherapy recommendations provided by the VA/DoD guidelines [77]. A series of case reports noted that zolpidem, a non-benzodiazepine benzodiazepine receptor agonist, has some benefit for insomnia symptoms in PTSD [113]. There is evidence that trazodone, a 5-HT_2 antagonist/SSRI with sedative effects, can decrease sleep latency and nightmares in Veterans [114]. Similarly, Hertzberg and colleagues [115] found that trazodone improved sleep, as well as a range of PTSD symptoms, in a small Veteran sample.

Trazodone and SSRIs including fluvoxamine may have some utility in treating posttraumatic nightmares [114, 116], but they have not been studied in RCTs. Atypical antipsychotic medications and tricyclic antidepressants have been used, but the evidence base is of low quality [117]. Benzodiazepines and the SNRI venlafaxine have not been recommended for the treatment of nightmares [78]. The centrally active alpha-1 adrenergic antagonist prazosin has received the most attention as a pharmacological treatment for nightmares. Several controlled trials and a meta-analysis found significant improvements in nightmare frequency, as well as sleep quality and PTSD severity [118, 119]. However, a multicenter VA Cooperative study assessing the efficacy of prazosin on combat-related distressing dreams and global sleep quality [120] found no benefit of prazosin over placebo. As previously

mentioned, Raskind and colleagues [70] have suggested that a subpopulation of nightmare sufferers, those with noradrenergic hyperactivity, will respond best to prazosin. The VA/DoD clinical practice guidelines make no recommendations regarding prazosin for treating nightmares [77], while the American Academy of Sleep Medicine suggests prazosin as the first choice for pharmacologic therapy [78].

Treatment of obstructive sleep apnea. Several studies have provided preliminary evidence that compliance with continuous positive airway pressure (CPAP) treatment reduces nightmare frequency among both idiopathic and trauma-related nightmare sufferers [51, 121]. Two studies [122, 123] found that CPAP significantly alleviated posttraumatic stress symptoms in PTSD-diagnosed Veteran populations. Yet successful CPAP treatment in patients with comorbid PTSD/OSA may not lead to a remission of the nightmare disturbance [51]. El-Solh et al. [123] reported "a ceiling effect" that limited the impact of CPAP on nightmares in PTSD. Strict adherence to CPAP is essential to its efficacy [51, 122], and low CPAP adherence rate repeatedly has been observed in PTSD patients [124, 125]. Unfortunately, there are few effective interventions for promoting CPAP adherence [126].

22.5 Conclusions

As core symptoms of PTSD, insomnia and recurrent nightmares significantly contribute to the development and course of the disorder. Additionally, other sleep disorders, OSA in particular, may co-occur with PTSD and impact both clinical course and treatment efforts. Although there are theories that help to explain the relationship between trauma exposure and sleep disturbances, continued efforts are needed to assess these phenomena longitudinally and to clarify this link. Psychotherapeutic and pharmacological interventions targeting chronic insomnia and recurrent nightmares show promise in reducing these and other trauma symptoms. However, there is an urgent need for additional RCTs. Variables associated with treatment responsiveness should be investigated, with the long-term aim of personalizing sleep treatment for individuals with PTSD.

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Somatic Symptom Disorder and Sleep

23

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Abstract

Patients diagnosed with somatic symptom disorders often report local as well as generalized pain, fatigue, and sleep disturbance along with other symptoms. Sleep disorders like insomnia and OSA have been found to be associated with pain that runs a chronic course along with episodic exacerbations during the course of illness. Localized pain in orofacial and limbs have been reported by patients diagnosed with Obstructive Sleep Apnoea and Restless Leg Syndrome, respectively. On the other hand, generalized pain has been reported by cases of insomnia and circadian rhythm disorders. Although the literature has reported coexistence of somatic symptoms, pain and sleep disorders, the direction of causality can not be reliably established due to paucity of literature. Narrowing down on objective parameters of assessment relating to sleep disturbances in pain syndromes like Fibromyalgia and Chronic Fatigue Syndrome, specific signatures were noted in polysomnography. These findings have significantly been observed across a wide range of sleep parameters as well as in the micro-architecture of sleep. The management of sleep disorders through pharmacological as well as nonpharmacological methods has been found to improve pain symptoms in these populations. This highlights the need to consider sleep disorders as a part of differential diagnosis of somatic symptom disorder. This chapter discusses the relationship of pain among patients with sleep disorders followed by examination and management of sleep quality and sleep architecture among patients with fibromyalgia and chronic fatigue syndrome.

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symptom and related disorders is a group of different disease that are characterized by preoccupation with somatic symptoms which is either in absence of any identifiable pathology or if pathology could be identified preoccupation with the nature and severity of symptoms is out of proportion [1]. As of present understanding somatic symptom disorders can be divided into two groups- first where somatic symptoms and pain are the main components of the complaints and second where patients have excessive anxiety regarding harboring some other medical illness [1]. Sleep quality and sleep duration is associated with perception of pain and emotional well-being. Somatic symptoms along with depression and emotional wellbeing has been found to be associated with insomnia [2]. In middle aged women, insomnia has been found to be associated with insomnia [3]. It has been suggested that while insomnia exacerbates generalized pain in muscle and joints, at the same time, pain may also interfere with the sleep [3]. Similar findings have been observed in young people having post-traumatic stress [4]. In these patients, perceived sleep quality has been found to mediate the association between somatic pain and post-traumatic stress [4]. Though sleep quality appears to worsen among a number of sleep disorders for example, obstructive sleep apnea, hypersomnia as well as insomnia, association with somatic symptoms has been observed in patients with insomnia only [5]. However, whether similar difference exists in general population is a matter of further research as this study was conducted in only in a small sample of patients having traumatic brain injury [5]. Data from 10 genome wide association studies reported a bidirectional association between insomnia and somatic pain even after controlling for age and gender [6]. Interestingly, while insomnia was found to be major risk factor for generalized as well as localized pain, pain contributed little to insomnia [6].

Thus, it becomes clear that insomnia increases the pain perception. However, what happens to the nights where patients with insomnia have better sleep as insomnia is characterized by night to night variability in symptoms. If the sleep quality and duration is associated with pain, then nights of good sleep must improve pain symptoms. Like the results of earlier studies, it has been found that habitual severity of insomnia is associated with habitual severity of somatic symptoms and pain even after controlling for potential confounders like distress, depressive symptoms, somatization and anxiety [7]. However, a good night sleep improves the pain symptoms significantly, suggesting both short term as well as long term association between the two, in an asymmetric manner. Poor sleep at night increases the pain on subsequent day in greater magnitude compared to lowering of pain after good sleep at night [7]. Similarly, greater pain during the day disrupted sleep at greater magnitude compared to improvement in sleep following a day with lesser pain [7]. Thus, sleep quality and insomnia have been found to be associated with somatic symptoms and pain in a complex relationship.

Despite the bidirectional association between somatic symptoms and sleep disorders, this area is not well researched. Despite a careful search, authors could not find literature that have examined sleep quality and sleep disorders among patients with somatic symptoms disorders according to established criteria. Hence, this chapter will first discuss the relationship somatic symptoms among patients with sleep disorders followed by examination of sleep quality and sleep architecture among patients with fibromyalgia and chronic fatigue syndrome.

23.1 Sleep Disorders and Somatic Symptoms

Bidirectionality in causation between sleep and pain has been investigated in various longitudinal studies. It was suggested that the altered cognitive processes resulting from a disturbed night's sleep led to the enhanced attention towards pain sensation in the next day. In a similar manner, a day with more reported pain symptoms was followed by poor nocturnal sleep, perhaps related to the distress associated with pain [8]. A United States National Survey has pointed out that the perceived pain ratings have an inversely proportional relationship with previous night's sleep duration, displaying a U-shaped curve [9]. As already discussed, relationship appears bidirectional. While some studies reported sleep quality to be a predictor of next day pain and not vice versa [10–12], some others suggested pain to be the predictor of subsequent sleep disturbances [13–15].

23.2 Sleep Deprivation

Although there is no dearth of good literature regarding sleep deprivation producing painful responses in healthy subjects as well as hyperalgesic responses in patients with pre-existing pain conditions [16–18], longitudinal studies which can establish the causality are still limited. Disorders of insomnia were found to predict a majority of the risk of developing new widespread pain [19]. On the other hand, good sleep, having fewer sleep problems, can become a good predictor for musculoskeletal pain-free status [20]. Various longitudinal studies have demonstrated insomnia complaints to be responsible for the onset of chronic musculoskeletal pain [21–23]. A close association between insomnia and pain is evident by the finding that treatment of insomnia in patients with osteoarthritis, results in betterment of pain and fatigue [24].

23.3 Obstructive Sleep Apnea (OSA)

There has been literature showing morning headaches and orofacial pain in patients suffering from OSA [25–27]. Apart from these local site pains, which are not specific to OSA and may be present in any sleep disorder; evidences of significant prevalence of widespread musculoskeletal pain has been reported by Aytekin et al. [28]; with

higher levels of pain and disability and poorer Quality of Life among women. Association between OSA and pain has been refuted by Li et al. [29] who did not find an association between OSA and musculoskeletal pain, although self-reported sleep quality had an association with joint pain. Similarly, chronic bladder and pelvic pain producing condition named Interstitial Cystitis has been found to occur more in OSA patients, compared to non-OSA subjects [30]. However, experimental data found that CPAP therapy (gold standard treatment for OSA) led to reduction in pain sensitivity in pain free and well as patients having chronic pain [31]. Whether this effect is mediated through amelioration of OSA symptoms or improvement in sleep quality or both, is still to be investigated. The limited number of studies, small sample sizes and weak study designs make it difficult to comment on the directionality of causation between OSA and pain; and further research is thus warranted.

23.4 Restless Legs Syndrome (RLS)

Comorbid pain syndromes are a commonality with RLS, leading to various therapeutic and prognostic implications. There are four pain syndromes most often found with RLS. Headache is one of the foremost pain syndromes associated with RLS, specifically migraine. Patients with RLS were found to have an increased risk of developing migraine; stronger association being with those accompanied by aura [32]. Indian data reflected this coexistence to be as high as more than 50% [33]. A recent systematic review and metaanalysis by Ghasemi et al. [34] showed a significant prevalence of RLS (16.3%) in patients with migraine, however, direction of causality could not be commented. It also showed that the prevalence decreases with increase in sample size of studies; whereas it increased with the recency of year of publication of studies. The pathophysiology of coexistence of RLS and migraine has been attempted to be explained by the common roles of dopamine and melatonin, iron metabolism, genetic factors, and that of extrapyramidal system [35], but a consensus is yet to be reached.

Prevalence of multisite musculoskeletal pain is common in RLS, as evidenced by recent research [36]. The authors have found 65.6% of patients with RLS to have pain complaints and a significant proportion of them having multisite pain. Strong associations were found between diagnosis of RLS and long duration pain and multisite pain. An increase in inflammatory markers and decrease in pain thresholds have been suggested to be the common factors linking these two syndromes of RLS and multisite pain.

About one-fifth of the patients with RLS have been found to have somatoform pain disorder [37]. On the other hand, around 28% of patients with somatoform pain disorder have been diagnosed with RLS [38]. A larger proportion of those with RLS had continuous course of pain disorder, longer duration of pain disorder, and higher daytime sleepiness. The shared mechanisms and causality still needs vast research.

23.5 Other Sleep Disorders

Narcolepsy mainly comprises of excessive daytime sleepiness, abnormal REM manifestations, with or without cataplexy episodes. Narcolepsy has been found to increase the incidence of musculoskeletal conditions like low back pain, arthrosis, and arthritis [39]. Other than these, headaches like migraine and tension type headache occurred more in narcolepsy subjects with migraine in about half of the narcolepsy patients [40, 41]. Migraine usually starts after that of narcolepsy symptoms, suggesting that either poor sleep quality can precipitate migraine or both disorders have shared pathophysiology [40]. Interestingly, subtypes of narcolepsy appears to influence migraine with greater prevalence of migraine observed in cases of narcolepsy with cataplexy than that of those without it [42].

Repetitive clenching and grinding of teeth, with or without thrusting or bracing of mandibular area; all done during sleep, is known as sleep bruxism. Pain, in the form of various jaw muscle pain and morning headache, is a criterion for diagnosis of bruxism. The frequency of chronic pain in subjects with sleep bruxism was significantly higher than that in subjects with no sleep bruxism [43]. Headache and orofacial pain have also been found to be significantly higher in these patients [26]; causality still remains a controversial issue.

23.6 Prevalence of Sleep Disorders and Sleep Architecture in Somatic Symptoms

23.6.1 Fibromyalgia

Fibromyalgia (FM) is a disease characterized by diffuse and chronic musculoskeletal pain, without an identified cause [44, 45]. Some authors consider FM to be a neurobiological disease caused by the abnormal processing of pain [46]. Factors in the development of the disease are central sensitization, genetics, endocrine disorders, sleep disorders, psychosocial variables, and physical stress [47]. Sleep disorders in patients with FM may be related to the central inhibition of serotonin synthesis, leading to the elevation of substance [48].

Epidemiological studies have sought to clarify the relationship between sleep and FM symptoms. These researchers have demonstrated that populations with poor sleep quality have a greater risk of developing symptoms associated with FM, such as chronic pain, anxiety, and depression, leading to a repetitive cycle between FM and sleep disorders [49, 50].

The most common symptom of FM is sleep disturbance, which is often reported by more than 90% of study participants [51, 52]. Experimental studies have demonstrated a relationship between pain and sleep disorders, in which pain reduces sleep quality and sleep deprivation increases pain [53]. This leads to a vicious cycle that can influence the onset and aggravation of other symptoms [54, 55]. Two-thirds of FM cases are due to sleep disorders [56]. However, sleep disturbance cannot be considered as a component in the pathogenesis of FM [57, 58]. The causal

relationship between sleep and pain remains uncertain; however, it is widely accepted as bidirectional [59, 60].

Most of the participants in studies have been women since prevalence has been observed as higher in them. The most commonly used instrument for self report has been PSQI for fibromyalgia patients with sleep related problems [58].

Currently, the gold standard to diagnose sleep disorder is an overnight polysomnogram (PSG) [61]. PSG is a comprehensive sleep study which includes the recording of electroencephalography (EEG) which is a record of brainwave activity, electromyography (EMG) which records leg movements made during sleep, electro-oculography (EOG) which records eye movement, and also breathing rate, heart rate, oxygen level in the blood, and snoring and other noises made during sleep [62].

There are a few studies supporting the view that disordered sleep physiology is the root cause of generalized myalgia and musculoskeletal pain. In general, disturbances to slow wave sleep produce increased sensitivity to pain. It has been shown that symptoms of fibromyalgia can be reproduced in healthy volunteers subjected to deprivation of slow wave sleep [63, 64]. Sleep is affected by pain, but sleep deprivation also lowers the threshold for pain as evidenced by studies in young healthy individuals who were deprived of slow-wave sleep. This view gained further momentum when it was observed that by pharmacologically increasing the duration of slow-wave sleep with an endogenous neuropeptide, sodium oxybate, which is a potent GABA-B agonist, daytime pain and fatigue experienced by fibromyalgia patients was greatly diminished, and their quality of life measures improved [64].

About 2–15% of general population has been seen to suffer from *non-restorative sleep*. The non-restorative sleep would refer to not waking up feeling well rested albeit laying in bed for long hours [65]. This percentage goes up to about 60–90% in those suffering from fibromyalgia.

23.6.1.1 Sleep Architecture in Fibromyalgia

In a systematic review of 16 studies, increased pain in fibromyalgia was associated with reduced sleep quality, sleep efficiency and total sleep time as well as increased sleep disturbance, sleep onset latency and total wake time [66]. In a meta-analysis of 25 case-control studies that assessed sleep using polysomnography and PSQI, significant differences in sleep related parameters were found [67]. They were longer wake up after sleep onset (WASO), lower sleep efficiency, shorter total sleep time, an overall decreased sleep quality and more difficulty initiating sleep compared to the healthy controls. They noted a discrepancy where there were more sleep difficulties in subjective reports when compared to objective assessment.

The most common abnormality reported was a significantly increased Stage I sleep with reduced Stage 2 and Stage 4 sleep and longer sleep latencies and awakenings compared to healthy controls [68, 69].

Moldofsky et al. observed that alpha EEG anomaly during the NREM sleep on visual analysis of EEG has been a biological correlate of chronic pain as well as non restorative sleep complaints in those suffering from FM, although it was then not consistently found across all studies. The earliest findings were an alpha-wave

intrusion into the delta wave sleep during the stages 2–4 of NREM sleep phase. This is characterized by alpha wave activity (frequency 7–11 cycles per second) that is superimposed on the delta wave sleep (frequency 2 cycles/s and amplitude >75 μV), as a marker of the sleep impairment typical of FM [70]. Of note were other findings like increased Stage I sleep, decreased delta wave sleep and raised number of arousals [63, 71]. This was associated with a perception of shallow sleep and increased arousals [72]. Further, studies mentioned much distinct patterns of the alpha activity during sleep: phasic alpha-delta activity which showed lowest total sleep time and greatest number of symptoms; tonic alpha continuous throughout NREM sleep; and low alpha wave activity [73]. Non-quantitative methods have shown that there are correlations between symptoms of fibromyalgia and different subtypes of sleep alpha activity [73]. Phasic alpha as compared with tonic alpha intrusions have better correlations with increased pain after sleep and reports of poor sleep.

Sleep fragmentation has been observed in a number of studies with evidence of greater number of arousals and alpha K complexes in those suffering from fibromyalgia. This has been coupled with increased sympathetic activity overnight in those suffering from it compared to healthy controls.

Cyclic alternating patterns (CAP) are a periodic EEG sleep phenomenon that provides objective physiological measure of sleep stability. The CAP phase A1 pattern is considered to be an index of sleep stability, whereas CAP phase A2 and A3 are markers of progressive sleep instability or poor sleep quality. CAP phase A2 and A3 have been found to as associated with disease severity in FM patients. They have been present more often than controls as a cause of sleep fragmentation in this condition. It corresponds to a prolonged oscillation of the arousal level between two reciprocal functional states termed phase A (greater arousal) and phase B (lesser arousal), and in the dynamic organization of sleep it expresses a condition of instability of the level of vigilance that manifests the brain's fatigue in preserving and regulating the macrostructure of sleep [74].

Spectral analysis of EEG showed that patients with FM showed increased power in alpha band and a decreased power in lower frequency during Stage 2–4 and all sleep cycles which could also be appreciated in healthy individuals as well as those with CFS and Rheumatoid Arthritis [75].

23.6.2 Chronic Fatigue Syndrome

The earlier studies have contrasted with later ones where they have reported that about a half of patients with CFS could suffer from sleep apnoea, periodic limb movement or restless leg syndrome [76–78]. The results were not shared by later studies as polysomnography was no longer advised in the diagnosis of sleep disorders for the fatigued [79–81]. Prevalence rates of CFS in sleep disordered breathing was 10% and in those with insomnia was 19% according to some population based studies [82].

In patients with FM alone, the sleep disorders have ranged from 45–96% acc to various studies, whereas in patients having CFS with FM were found to have about 7% prevalence of sleep disorders [79, 83, 84].

23.6.2.1 Sleep Architecture in Chronic Fatigue Syndrome

Reduced sleep efficiency has been the most consistent finding. It refers to proportion of time spent sleeping relative to the time available for sleeping. The range has varied from 75–90%. This may be due to increased sleep onset latency or multiple awakenings/arousals and has been reported along with an overall decrease in stage 4 sleep [76, 85–87].

CFS patients have been thought to have a dysfunction in switching mechanism governing sleep stage transitions and the unrefreshing sleep may be due to sudden arousal from Stage 1 and REM sleep. They had greater probabilities of transition from REM sleep to wake compared to healthy controls which has been interpreted as lower sleep pressure [88].

23.7 Treatment

23.7.1 Pharmacological

Administering Nefazodone for 6 weeks has been found to result in about 70% improvement for people with sleep disturbances suffering from CFS. Galantamine, low-dose Clonidine, Valganiciclovir and Dextro-amphetamine weren‘t found to have no significant benefit for those with CFS [89–92].

In FM, Amitriptyline, Cyclobenzapine and Sodium Oxybate have yielded positive results [93–96]. Zolpidem has reported increased total sleep time, fewer awakenings and reduced sleep onset latency in a double blind study [97]. Zopiclone in a double blinded study showed to increase the slow wave sleep [98]. Randomised placebo-controlled crossover trial for Pregabalin has demonstrated efficacy in doses of 150–450 mg/day in patients with FM [99]. Sleep disturbances have been seen to improve with administration of Melatonin in various dose ranges. They have provided positive results in various study designs [100–102].

23.7.2 Non-pharmacological

1. Sleep Hygiene
   The importance of sleep in moderating pain, fatigue, and cognitive symptoms of the disease should be explained to all with diagnosis of fibromyalgia. For those who do not have chronic insomnia, basic sleep hygiene is appropriate. Specific therapies beyond basic sleep hygiene are needed for those with sleep disorders.
2. Cognitive Behavior Therapy
   The focus of behavioral interventions gained traction and have led to improvement of symptoms. RCT’s have shown good results with cognitive behavioral

therapy for insomnia (CBT-I) which involves sleep education and sleep hygiene training, as well as cognitive behavior therapy for pain (CBT-P), involving pain education and adaptive techniques training in patients with fibromyalgia [103]. These treatments which demonstrate benefits may be associated with cortical plasticity.

23.7.2.1 Balneotherapy

Passive immersion in hot baths (36 °C) [104] benefiting sleep quality, sleep efficiency, decreased sleep onset time and decreased number of awakenings as measured by polysomnography have been observed [105]. It is used in treatment of FM. The actions of passive body heating on sleep could be independent of fibromyalgia though.

In patients of CFS, a group-based 12-week cognitive behavioral stress-management intervention group showed improvements in unrefreshing sleep. They were trained with specific relaxation techniques, including progressive muscle relaxation and visualization techniques as well as teaching to better recognize how stress impacts them emotionally and physically, and the relationship between thoughts, feeling, and behaviors [106].

A multi-convergent therapy which combined cognitive behavioral therapy and graded exercise therapy was studied in a randomised control trial for patients with CFS. It showed improvements in sleep quality at post-therapy in patients with CFS. After 10 sessions of 1 h showed a maintenance of effect at 6 month follow up [107]. However, none of these approaches have been placed in any of the guidelines, and further research is required in this area.

In conclusion, sleep disorders and somatic symptoms disorders appear to have bidirectional relationship. Though literature is scanty, but it is important to consider sleep disorders in the differential diagnosis of somatic symptoms disorders as improvement in sleep has been found to improve somatic symptoms.

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Sleep, Sleep Disorders, and Sexual Dysfunctions

24

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Abstract

Good sleep is necessary for physical and mental health of the individual. The fact that sleep disorders are quite frequent in the general population is typically underestimated because of a lack of public awareness, preliminary diagnoses, and the exorbitant cost of therapy. According to recent researches, compromised sleep quality and sleep disorders affect multiple aspects of human health including sexual function. The most prevalent sleep problems related to sexual dysfunction include obstructive sleep apnea, chronic insomnia, shift work disorder, and narcolepsy. Consequently, cautious attention should be paid to the diagnosis and treatment of concomitant sleep disorders in patients with sexual dysfunction. In this chapter, etiopathogenesis, approach, management of sexual dysfunctions and their association with common sleep disorder are discussed. With understanding of sexual dysfunction and how they are impacted by sleep disorders, the sleep physician can ensure that sleep disorders are recognized as a significant contributor to sexual dysfunction in their patients in order to give them the optimal treatment for overall health and well-being.

Keywords

Sleep · Sexual dysfunctions · Erectile dysfunction · Ejaculatory dysfunction · Sleep disorders

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24.1 Introduction

Sleep is an essential complex neurological state for the good health and well-being of an individual. Although sleep occupies a significant proportion of our lives, it did not receive much attention from clinicians and researchers for a long time. In the last 50 years, sleep and pertaining disorders received proper attention from the scientists, post which the clinicians started to diagnose, analyze, and treat it systematically. It made us recognize how imperative adequate sleep quality and sleep duration are to physical, mental, and sexual health and the quality of life. Any alteration in the pattern, quantity, and quality of sleep results in sleep disorders.

Recently, there is an increasing evidence that sleep disorders affect sexual health and are related to various sexual dysfunctions. Sexual dysfunction is not a diagnosis but an umbrella that encompasses one or more distressing situations interfering with a person's ability to enjoy satisfying sexual health. This overlooked topic lies at the interface of multiple specialties, including urology, andrology, neurology, psychiatry, and sleep medicine, and will be dealt with in detail in this chapter.

24.2 Normal Sleep Pattern and Sexual Function

Sleep is an intricate neurological state, which primarily functions to provide rest and, thus, to restore the energy level of the body. In adults, a sleep of about 8 h is considered fully restorative and sufficient [1]. However, there is a wide variation among individuals concerning their level of stress, age, and habits. Normal human sleep is divided into non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is divided into three sleep stages I, II and III based on the polysomnogram (PSG), with each stage being characterized by its particular electroencephalographic (EEG) waveforms [1, 2] (Fig. 24.1).

Usually structured adequate sleep has a significant effect on the pituitary-gonadal axis in men and is imperative for the normal sexual functioning of the body [3, 4]. In normal men, total and free testosterone levels rise as soon as the person starts to sleep and reaches its peaks at first REM sleep and remains at that level till the person wakes up. This rhythmic secretion of testosterone is due to the secretion of growth hormone-insulin growth factor 1 (GH-IGF1) by the anterior pituitary, which is majorly secreted in NREM stage 3 or 4 of the sleep cycle [3–5]. These testosterone bursts during REM sleep are significant for normal sexual functioning. Chronic sleep deprivation or sleep fragmentation prevents the surge of testosterone levels during REM sleep, and this reduction in amplitude of testosterone surge leads to low morning testosterone levels [5]. Chronic sleep deprivation of about 3 h of nighttime sleep every day leads to about a 15% decrease in serum testosterone levels in healthy young individuals [6–8]. This fall in serum testosterone level translates into low sexual drive or decreased vigor and might lead to erectile dysfunction in some patients. The decrease in serum testosterone level can also lead to sexual dysfunction in females, namely sexual arousal disorder [9, 10].

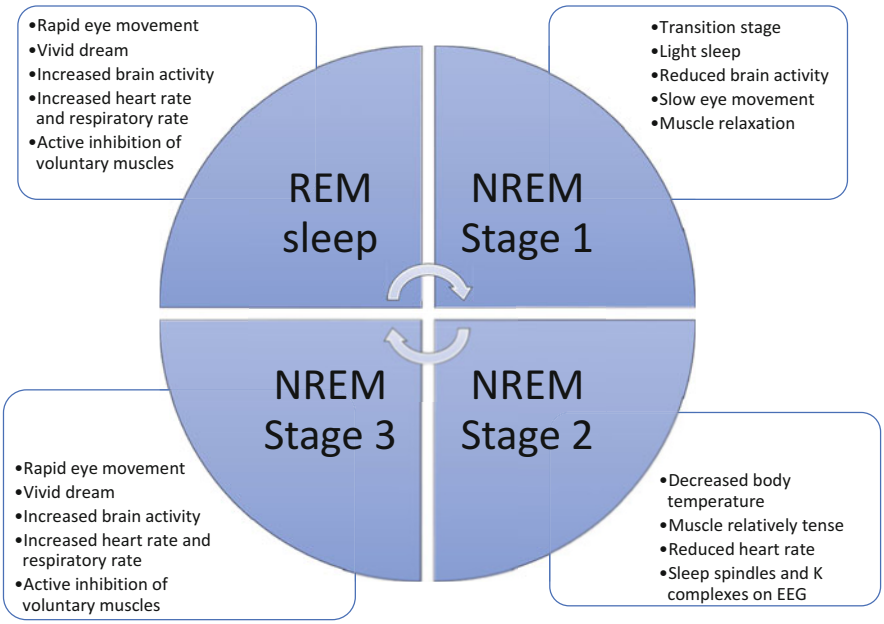

Fig. 24.1 Stages of sleep cycle with associated changes in human body during each stage of sleep cycle

On the other hand, sexual activities also have been found to have a conducive effect on sleep quality [11]. There occurs a surge in oxytocin and prolactin levels with a decline in serum cortisol levels following sexual intercourse. These hormonal changes reduce stress levels and promote sleep onset post sexual intercourse [12, 13].

24.3 Sexual Dysfunction and Sleep Disorders

Physical aspects of sexual response were first elucidated in 1966 by Masters and Johnson and later modified by Kaplan in 1977. The sexual response cycle refers to a series of physiologic and emotional changes that occur when a person becomes sexually aroused and participates in sexually stimulating activities, including intercourse and masturbation. In healthy individuals, both sexes experience the various stages during the sexual response cycle [14, 15]. These stages of the sexual response cycle are interrelated, with each phase stimulating the subsequent phase and being stimulated by the antecedent one [16].

- **The sexual desire stage**: This is also known as motivation for sex or libido. A satisfying and pleasant sexual event has a reinforcing effect on the individual,

Table 24.1 Sexual dysfunction types (according to DSM-5) [30]

Both men and women	Men	Women
Orgasmic disorder	Erectile disorders	Female sexual arousal disorder
Medication-induced sexual disorders	Male hypoactive sexual desire disorder	Genito-pelvic pain/perception disorder
Unspecified sexual dysfunction	Ejaculation disorder	Female orgasmic disorders

leading to the motivation for the next sexual response cycle. A dissatisfaction and unpleasant sexual experience might decrease the desire to repeat the sexual event.

- **Excitement phase**: This phase lasts from a few minutes to a few hours and is characterized by increased genital sensitivity with engorgement of erectile tissues associated with tachycardia, tachypnea, and sexual pleasure.
- **Plateaus phase**: In this phase of the sexual cycle, intensifying the changes during the excitement phase occurs. Erectile tissues get further engorged with increased sensitivity, accompanied by increased heart rate, blood pressure, and muscle tension.
- **Orgasm phase or climax phase**: It follows after a variable period of sexual stimulation and arousal and is marked by a temporary sensation of peak pleasure associated with a generation of well-being and contentment.
- **Resolution phase**: In this phase, the sexual excitement falls back to the baseline level. It is marked by sexual satiety sense with a lack of more desire for sex. It involves restoration of pelvic blood flow with heart rate returning to their baseline levels.

The sexual desire stage of the sexual response cycle is significantly regulated by the level of testosterone in the body of men, and testosterone therapy can improve the libido and sexual desire in men with total testosterone levels <12 mmol/L [17]. The excitement and plateaus phase of the sexual response cycle leading to penile erection is also dependent on the testosterone levels in the body. However, the relationship is weaker compared to the sexual desire phase. Approximately 30% of men with inadequate erection response have low serum testosterone levels [17].

As mentioned earlier, any significant alteration in the phases of the sexual response cycle leads to an array of sexual disorders in both men and women (Table 24.1). Although some sexual dysfunctions differ, still men and women can report similar problems about sexual response.

Sexual dysfunctions associated with sleep disorders are as follows:

1. **Erectile dysfunction disorder (EDD)**: According to American urology Association (AUA), EDD is the clinical condition characterized by the failure to attain and maintain an erection for satisfactory/sufficient intercourse. The erectile response is mediated by a combination of central (psychogenic) innervation and peripheral (reflexogenic) innervation. Neural input to smooth muscle tone is crucial for initiating and maintaining an erection [18, 19]. **Erectile dysfunction (ED) results from three basic neurovascular mechanisms**:
   - Failure to initiate (related to psychogenic, hormonal, or neurogenic cause)
   - Failure to fill (related to arterial insufficiency)
   - Failure to store adequate blood volume within the lacunar network in corpora of the penis (related to venoocclusive dysfunction)

   Standardized questionnaires are available to assess erectile dysfunction, including the International Index of Erectile Function (IIEF) and abbreviated IIEF-5 (Sexual health Index for Men (SHIM)) score [20]. These are often used in clinical practice to monitor and quantify erectile function, orgasmic function, sexual desire, and overall satisfaction [20]. IIEF 15 score comprises 15 questions on five sexual domains that assess erection, desire, intercourse satisfaction, orgasmic function, and overall satisfaction of the individual. Severity of erectile dysfunction (ED) is grade as no (>25), mild (17–25), moderate (11–16), and severe ED (</=10) based on questionnaire scoring [20]. The primary evaluation begins with the patient's medical, surgical, sexual, and psychosocial history. Next, the potential basis of EDD is probed and classified as organic, psychogenic, or mixed. This confers to a presumed psychological or interpersonal determinant (psychogenic), a specific endocrinologic, neurologic, or cardiovascular cause (organic), or concomitant presence of psychological factors with organic causes (mixed). Nocturnal erections, also known as sleep-related erections (SRE), occur during REM sleep and are associated with testosterone surge during REM sleep [21, 22]. SREs require intact neurological and circulatory systems and often serve in clinical practice as a marker of distinguishing organic EDD from psychogenic EDD [21, 22].

   EDD is the most common sexual dysfunction linked to sleep disorders. It is associated with multiple sleep disorders like obstructive sleep apnea (OSA), chronic insomnia, Restless leg syndrome (RLS), period leg movement during sleep (PLMS), and narcolepsy [23]. Its etiopathogenesis in these sleep disorders is dealt with in detail later in this chapter.
2. **Loss of libido or decreased sexual arousal disorder**: Decreased arousal disorder or female sexual interest disorder is characterized by the presence of at least three of the following symptoms in women lasting for more than 6 months and causing significant distress
   - Decreased sexual interest/desire or receptivity to partner's initiation
   - Decreased arousal/interest in response to sexual cues
   - Decreased pleasure or sensation during sexual response
   - Absent or decreased sexual fantasies or thought
   - Decreased or absence of initiation of sexual activity

- Decreased genital or nonessential sensations during sexual activity
  In men, for the diagnosis of male hypoactive sexual disorder, a person should have the symptoms of reduced sexual fantasies with decreased desire for sexual activity for at least 6 months and resulting in significant distress to the affected person [24].

  Hypoactive sexual desire disorder or decreased libido is seen in sleep disorders like chronic insomnia, narcolepsy, and OSA [24, 25]. Relationship between decreased libido and genital response with a sleep disorder like insomnia has been more strongly associated with women than men [24]. Many factors are attributed to decreased libido in individuals with sleep disorders ranging from decreased testosterone levels to imbalance of neurotransmitters in the brain due to sleep deprivation, and are described later in detail.

3. **Ejaculation disorder**: Ejaculatory disorders are among the most common male sexual disorders with a spectrum consisting of delayed ejaculation (DE), premature ejaculation (PME), anejaculation (AE), retrograde ejaculation (RE), painful ejaculation, post orgasmic illness syndrome (POIS), and ejaculatory anhedonia. Normal ejaculation activity is divided into three phases: emission, ejection, and orgasm [26].
   The emission process involves the expulsion of sperm and seminal fluid in the urethra due to synchronized contraction of vas deferens, seminal vesicles, and the prostate. It is mediated by the synergic activation of the parasympathetic and sympathetic pathways.

   Ejection or expulsion of semen involves the pulsatile contraction of pelvic floor muscles and relaxation of the internal urinary sphincter. It is mediated by somatic nerves (S2–4) and sympathetic spinal cord reflex.

   Orgasm or climax occurs due to the cerebral processing of sensory stimuli from the pudendal nerve due to increased pressure in the verumontanum and posterior urethra and contraction of accessory sexual organs.

   Multiple central neurotransmitters are involved in the normal ejaculation process, including dopamine, norepinephrine, oxytocin, nitric oxide (NO), and gamma-aminobutyric acid (GABA) [26]. Therefore, any imbalance in these neurotransmitters can predispose to disorders related to ejaculation.

   Premature ejaculation is defined by AUA as a clinical condition with ejaculation occurring sooner than desired, either before or shortly postpenetration, and causing significant distress to one or both the sexual partners. It is associated with sleep disorders like restless leg syndrome and narcolepsy. Dopamine plays a vital role in promoting seminal emission acting via D2 receptors in the medial preoptic area of the brain (MPOA) CNS [27]. Therefore, the association of PME with these disorders is proposed due to central dopamine imbalance ensuing in both of these disorders.

   Delayed ejaculation (DE) and anejaculation (AE) are unique forms of male sexual dysfunction. According to DSM-V, DE is defined by the presence of either one of the two symptoms, namely absence of substantial delay or marked infrequency of ejaculation that is present at least for more than 75% of occasions

for a minimum duration of 6 months. DE and AE disorders are usually associated with medications like antidepressants (TCAs) often used in the treatment of narcolepsy. These disorders are as a result of an imbalance of centrally acting neurotransmitters like serotonin in the brain [28].

Ejaculatory anhedonia/pleasure dissociative orgasmic dysfunction: These are the clinical conditions characterized by the experience of ejaculation without the feeling of orgasm or pleasure. These disorders are quite rare and poorly studied in the literature. Etiopathogenesis of these disorders involves the imbalance of central neurotransmitters like dopamine.

Unspecified sexual dysfunctions: There are multiple unspecified sexual dysfunctions associated with sleep disorders like sexsomnia or sexual behavior in sleep (SBS), hypersexuality seen with Kleine-Levin syndrome, sleep-related painful erection (SRPE), nocturnal sexual delusions and hallucination associated with primary psychotic disorders, narcolepsy, and other neurological diseases such as parkinsonism [29].

24.4 Etiopathogenesis, Approach, and Treatment to Sexual Dysfunction in Common Sleep Disorders

As per the International Classification of Sleep Disorders (third edition) [31], there are more than 100 types of sleep disorders. Research studies have found numerous ways in which these sleep disorders affect the sexual health of the individual and cause sexual dysfunction (Table 24.2). Some common sleep disorders associated with sexual dysfunction will be dealt with here:

24.4.1 Obstructive Sleep Apnea

Obstructive sleep apnea is a clinical condition characterized by reduced airflow due to collapse of the upper airway leading to loud snoring and apneic or hypopnea episodes.

OSA severity is based on the frequency of breathing disturbances (apnea-hypopnea index (AHI)), the amount of oxyhemoglobin desaturation with respiratory events, the duration of apneas and hypopneas, the degree of sleep fragmentation, and the level of daytime sleepiness or functional impairment [32].

Obstructive sleep apnea (OSA) has been associated with a significantly higher risk of erectile dysfunction (ED). Several studies have shown a high prevalence of ED among male OSA patients, reaching up to 70.0% [32]. The severity of OSA, though not consistent, is considered to be an essential factor in the development of ED.

Several theories have been proposed behind the interaction mechanism between OSA and ED, including peripheral neuropathy due to hypoxemia, testosterone effect, or endothelial dysfunction of vessels [23]. Various studies have found lower serum testosterone in male patients with OSA. Moreover, there is a negative

Table 24.2 Common sleep disorders with associated sexual dysfunction and responsible etiological factors

Common sleep disorders	Associated sexual dysfunction	Etiology
Obstructive sleep apnea	Erectile dysfunction	Endothelial dysfunction of vessels, peripheral neuropathy due to hypoxemia, and low testosterone effect (hypogonadism indeterminate)
	Decreased libido/ hypoactive sexual desire disorders	Lower testosterone levels in men, and lower estrogen, progesterone, and 17-OH progesterone levels in women Poor general quality of life and mood
Narcolepsy	Decreased sexual drive and arousal	Hypocretin deficiency in CNS/loss of orexin neurons in lateral hypothalamus, dopamine paucity in CNS, and excessive sleepiness
	Catalepsy associated with narcolepsy	Catalepsy causing sexual cycle disruption
	Erectile dysfunction	Association of diabetes with narcolepsy and use of tricyclic antidepressants (TCAs) in treatment
Insomnia, chronic sleep insufficiency	Erectile dysfunction	Association with diabetes mellitus (DM), metabolic syndrome, and obesity Medication induced
	Decreased libido	Decreased testosterone levels and depressed mood
Circadian rhythm disorders	Abnormal erectile response	Imbalance of central neurotransmitters like oxytocin and dopamine Low serum testosterone levels
	Decreased sexual arousal	Excessive tiredness, fatigue, low testosterone level, and decreased central dopamine levels
Restless leg syndrome (RLS)	Erectile dysfunction	Central dopaminergic imbalance
	Premature ejaculation	Imbalance in central dopaminergic and serotonergic pathway
Periodic limb movement during sleep (PLMS)	Erectile dysfunction	Fragmented REM sleep lowering testosterone level
	Sexual arousal disorder	Low testosterone levels
Abnormal sexual behavior during sleep, sleep sex, and sexsomnia	Disturbed interpersonal relationship/unspecified sexual dysfunction	Disturbed NREM sleep and unknown etiological causes

correlation between serum testosterone levels and apnea-hypopnea index (AHI) in OSA. This means patients with higher AHI scores have lower serum testosterone implying that the severity of hypopnea and apnea is related to serum testosterone levels in OSA [33]. Contrarily testosterone has also been implicated in aggravating sleep apnea, and studies have shown that its supplementation in hypogonadal

patients aggravates sleep apnea. Hence, a complicated correlation exists between OSA and testosterone, implying extra caution should be taken to treat severe OSA patients and hypogonadism with testosterone replacement therapy [33]. Patients with OSA with concomitant ED have also been found to have elevated serum inflammatory marker levels such as lactate dehydrogenase (LDH), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor α (TNF α), interleukin (IL)-6, and IL-8. These inflammatory markers usually get elevated in cases of any endothelial insult and, thus, serve as a surrogate marker of vascular endothelial injury. Their elevation to significant levels in patients with OSA with ED implicates the role of vascular endothelial dysfunction in the pathogenesis of ED in OSA [34].

Obstructive sleep apnea (OSA) with erectile dysfunction and hypogonadism requires multidisciplinary management, and an approach to its management is detailed below (Fig. 24.2).

24.4.1.1 Approach to a Patient with Obstructive Sleep Apnea with Erectile Dysfunction

Evaluation

- A thorough history, including sexual, medical, and psychosocial history, is needed, and a focused local examination is used to establish the diagnosis. A validated questionnaire like The International Index of Erectile Function (IIEF) should be used to assess all the domains of sexual function.
- Recommended laboratory tests include serum chemistries, fasting glucose, complete blood count, lipid profile, and total serum testosterone to check any reversible risk factors and lifestyle factors.
- Specialized evaluation and testing may be done to define and classify the etiology of erectile dysfunction as vasculogenic, neurogenic, psychogenic, or endocrinologic. It includes vascular evaluation of ED by Duplex USG of penis post pharmacostimulation or combined intracavernosal injection and stimulation, penile angiography or dynamic infusion cavernosometry, and cavernosography. Other essential tests to identify the cause of ED include nocturnal penile tumescence monitoring (NPT), detailed neurological, hormonal, and psychological evaluation.
- Neurophysiologic evaluation: Nocturnal penile tumescence and rigidity (NPTR) can be carried out along with a sleep study for OSA in men [33].

Treatment

A comprehensive approach to obstructive sleep apnea-hypopnea syndrome (OSAHS) is needed to reduce risk factors and comorbidities. The clinician should seek to identify and address lifestyle and behavioral factors and comorbidities that may be exacerbating OSAHS.

Patient education, lifestyle modifications, psychosexual counseling, and management of associated comorbid risk factors constitute the initial essential management of EDD. As appropriate, treatment should aim to reduce weight; optimize sleep duration (7–9 h); regulate sleep schedules (with similar bedtimes and wake times

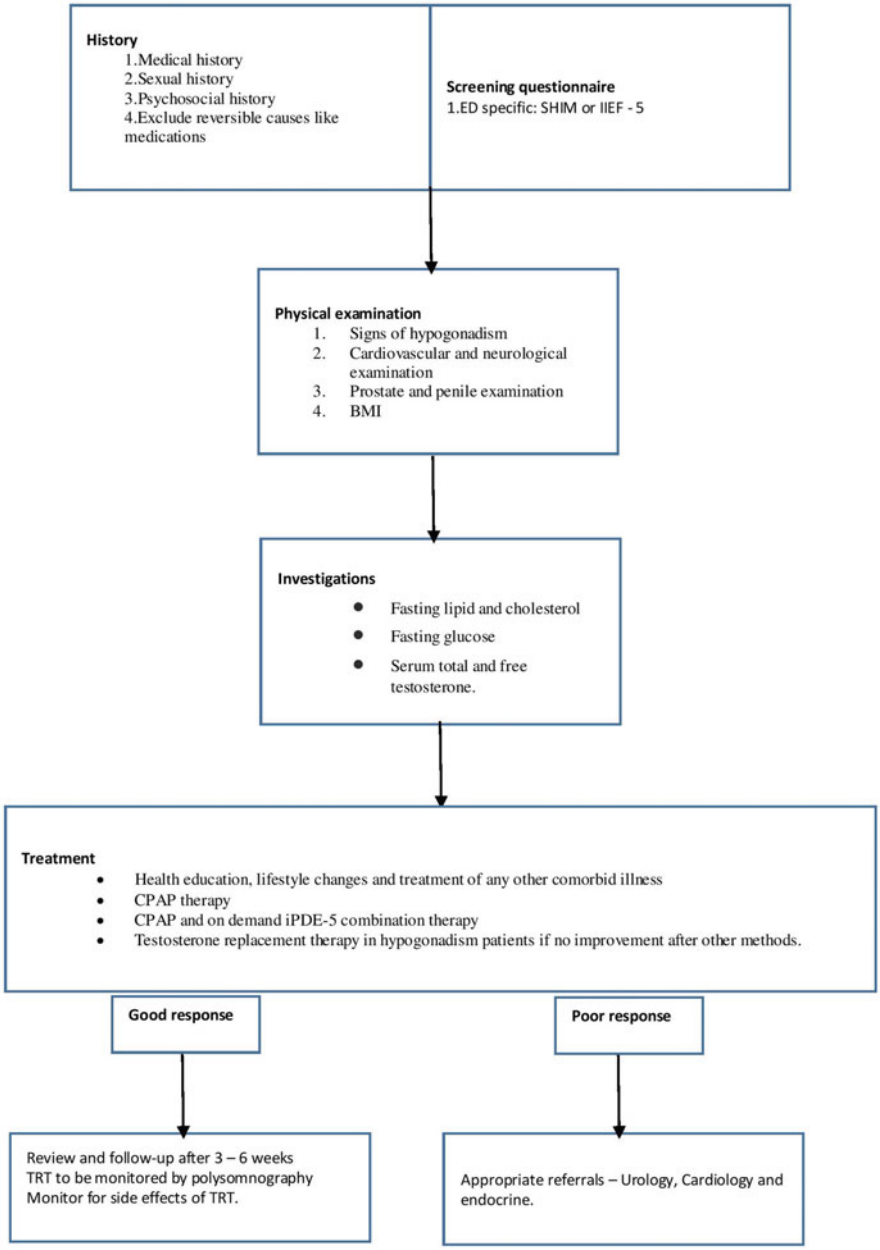

Fig. 24.2 Algorithm for management of obstructive sleep apnea-related hypogonadism and erectile dysfunction

across the week); encourage the patient to avoid sleeping in the supine position (if OSA is position dependent); treat nasal allergies; increase physical activity; discourage the use of alcohol (which impairs pharyngeal muscle activity) within 3 h of bedtime, and minimize the use of sedating medications.

Management of OSA is the most critical factor in the improvement of erectile function. American Academy of Sleep Medicine guidelines recommend that pneumatic splinting of the upper airway is the treatment of choice for moderate and severe OSA [35]. Patients with mild OSA may also be offered positive airway pressure therapy if they have clinical symptoms like excessive daytime sleepiness. Various treatment options available are as follows:

1. Continuous Positive Airway Pressure (CPAP)
   CPAP improves respiratory and neurological parameters for OSA patients [36]. Margel et al. studied erectile function in 60 patients using the IIEF-5 questionnaire post 12 months of CPAP therapy. They reported that 20% of patients in the study group of 60 who adhered to long-term CPAP treatment had improved IIEF score by at least four points. In comparison, 18% of patients in the study group had worsening of erectile function, which was correlated with noncompliance to CPAP therapy and mild OSA [36].

   Budweiser et al. studied 91 OSA patients with moderate-to-severe ED (IIEF score <17) and no comorbidities for a mean follow-up of 3 years and found significant improvement in sexual function (IIEF-5) ($p = 0.014$). They also showed that the beneficial effects of CPAP were maintained over the long term [37].

   Pascual et al. conducted an open-label randomized controlled trial in 77 moderate-to-severe OSA patients with ED. IIEF-15 score of less than 25 was used to define ED. The patients were randomized to CPAP and no CPAP arms. A significant increase in erectile function, sexual satisfaction, and overall satisfaction domain of IIEF-5 score was found in the CPAP group. However, CPAP treatment did not affect the hormonal, psychological, or biochemical profiles of the patients [38].

   In summary, available evidence confirms a close correlation between ED and OSA. It suggests the need to screen ED in OSA patients, which can be further treated using multimodality treatment as given below.
2. Continuous Positive Airway Pressure with Oral Phosphodiesterase-5 Inhibitors (PDE-5)
   The overall satisfaction achieved with combined CPAP and PDE-5 inhibitor treatment is significantly higher than either therapy alone. Thus, a combination of CPAP therapy and 100 mg sildenafil on demand is a good treatment option for ED patients with mild-to-moderate OSA [39].

   Perimenis et al. conducted a randomized trial in 40 patients suffering from OSA and EDD. After a 4-week treatment with CPAP to all participants, patients were randomly allocated to CPAP + 100 mg sildenafil or CPAP alone for 6 weeks. The crossover was done after a 1-week washout period. There was a significant increase of around 40% more successful intercourse attempts in

the combined arm (61.1% vs. 24.8%) during the study period of 12 weeks. The overall satisfaction assessed as an IIEF score for ED was 70% higher in the combined treatment arm than the CPAP group alone [40].

Li et al. performed a meta-analysis and showed a statistically significant difference toward patients using sildenafil in intercourse attempts, IIEF score, and satisfaction level of the patient compared to CPAP therapy alone [41].

3. Oral Phosphodiesterase-5 Inhibitors (iPDE-5) Alone
The use of iPDE-5 alone is controversial due to the worsening of ventilatory events in patients with severe OSA [42].

Roizenblatt et al. in a study of 13 patients with severe OSA, compared placebo to 50 mg sildenafil in a double-blind crossover trial. They showed that mean oxygen saturation decreased ($P = 0.03$), and there was an increase in apnea-hypopnea index ($P = 0.001$) in the sildenafil arm. There were also increased obstructive events in the sildenafil arm [42].

Neves et al. conducted a trial in 13 patients to assess the effects of sildenafil on autonomic functions in OSA patients. They showed a worsening of respiratory functions and risk of increased cardiac events due to autonomic function impairment in sildenafil-treated severe OSA patients [43]. Thus, the use of oral iPDE-5 alone without any CPAP therapy in patients with severe OSA with ED might lead to disastrous consequences and, hence, is relatively contraindicated.

4. Continuous Positive Airway Pressure and Surgical Treatment
Khafagy and Khafagy conducted a trial in 80 male patients analyzing IIEF-5 and nocturnal penile tumescence before and after 3 months of treatment with CPAP uvulopalatopharyngoplasty with adjunctive nasal surgeries. They found a statistically significant improvement in both erectile function tests ($P < 0.05$) [44].

Approach to a Patient of Obstructive Sleep Apnea with Hypogonadism

Evaluation

Hypogonadism diagnosis is based on persistent signs and symptoms of androgen deficiency like absence or regression of secondary sexual characters, abdominal adiposity, low hemoglobin, muscle wasting, decreased bone mineral density, and reduced sperm count along with consistently low testosterone levels (<300 ng/mL). Adult-onset hypogonadism is associated with loss of vigor, obesity, and sexual dysfunction.

- A thorough history and physical examination should be followed by serum testosterone measurement.
- The measurement of serum testosterone should be done before 11 am and preferably in a fasted state. It is recommended to measure testosterone on at least two occasions.
- Assess LH and FSH serum levels to differentiate primary and secondary hypogonadism. In primary hypogonadism, also called hypergonadotropic hypogonadism, since there is a primarily testicular failure, levels of

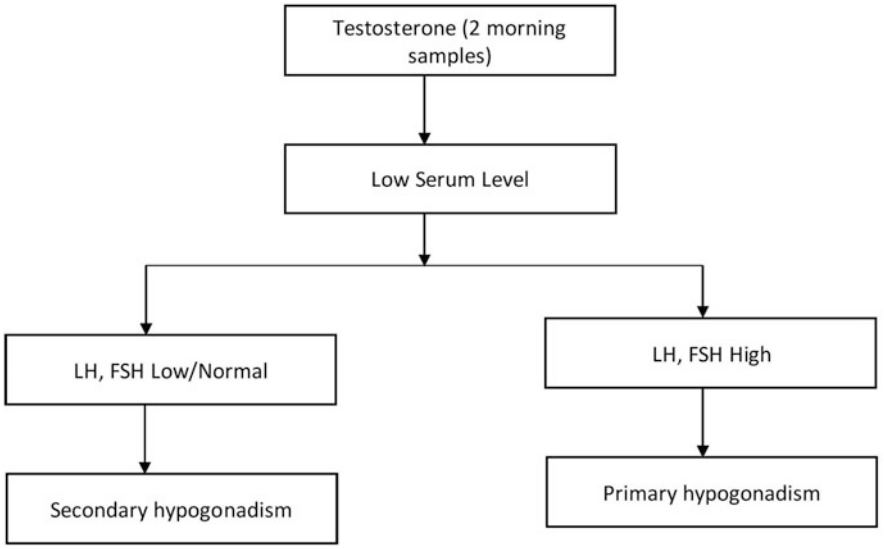

Fig. 24.3 Algorithm to differentiate primary and secondary hypogonadism based on serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels

gonadotropins (LH and FSH) are high due to the loss of negative feedback by testosterone and inhibin produced from the testis.

Contrarily in secondary hypogonadism, there is primarily the affection of the pituitary or hypothalamus due to any congenital or acquired cause resulting in decreased secretion of FSH and LH, which results in testicular failure to produce androgens and sperms (Fig. 24.3).

Treatment

Improved lifestyle, reduction of weight, and treating any other associated comorbidities should always be a part of the treatment of hypogonadism in patients with OSA.

There is a linear correlation between weight loss and increased plasma testosterone levels in obese men [45]. Historically, testosterone replacement therapy was considered dangerous in patients with severe OSA as it can exacerbate symptoms and interfere with central response to hypo- and hypercapnia [46].

- Effect of OSA treatment on serum testosterone
  Grunstein et al., in a study of 40 men, showed that patients with severe OSA treated with CPAP therapy showed a significant increase in serum hormone-binding globulin and testosterone levels at 3 months after treatment [47]. Another prospective study of uvulopalatopharyngoplasty for OSA showed increased testosterone levels and sexual function at 3 months postsurgery. However, there was no change in LH or FSH in this study [48]. A majority of studies show no

change in serum LH, FSH, or testosterone levels post CPAP therapy for 1–-39 months [49–51].

- Testosterone replacement therapy (TRT)
  Shigehara et al. performed a study on 48 OSA patients with hypogonadism. Following testosterone replacement therapy, there was an improvement in sleep disturbances compared to placebo at 12 months [45].

  Melehan et al. conducted a randomized control trial in 67 obese men with OSA. The patients were randomized to receive intramuscular injections of either testosterone undecanoate 1000 mg or placebo at baseline, 6 and 12 weeks. Testosterone increased sexual desire ($P = 0.004$), although there was no significant difference in erectile function, frequency of sexual attempts, orgasmic ability, and general or sleep-related quality of life. Improvement in quality of life was evident only in patients with testosterone levels below 8 nmol/L [52].

  However, this improvement only in the sexual desire domain of IIEF score with testosterone replacement therapy (TRT) needs to be balanced against more serious adverse effects of TRT on exacerbation of OSA symptoms. CPAP and iPDE-5 seem to be the safe options for improving the sexual functions in these patients. Testosterone replacement therapy should be used with caution, especially if the patient is not on CPAP therapy, and mildly, as testosterone replacement is itself a risk factor for OSA development. Testosterone replacement therapy in patients with OSA needs to be monitored by polysomnography to detect any worsening of symptoms.

24.4.2 Narcolepsy

According to the International Classification of Diseases, it can be defined as a condition characterized by recurrent episodes of daytime somnolence, and lapses in consciousness (microsomia) may be associated with automatic behaviors and amnesia. Cataplexy (loss of tone of muscles suddenly due to emotion), sleep paralysis, and hypnagogic/hypnopompic hallucinations frequently accompany narcolepsy. The pathophysiology of this disorder includes sleep-onset rapid eye movement (rem) sleep, which usually follows stage III of sleep. Narcolepsy is a neurological disorder affecting 1 in 2000 individuals with equal gender predominance.

The most important discovery in narcolepsy, which resulted from animal experiments, was identifying the relationship between hypocretin-1 (also known as orexin) and narcolepsy. It was shown that local injection of hypocretin-1 (orexin-A) at the medial preoptic area produced sexual arousal in male rats. Hypocretin-1 is a neuropeptide confined to a small number of cells in the hypothalamus. Patients with narcolepsy have lost these hypocretin-producing cells leading to associated sexual dysfunction in the form of decreased sexual drive and arousal [53, 54].

The prevalence of sexual dysfunction in a patient with narcolepsy ranges from about 40 to 70% [54]. Several possible etiologies were reported in the literature for sexual dysfunctions related to Narcolepsy, such as:

- Loss of libido due to excessive sleepiness. It has been seen that chronic deprivation of sleep leads to loss of sexual drive and erectile dysfunction mediated by the imbalance of autonomic nervous system activity and levels of central neurotransmitters like serotonin occurring due to excessive sleepiness [54].
- Association of diabetes with narcolepsy: There is an increased risk of metabolic disorders such as noninsulin-dependent diabetes mellitus (NIDDM) and obesity in patients with narcolepsy [55, 56]. There is an established relationship between diabetes and erectile dysfunction due to vascular and neurogenic dysfunction in diabetes. Diabetic patients have autonomic dysfunction, penile vascular inadequacy, increased spinal reflex latencies, and decreased nocturnal penile tumescence, leading to organic erectile dysfunction in males.
- Cataplexy associated with sexual arousal: Around 60% of patients with narcolepsy suffer from catalepsy. Catalepsy is a sudden loss of tone in a group of muscles triggered by some intense emotional activity. Several cases have been reported in men and women where sexual arousal led to cataleptic episodes, thus disrupting the sexual cycle [57].
- Treatment-induced erectile dysfunction: Tricyclic antidepressants (TCAs) often used in the management of narcolepsy have a profound effect on sexual function and lead to disruption of normal sexual health. Most of these medications have an added anticholinergic action, leading to the parasympathetic blockade, causing autonomic dysfunction leading to erectile dysfunction. In addition to this, many CNS stimulants like dextroamphetamine, methylphenidate, and pemoline prescribed for the management of narcolepsy also interfere with sexual response and aggravates the ejaculatory, erectile, and libido problems in patients with narcolepsy. This effect is presumed to be due to their anticholinergic properties [58].
- Dopamine paucity theory: Another theoretical possibility of sexual dysfunction in narcolepsy is dopamine related. In narcolepsy, studies have shown that there is a widespread paucity of dopamine in the CNS with increased sensitivity to Ach [59]. This decrease in dopamine levels in CNS affects the sexual reward center in the brain, thus reducing sexual motivation and leading to sexual arousal disorders.

24.4.2.1 Treatment of Sexual Dysfunction in Narcolepsy

A careful history and history from spouse or relatives, examination, and polysomnography can help detect sexual dysfunction disorders associated with narcolepsy [60]. There is a paucity of literature describing the treatment of sexual dysfunction associated with narcolepsy. The treatment of such disorders involves the treatment of narcolepsy. Most of the cases reported in the literature were cured by amphetamine therapy or clomipramine with modafinil. If sexual dysfunction persists, then the affected person should be referred to an urologist to evaluate and treat sexual dysfunction as it is done in primary disorders of sexual dysfunction [60].

24.4.3 Insomnia, Chronic Sleep Insufficiency

Insomnia is the most prevalent sleep disorder. Around 20% of the total population meets the diagnostic criteria for insomnia disorder [61]. It is characterized by difficulty initiating or maintaining sleep, awakening earlier than desired or resisting going to bed on an appropriate schedule. Insomnia is more common in older individuals and is an independent risk factor related to sexual dysfunction. The most likely cause for this sexual dysfunction is decreased serum testosterone levels in patients with chronic insomnia. A study conducted by Schmid et al. has shown that duration of sleep modulates the level of serum testosterone, and morning testosterone levels get significantly reduced in patients with sleep loss [62]. Serum testosterone reaches its peak level after the first 3 h of night sleep and at the end of REM sleep. Insomnia or prolonged wakefulness, thus, results in a decrease in serum testosterone levels leading to sexual dysfunction. Also, chronic insomnia predisposes to conditions like T2DM, metabolic disorder, or hypertension, which in themselves are the established risk factors for sexual and erectile dysfunction [63]. Testosterone has a vital role in increasing muscle mass, bone mineral density, and elevating mood in addition to sexual function [64, 65]. Hence, chronic insomnia has significant consequences on physical, mental, and sexual health. The reason for this association is not apparent and needs further research.

We are describing a brief approach to a patient with insomnia and sexual dysfunction in this section.

24.4.3.1 Evaluation

The history and physical examination related to sexual dysfunction should be a part of the evaluation of insomnia. Any medication being used by the patient is an essential part of history evaluation. There has been recent increased use of polypharmacy for focal indications, resulting in insomnia as a side effect [66]. Sexual side effects associated with selective serotonin reuptake inhibitors (SSRIs) like citalopram, fluoxetine, escitalopram, etc. include delayed ejaculation, delayed orgasms, decreased sexual libido, and arousal difficulties. SSRIs should be changed to selective norepinephrine reuptake inhibitors (SNRI), which have fewer side effects of sexual dysfunction.

24.4.3.2 Treatment

The essential component of the treatment of sexual dysfunction with insomnia is the treatment of the primary sleep disorder. Cognitive behavior therapy and pharmacotherapy are the treatment options. The sexual dysfunction might improve with the treatment of the primary disease. If there is no improvement in the follow-up, a specialist urological consultation can be given for sexual dysfunction [67].

24.4.4 Circadian Disruption Sleep Disorder

Circadian rhythm sleep disorders are caused due to the desynchronization of internal sleep-wake body rhythm and external environment light-dark cycle. It includes clinical conditions like "Jet lag" disorder, "Shift work sleep disorder" (SWSD), or "Altered sleep phase" disorder [68].

The jet lag disorder occurs due to rapid travel across multiple time zones. Factors influencing the severity of symptoms experienced by the travelers include the direction of air travel, the number of time zones crossed, and the timing of the flights. Symptoms include excessive daytime sleepiness, insomnia, reduced alertness, and physical and mental fatigue. Although transient, it can cause long-term consequences like cognitive deficits, gastrointestinal motility disorders, and increased risk of infertility, cancers, and cardiac diseases.

Similarly, shift work that also disrupts the body's circadian rhythm affects the individual's physical, mental, and sexual health. According to estimates, about 15% of the world's workforce is employed in shift work [69]. SWSD is characterized by at least 1 month of insomnia, excessive sleepiness, and disruption of social and occupational schedule resulting from the shift work schedule. SWSD suffers from many adverse consequences, including gastrointestinal motility disorders, sexual dysfunction disorders, chronic insomnia, increased daytime sleepiness, increased risk of road traffic accidents and accidents at the workplace, and increased probability of depression, myocardial infarction, and cardiovascular diseases [25, 70]. As described earlier, serum testosterone levels begin to rise at sleep onset and reach the highest point at the first REM sleep cycle. It can be deduced that sleep disruption due to shift work would lessen serum testosterone levels leading to sexual dysfunction. As described earlier, testosterone affects sexual function at multiple levels involving CNS, PNS, and target tissues. Testosterone is associated with releasing central neurotransmitters such as dopamine and oxytocin, which play an essential role in normal erectile response during the sexual cycle. Low testosterone levels can lead to hypogonadism, which further translates to decreased libido, erectile dysfunction, fatigue, and muscle mass loss. Recently, Rodriguez et al. found that men with SWSD have a poor erectile function that is even worse in night-shift workers. It has also been appreciated that testosterone therapy in patients with SWSD might partly ameliorate risk for sexual dysfunction and hypogonadal symptoms but is not free of side effects [70]. No study has been conducted to assess, compare, and standardize the treatment options in sexual dysfunction associated with these circadian rhythm disorders. A specialist urology referral should be taken to treat sexual dysfunctions in such patients treated in the line of primary sexual dysfunction and sleep disorder. Such patients should be enrolled in clinical trials to assess response to treatment and further standardization of treatment protocol.

24.4.5 Restless Leg Syndrome

It is a neurological disorder characterized by a peculiar unpleasant sensation in limb like pulling or creeping that usually occur in the night while muscles are relaxed. Sensations give an irritable desire to move the limb, following which sensation gradually subsides. It affects about 15% of the general adult population [71]. Although etiopathology of RLS is still elusive, the hypofunction of dopaminergic system in CNS is considered to have a role in disease pathogenesis [71]. RLS is more commonly found in individuals with iron deficiency and CKD patients on dialysis [72]. Dopaminergic function in CNS plays a pivotal role in normal erectile functioning during the sexual response cycle; thus, patients with RLS often suffer from ED [72]. Gao X et al. concluded that patients with RLS who experienced more than 14 episodes every month had about a twofold higher risk of having ED than men without RLS [73].

No study has been conducted yet to see the effect of dopaminergic agonists like ropinirole and pramipexole used in treating RLS on erectile dysfunction. Literature also suggests the role of PDE-5 inhibitors like tadalafil in patients with concomitant ED and RLS. Further studies analyzing treatments for patients with comorbid ED and RLS are necessary.

Kurt et al. found a positive correlation between premature ejaculation (PE) and RLS. It was assumed to be due to dysfunctional serotonergic and dopaminergic systems in CNS. Moreover, it was also found that the prevalence of PE increased with the severity of RLS [74]. More studies need to be conducted to elucidate the etiopathogenesis relationship between PE and RLS. Suppose a person continues to have sexual dysfunction even after starting RLS treatment, a specialist urologist opinion should be taken; and the patient's sexual dysfunctions are treated in the same way as in standard urological practice.

24.4.6 Periodic Limb Movement During Sleep (PLMS)

It is a type of neurological disorder marked by repetitive stereotypical movements of the limbs involving the lower extremity. According to the World Association of Sleep Medicine, PLMS is diagnosed when four or more consecutive leg movements last for a duration of 0.5–10 s with an EMG increase of more than eight microvolts above the resting baseline. The interval between consecutive limb movements should be between 5 and 90 s.

These movements disturb sleep and comprise surges of muscle activity during sleep, thus resulting in both EEG arousals and autonomic arousals. PLMS is a common sleep disorder with a prevalence of about 20% in the general population [72].

PLMS is frequently associated with RLS and other sleep disorders like narcolepsy and OSA. About 80% of patients with PLMS have coexisting ED or sexual arousal disorders [53]. The likely etiology for this correlation is again hypothesized to be due to disturbed nighttime REM sleep preventing testosterone surges. The

prevalence of ED is directly proportional to the severity of PLMS and the age of the individuals with PLMS [75, 76].

Studies have shown that treatment with nonergot containing dopaminergic agonists like pramipexole, ropinirole, and rotigotine significantly reduced the PLMS symptoms. They are considered the first-line agent for the same. Anticonvulsants, benzodiazepines, and gamma-aminobutyric acid agonists like pregabalin and gabapentin are also used to treat the symptoms of PLMS. However, treatment is given only when the patient has frequent arousals or persistent excessive daytime sleepiness [72].

24.4.7 Sleep Sex or Sexsomnia or Atypical or Abnormal Sexual Behaviors During Sleep (ASBS)

Atypical or abnormal sexual behaviors can occur during sleep and are recognized as parasomnia according to ICDS-3 classification. Parasomnias consist of a group of sleep disorders with abnormal physical events and experiences. They appear during, within, or after arousal from sleep. Sexsomnia is classified as a disorder of arousal from NREM sleep and consists of sexual activities like masturbation, spontaneous orgasm, attempted sexual intercourse, sexual vocalizations. Sexsomnia either gets identified in patients with already known NREM sleep parasomnias like sleepwalking, sleep-related eating, or occurs in patients of OSA. Sexsomnia is associated with a variety of problems like disturbed interpersonal relationships due to disturbed sleep of the partner, physical injury to the partner, or psychological disturbance to the partner, and thus, can lead to marital or relationship strain. Hence, it is essential to recognize, diagnose, and treat these sleep-related disorders for the physical, mental, and social well-being of the individual.

24.4.7.1 Approach/Treatment of Patients with ASBS or Sleep Sex or Sexsomnia (Fig. 24.4)

The evaluation of a patient with parasomnia, OSA, and seizure-induced sleep sex begins with thorough history and examination. Cases of severe psychosocial ramifications and dissatisfied marital relationships are common in such cases. Polysomnography with or without nocturnal penile tumescence and rigidity would be sufficient to diagnose such patients [60].

The trigger for these sexual events is related to the primary disease [60, 77]. The treatment of the primary disorder resulted in a cure in almost all the cases reported in the literature [60].

- Benzodiazepine clonazepam is effective in all parasomnia cases.
- CPAP is effective in parasomnia with sleep sex related to OSA.
- Anticonvulsant medications were effective in cases of seizure-induced sleep sex.

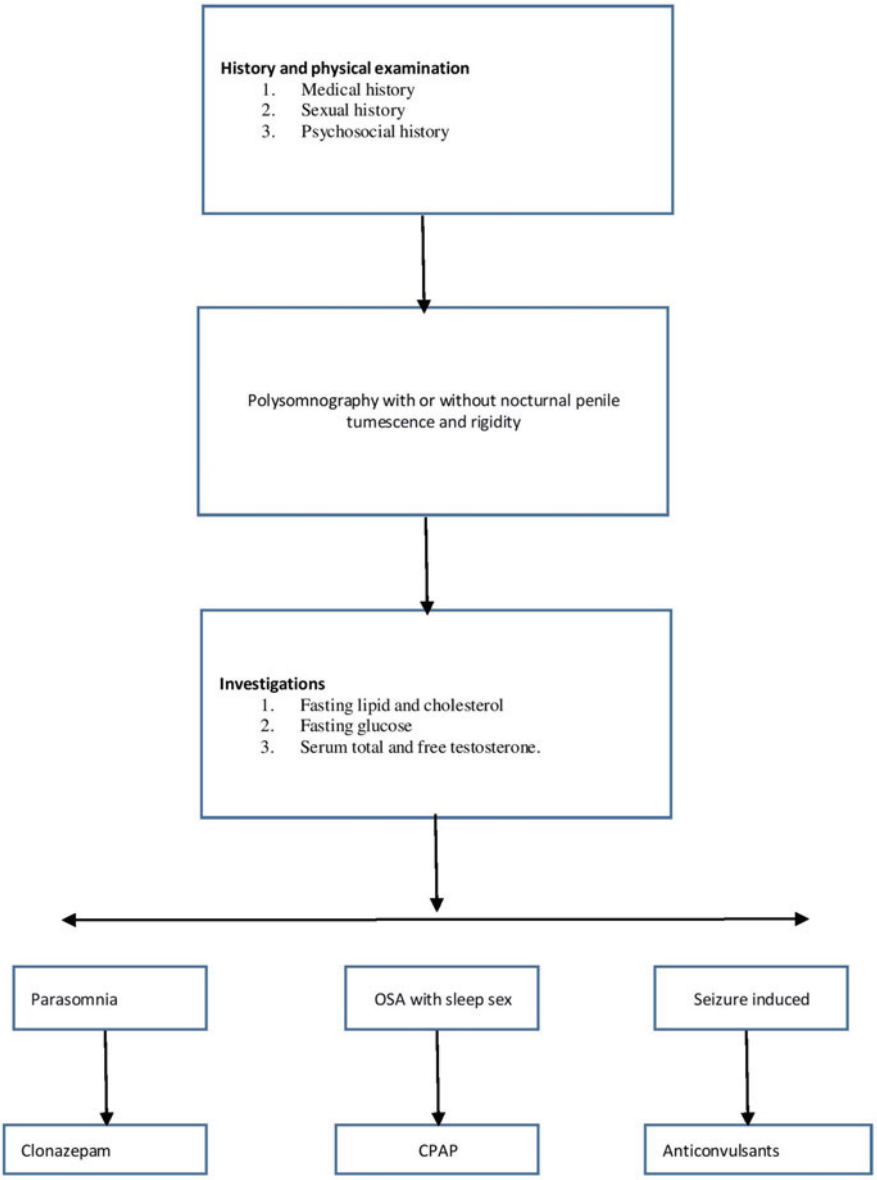

Fig. 24.4 Algorithm for management of abnormal sleep-related sexual behaviors

24.5 Conclusion

Sleep is an essential biological process that is of paramount importance for physical and mental well-being. Though very common in the general population, sleep disorders are often missed due to the lack of public awareness, inadequate diagnostics, and the prohibitive cost of treatment. Sleep disorders also significantly affect the sexual health of the individual. With a complete understanding of sleep physiology and common sleep disorders, the specialist can ensure that sleep disorders are considered a contributor to sexual dysfunction in their patients to provide them with the optimum treatment for improving overall health. Future research is warranted in this often neglected field to elucidate the mechanisms between sleep and sexual dysfunction disorders. It will lead to the development of treatment modalities that can better address these comorbid conditions together.

24.6 Summary

- Structured adequate sleep is imperative for the normal sexual functioning of the body.
- Patients presenting with sexual dysfunction might be suffering from a sleep disorder that aggravates their sexual dysfunction.
- Obstructive sleep apnea, chronic insomnia, shift work disorder, narcolepsy, Periodic limb movement during sleep (PLMS), and restless legs syndrome are some of the common sleep disorders associated with sexual dysfunction.
- ED is one of the most common sexual dysfunction associated with sleep disorders. Endothelial dysfunction of vessels, peripheral neuropathy due to hypoxemia, and low testosterone levels are a few of the causes implicated in its causation in sleep disorders.
- Around 70% of male OSA patients have some form of ED, which significantly improves on treatment of OSA.
- Diagnosis and appropriate treatment of sleep disorders have shown improvement in sexual dysfunction scores, thus improving the individual's quality of life.
- Clinicians understanding the normal sexual function and how common sleep disorders can cause sexual dysfunction can ensure that sleep disorders are studied as a contributor to sexual dysfunction in their patients to deliver them with the best treatment for overall health and well-being.

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Sleep and Attention-Deficit/Hyperactivity Disorder

25

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is often associated with comorbid sleep disturbances. Sleep disturbances may be a risk factor for development of the disorder, a symptom of a comorbid psychiatric/primary sleep disorder, or a side effect of medications used to treat ADHD. Current guidelines recommend assessing sleep problems prior to initiating pharmacotherapy, yet not all clinicians are aware of the extent to which ADHD and sleep have been associated. As such, this chapter (1) provides information regarding the nature of the associations between ADHD and primary sleep disorders, comorbid psychiatric disorders, and medications aforementioned; (2) describes overlapping pathophysiology; and (3) discusses implications for treatment.

Keywords

Attention-deficit/hyperactivity disorder · Sleep · Insomnia

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25.1 Overview

Attention-deficit/hyperactivity disorder (ADHD) is a medical condition affecting 3–7.5% of the population, marking it as one of the most prevalent disorders presented to mental health specialists [1, 2]. It is characterized by a persistent pattern of inattention, and/or hyperactivity-impulsivity, and can be further specified by a predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, or by a combined presentation of the two [3].

It has been reported that 35–70% of individuals with ADHD experience some type of sleep disturbance, and this number varies based on gender, age, ADHD subtype, psychiatric comorbidities, and medication use [4].

The associations between sleep and ADHD are multifaceted and complex. It is not clear whether lack of sleep mimics symptoms of ADHD or if ADHD is intrinsically associated with sleep disturbances [5, 6]. In addition, sleep disturbances in individuals with ADHD could be caused by a comorbid primary sleep disturbance; comorbid psychiatric disorders that co-occur with ADHD; or could be a side effect caused by medication used for the treatment of ADHD.

The aim of this chapter is to describe what is currently known about each of the areas above, while explaining the underlying pathophysiology, reviewing relevant findings, and discussing implications for treatment.

25.2 Primary Sleep Disorders and ADHD

Sleep problems commonly reported in individuals with ADHD include restless legs syndrome (RLS), sleep disordered breathing (SDB), and delayed sleep phase syndrome (DSPS). Clinical characteristics, pathophysiology, and associations with ADHD will be discussed in the following sections.

25.2.1 Restless Legs Syndrome

25.2.1.1 Clinical Characteristics

RLS is a sensorimotor disorder characterized by discomfort affecting the limbs and an irresistible urge to move them. Symptoms tend to be triggered by periods of rest or inactivity such as attempting to fall asleep. Physical activity can partially relieve this uncomfortable sensation; however, symptoms often recur once the movement stops. Patients typically describe it as a feeling of crawling or tingling. The severity of symptoms can range from irritating to painful and tend to worsen during the night, making it difficult for an individual to fall asleep or return to sleep after waking up [7]. The inadequate sleep associated with RLS often leads to daytime sleepiness and fatigue the following day [8].

Prevalence

RLS affects 3.9–14.3% of the general population [9]. 1.9% of 8- to 11-year-old children and 2.0% of 12- to 17-year-old adolescents also meet the criteria for RLS, where 1.0% experience severely distressing symptoms more than twice a week [10].

25.2.1.2 Association of RLS and ADHD

Twenty-six percent of children with ADHD have been shown to display symptoms of RLS as compared to 5% of those without ADHD and 20–25% of children with RLS displayed symptoms of ADHD [11–14]. The presence of RLS worsened ADHD symptoms, and symptoms of ADHD were most severe in patients who had both ADHD and RLS [15, 16].

Subjective parental reports displayed more bedtime resistance, sleep onset difficulties, greater night awakenings, and more signs of restlessness among children with ADHD and RLS symptoms [17]. The association between adult ADHD and RLS using self-report instruments also showed that adults with ADHD had higher odds of being diagnosed with RLS [18].

Inattentiveness, impulsiveness, moodiness, and hyperactivity are frequently observed in children with RLS [14]. This could result from sleep disturbances or deprivation in this population suggesting that daytime manifestations of symptoms, such as restlessness and inattention, could be caused by sleep deprivation hence "mimicking" ADHD symptoms [19].

25.2.1.3 Pathophysiology of RLS

Pathophysiological mechanisms underlying RLS have been linked to dopaminergic abnormalities and iron deficiency in the brain [20, 21]. Higher prevalence in individuals who have an affected first-degree relative, along with the current increase in RLS diagnosis in children may also suggest a genetic inherited susceptibility of the disorder [22].

Dopaminergic Abnormalities

A malfunction of the dopamine receptors has been found in individuals with RLS. An overall downregulation of white blood cell D2-subtype dopamine receptors was linked to a diagnosis of RLS [23]. This downregulation is not reversed by medication; however, patients who were medicated had higher concentrations of plasma dopamine levels as compared to those who were unmedicated and controls, suggesting evidence for receptor malfunction. Positron emission tomography (PET) imaging found the dopamine system in both striatal and extrastriatal brain regions was implicated in the pathology of individuals with RLS [24]. Improvement of RLS symptoms with dopamine agonists have also been seen in numerous studies demonstrating the involvement of abnormal dopaminergic activity in the manifestations of RLS symptoms [25, 26].

Iron Insufficiency

Studies using MRI techniques revealed decreased iron concentrations in the substantia nigra, a region where dopamine-producing cells reside, as well as a strong

relationship between iron concentrations in the substantia nigra and severity of RLS symptoms [27–29]. Lower iron levels were also reported in adults with RLS who underwent cerebrospinal fluid analysis [30]. Although iron deficiency is associated with RLS, only about 25% of patients with RLS appear to have insufficient iron, suggesting the deficiency is not related to serum iron [31]. In fact, RLS has been associated with low blood concentrations of ferritin, the protein that serves to store the iron in tissues, which can explain how blood concentrations of iron could be deemed sufficient even when the levels in the cerebrospinal fluid are lacking [22]. Treatment of iron deficiencies with iron supplementation have been shown to improve RLS symptoms in certain candidates, however, others have found mixed results [30, 32–35].

25.2.1.4 Overlapping Pathophysiology

RLS and ADHD may have a common underlying dopaminergic pathway where they both share a probable central nervous dopaminergic malfunction [30, 36]. Children with ADHD have been shown to have significant iron deficiencies, which may be linked to the expression of ADHD symptoms [37–39]. Iron deficiency could be a contributor in the pathophysiology of patients with ADHD and RLS given that iron is a cofactor of tyrosine hydroxylase, which plays a crucial role in brain dopamine productions [15, 30, 40, 41]. Dopamine receptors and dopamine transporter genes have also been altered through iron deficiency suggesting that brain iron levels could influence dopaminergic functions as well as expression of ADHD symptoms [42].

25.2.1.5 Implications for Treatment

Nonpharmacological as well as pharmacological options have been recommended for RLS. If iron deficiency is found in individuals with RLS, it can be improved with iron supplementation with doses of 80 mg/day also improving ADHD symptoms [43, 44]. Levodopa and dopamine agonists have also been shown to reduce RLS symptoms associated with ADHD symptoms and improve sleep outcomes [14, 45, 46]. Nonpharmacological recommendations include adopting healthy sleep habits and avoiding caffeine, nicotine, and alcohol as these could exacerbate RLS symptoms [47].

Future research is still required to determine the causality of this relationship; however, clinicians should be aware of it and screen for symptoms of RLS in patients with ADHD and vice versa prior to developing treatment plans.

25.2.2 Sleep Disordered Breathing

25.2.2.1 Clinical Characteristics

SDB is characterized by an abnormal respiratory pattern or insufficient ventilation during sleep, which can lead to excessive sleepiness the following day and impact numerous aspects of health. The severity of symptoms of SDB ranges from snoring in the mildest form, where there is an inability to freely move air due to excessive tissue, to obstructive sleep apnea (OSA), the most severe form of SDB, where an

inability to freely move air occurs due to a partial or complete upper airway obstruction with five or more predominantly obstructive respiratory events per hour of sleep [7].

Prevalence

The prevalence of SDB is reported at 9% for women and 24% for men [48]. Pediatric studies report a prevalence of 3.6–7.7% for snoring, and a 1–4% prevalence for OSA in children and adolescents [49, 50]. Nine to thirty-eight percent of adults experienced more than five events of sleep apnea per hour and this prevalence increases in older men [51].

Prevalence of SDB and ADHD

Children with ADHD tend to have significantly higher levels of sleep disordered breathing than the general population, with prevalence of 1.2% in typically developing youth and 25–57% in youth with ADHD [4, 52–55].

OSA has been associated with ADHD in numerous studies and has often been underdiagnosed or misdiagnosed due to ADHD being the primary disorder investigated [56–59]. An apnea-hypopnea index of greater than 1 was found in samples of children with ADHD as well as in those with hyperactivity symptoms and was estimated at 42% and 55% [60–62].

25.2.2.2 Associations Between SDB/OSA and ADHD Symptoms

ADHD and SDB have been found to be associated with children and adults [63, 64]. Objective studies revealed excessive daytime sleepiness in those with SDB and ADHD [52]. SDB has been associated with increased symptoms of inattention, hyperactivity, and impulsivity and with cognitive deficits such as decreased working memory [58, 65–69]. SDB has also been found to exacerbate the symptoms of ADHD and to be associated with a range of daytime neurological and behavioral impairments often resembling the symptoms and characteristics of those with ADHD [70].

25.2.2.3 Pathophysiology of SDB/OSA

Intermittent hypoxia (IH) has been shown to result in neurocognitive functioning impairments such as deficits in vigilance, working memory, and executive functions as a result of (1) neuronal cell death and cortico-hippocampal damage; (2) damage to prefrontal cortex; and (3) brain inflammation manifested as increases in free radicals, inflammatory cytokines, and the C-reactive protein suggesting daytime cognitive and behavioral difficulties may be exacerbated through hypoxia [71–79].

25.2.2.4 Overlapping Pathophysiology

Intermittent hypoxia results in symptoms of inattention as well as impacts on development and behavior characteristic of ADHD, suggesting a common underlying mechanism for both ADHD and SDB [80, 81]. The severity of dysfunction in the prefrontal cortex seen in children with ADHD has been related to the increased

apnea-hypopnea index and resulting neurocognitive functioning impairments [81, 82].

Neuroimaging studies have revealed decreased hippocampal volume in patients with OSA contributing to ADHD-like motor and attentional deficits [6, 69, 83]. Similarly, studies using neuroimaging have revealed decreased hippocampal subfields in those with ADHD, which could account for similar daytime symptoms presented with ADHD and SDB [84]. Further research on ADHD and OSA is required to determine whether decreased hippocampal volume in ADHD is a risk for OSA, or if the impairments of OSA are likely to exacerbate ADHD symptoms.

Higher obesity rates have also been shown in individuals with OSA and in those with ADHD [85], as it can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and through central nervous system-acting signaling proteins (adipokines) that may affect airway neuromuscular control. These differences can produce alterations in the mechanical and neural control of upper airway collapsibility, which determine sleep apnea susceptibility [86]. Obesity potentiates and predisposes individuals to OSA. Since high levels of obesity are found among individuals with ADHD, there could be a common underlying pathophysiology [87, 88]. Enlarged tonsils and adenoids are also presenting factors among children with OSA and ADHD, which can cause poor sleep and result in attention problems the following day [66, 89].

25.2.2.5 Implications for Treatment

Clinicians should inquire about SDB/OSA in children with ADHD symptoms. Treatment of SDB/OSA including weight loss, positive airway pressure therapy, and adenotonsillectomy should be considered as it could result in improvements in ADHD symptoms [8, 65, 89–91].

Weight Loss

Through exercise and healthy eating individuals with OSA can help reduce the weight that is contributing to sleep apnea. In obese individuals, weight loss has been successful in improving SDB symptoms. A positive association has related the amount of weight lost to the improvement of symptoms [92, 93].

Continuous Positive Airway Pressure Therapy (CPAP)

CPAP uses mild air pressure via a face mask to keep airways open during sleep and has been validated as an efficient treatment for OSA. In adults and adolescents, positive airway pressure therapy remains the first line of treatment [75]. Improvement in OSA as well as the diminishment of symptoms of ADHD, daytime sleepiness, and internalizing behaviors as a result of CPAP therapy have been reported [94–96].

Surgical Intervention

Adenotonsillectomy is the surgical removal of the adenoids and tonsils, whereas a tonsillectomy is the removal of solely the tonsils. It remains the first line of treatment for children with OSA [97]. These procedures have been shown to resolve OSA in

more than 85% of children, resulting in a significant decrease in ADHD symptoms [75, 98].

The childhood adenotonsillectomy trial (CHAT) explored the neuropsychological and health outcomes and efficacy of adenotonsillectomy in children with sleep disordered breathing and found benefits associated with surgical treatment [99–101]. Other studies have found that adenotonsillectomy had a medium relationship with decreased ADHD symptoms in children with OSA, resulting in an increase in daytime vigilance and decrease in hyperactive behaviors [53]. Studies have reported that treatment with adenotonsillectomy resulted in significant improvement in behavior as well as reversal of ADHD symptoms similar to the results seen with stimulant medication [62].

25.2.3 Delayed Sleep-Wake Phase Disorder

25.2.3.1 Clinical Characteristics

The main feature of circadian rhythm sleep disorders (CRSD) such as delayed sleep-wake phase disorder (DSWPD) is a shift in the sleep-wake cycle where an alteration of the circadian rhythm results in a misalignment of sleep timing and socially acceptable bedtimes/wake times leading to difficulties falling asleep at the socially desired time [7]. This leads to delayed bedtimes and delayed sleep onset, decreased sleep duration, and excessive daytime sleepiness [58, 102].

Prevalence

DSWPD has an estimated prevalence of 0.17% in the general population. The prevalence rises from 3.3 to 16% in adolescents [103–105].

25.2.3.2 Association of DSWPD and ADHD

The prevalence of DSWPD in adults with ADHD rises to 26% as compared to 2% in controls [106]. The prevalence in children and adolescents has not been reported. The presence of ADHD has also been shown to increase the odds of having DSWPD [107, 108].

The secretion of melatonin under dim light conditions (dim light melatonin onset (DLMO)) is a marker of the circadian phase [109]. In individuals with ADHD, longer sleep latencies as well as evening chronotypes have been associated with a delayed DLMO. This is characteristic of DSWPD, suggesting that circadian mechanisms underlie the sleep onset insomnia reported by individuals with ADHD [110–116]. Delayed phase patterns of sleep and lower total sleep time have also been experienced by highly impulsive individuals, with results similar to individuals with ADHD [117].

25.2.3.3 Pathophysiology of DSWPD

Physiological, behavioral, and environmental factors may play a role in the development of DSWPD. Physiologically, the circadian clock of individuals with DSWPD is fixed at a later phase resulting in a propensity to sleep at a later time

[118]. A genetic predisposition for DSPS has been found through polymorphisms in the CRY1 segment of the *CLOCK* gene, a gene associated with chronotype diurnal preference and delayed sleep timing in individuals carrying these polymorphisms [119, 120]. The release of melatonin in DSWPD is usually delayed as compared to controls [121]. Lower levels of melatonin secretion have been positively associated with decreased volume of the pineal gland [122, 123].

During adolescence, the circadian clock is impacted by developmental changes and environmental factors, such as reduced parental influence, increased evening screen time, and extracurricular activities, which could all contribute to the preferred phase or eveningness chronotype [124].

25.2.3.4 Overlapping Pathophysiology

Studies investigating polymorphisms of the *CLOCK* gene in ADHD have discovered over transmission of a t-allele associated with delayed diurnal preference and a risk for DSPS [125, 126]. Single nucleotide polymorphisms in core circadian clock genes have also been associated with an increased risk for ADHD [127, 128].

Decreased pineal gland volumes have been associated with delayed circadian preference in adults with ADHD and have been shown to mediate symptom severity [129].

25.2.3.5 Implications for Treatment

Several treatment strategies could be used to treat DSWPD.

Chronotherapy

Chronotherapy alters sleep timing by intentional changes to the sleep/wake cycle using daily light exposure, and has been found to significantly advance bedtimes [130]. Along with the advancement of sleep-wake cycles, it has also been shown to significantly improve ADHD symptoms in those with DSWPD [131].

Bright Light Therapy

Bright light therapy has also been implicated in the treatment of DSWPD by exposing the retina to a recommended intensity of light for specific durations in the morning [128, 132]. Bright light therapy administered in the morning with 10,000-lux has been shown to improve ADHD and DSWPD symptoms [133–136].

Melatonin

Melatonin is a naturally occurring hormone synthesized by the pineal gland which modulates the sleep-wake cycle and has been widely used in the treatment of DSWPD [137, 138]. Doses of 0.5–3 mg 1–3 h prior to bedtime or up to 5 mg/day have been used as a safe and effective treatment option in advancing the circadian rhythm and lengthening sleep duration [58, 139–143]. The use of melatonin alone has been found to improve sleep onset latency, sleep duration, sleep efficiency, and reduced subjective difficulty falling asleep, as well as an advance in DLMO [116, 138, 142, 144–146].

In patients with ADHD prescribed stimulant medication, melatonin decreased their mean sleep onset latency as well [142, 145]. Objective findings using actigraphy and polysomnography have been mixed with some indicating positive treatment effects with melatonin and others showing no significant treatment effects [82, 147]. The discontinuation of melatonin use has been associated with a relapse of delayed sleep onset [148]. Overall, the use of melatonin for sleep problems in individuals with ADHD has been shown to be useful and successful.

25.3 ADHD and Psychiatric Comorbidity

25.3.1 ADHD and Anxiety Disorders

Anxiety disorders (AD) are a group of disorders that are characterized by excessive feelings of fear or worry. The prevalence of children and adolescents with ADHD having a comorbid diagnosis of at least one AD ranges between 26 and 42% [150–152]. The prevalence of children with ADHD having two or more AD among school-aged children with ADHD ranges from 28 to 33% [150, 152]. This rate increases throughout development with anywhere between 46 and 52% of adults with ADHD presenting multiple comorbid anxiety disorders [153].

The presence of a comorbid AD in individuals with ADHD may contribute to impaired sleep through increased irritability and restlessness [154]. Children with an AD and ADHD were reported as having had the highest rates of global sleep impairments [155, 156] in comparison to children with anxiety or ADHD alone. These impairments include parent-reported night waking, shorter sleep duration, daytime sleepiness, and long sleep latency compared to healthy control or ADHD only groups [155–158]. These associations remain relatively stable over time [159].

25.3.2 ADHD and Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a group of neurodevelopmental disabilities characterized by persistent deficits of social communication and social interaction, and restricted and repetitive patterns of behavior, interests, or activities, which are not better explained by intellectual disability or global developmental delay. The prevalence rate for ADHD symptomology in children, adolescents, and adults with ASD ranges between 31 and 83% [160–163]. The rate of reported sleep problems in ASD and ADHD ranges between 35 and 80% [164, 165].

The research in the area of sleep difficulties in individuals with comorbid ADHD with ASD is limited because the previous versions of the Diagnostic and Statistical Manual of Mental Disorders did not allow for a comorbid diagnosis of ADHD and ASD [166]. A few recent studies have documented sleep challenges in individuals with these comorbid conditions. In preschoolers with ASD, difficulty falling asleep, waking up crying in the middle of the night, waking up much earlier than usual, and cosleeping with a parent were associated with parental ratings of ADHD behaviors

[167]. In school-age children with a comorbid diagnosis of ADHD and ASD, nightmares, excessive sleepiness, sleeping less than other children, trouble sleeping, and total problematic behavior were reported by parents using the Child Behavior Checklist [166]. Other studies examining a wider age range (3–18 years old) revealed that comorbid ADHD is associated with parent-reported global sleep problems in ASD [160].

25.3.3 ADHD and Mood Disorders

Mood disorders are a group of conditions that are marked by long-lasting disturbed moods that impact daily functioning. The prevalence of the co-occurrence of mood disorders in youth with ADHD ranges between 22 and 30% [153]. According to the National Comorbidity Survey, the prevalence of a comorbid diagnosis of a mood disorder in adults with ADHD ranges between 13 and 38% [168]. Furthermore, major depressive disorder was found as being the most dominant mood disorder (17%) among adults with ADHD followed by dysthymia (13%) [168].

In children with ADHD, depressive symptoms were associated with parent reports of shorter sleep duration, increased daytime sleepiness, increased need to catch up on sleep during the weekend, and global sleep impairments as reported by the Child Behavioral Checklist [169, 170]. In a sample of adolescent males with comorbid depression and ADHD, depression was associated with the severity of self-reported insomnia, restless sleep, fatigue, and snoring [171]. A longitudinal cohort study found that adults with ADHD and depression self-reported shorter sleep duration (<6 h) and longer sleep onset latency (>30 min) [172]. The same study found through self-report measures that, compared to healthy controls, individuals with depression were more likely to have extremely late chronotypes [172].

25.3.4 Treatment Implications

The interplay between sleep and ADHD is multifaceted and tridirectional when considering the presence of other psychiatric comorbidities. For example, behavioral sleep interventions on children with ASD and ADHD have shown improvements on subjective measures of sleep onset delay, parasomnias, sleep duration, sleep anxiety, emotional functioning, conduct problems, peer problems, and ADHD symptomology [173]. Clinical research suggests that sleep-related problems are intensified when patients with ADHD present with a comorbid diagnosis of anxiety, depression, or autism spectrum disorder. Sleep intervention can serve as a central feature of effective and appropriate treatment. Therefore, it is important to consider addressing sleep difficulties, as poor sleep may be influencing the severity of ADHD symptoms and the associated comorbid conditions. Future research using objective measures of sleep can help to shed light on the directionality between comorbid conditions and sleep problems, as well as the understanding of the clinical features of ADHD associated with psychiatric comorbidities.

25.4 The Impacts of ADHD Medication on Sleep

Medications such as methylphenidate, atomoxetine, extended-release guanfacine, and extended-release clonidine are recommended for the treatment of ADHD by reducing behaviors associated with ADHD and improving functioning [149]. Medications prescribed to treat ADHD may potentially exacerbate sleep disturbances by impacting sleep onset, total sleep time, and sleep efficiency in children and adults.

25.4.1 Stimulants

Stimulant medications, such as methylphenidate, amphetamines, and dextroamphetamines, stimulate the central nervous system by blocking the reuptake of dopamine as well as increasing the synaptic release of dopamine and norepinephrine. This surplus of neurotransmitters leads to an increase in vigilance and mental awareness, which helps individuals with ADHD maintain attention throughout the day. Although these medications are approved to be effective treatments in relieving ADHD symptoms throughout the day, they have been reported to impact sleep [150]. Studies attempting to determine the impact of stimulant medication on sleep in individuals with ADHD have had mixed results.

Stimulant medications, including methylphenidate, amphetamine salts (amphetamine/dextroamphetamine), and lisdexamfetamine dimesylate, are typically prescribed to individuals with ADHD and have been associated with overall longer SOL, poorer sleep efficiency, and a reduction in total sleep time [151–157].

The extent to which these medications affect sleep depends on the individuals' age, the presence of prior sleep disorders, and dosing and medication schedules [158].

25.4.1.1 Age

Younger age groups were found to have more delays in sleep onset latency [159].

25.4.1.2 Medication Schedule

SOL was increased in both twice daily and thrice daily doses of MPH, and thrice daily doses of 8.8 +/− 5 mg MPH were found to decrease total sleep time as compared to twice daily and controls [160]. More frequent doses were indicative of higher SOL [151].

25.4.1.3 Doses

Becker et al. [161] also found that increased sleep problems were mediated by increases in MPH doses in boys with ADHD. Parent reports of insomnia were also increased for participants given higher doses of MPH [162].

Other studies report no significant impact of associations between MPH usage and sleep disturbances. Effects of once daily MPH treatment have had little evidence showing MPH to be the cause of sleep disturbances in children [163–165]. O'Brien

and colleagues [166] also found no differences to be associated with the use of stimulants in subjective and objective measures of sleep in individuals with ADHD compared to those with ADHD not on medication. In some cases, medication has reduced sleep duration but has not had effects on sleep efficiency [150]. Decrease in nighttime awakenings with patients on stimulants have also been positively reported [167]. In a pilot study assessing the effects before and after 6-month usage of immediate-release MPH in children with ADHD, no differences were found in sleep architecture using polysomnography. The differences seen in the sleep disturbances associated with MPH could be accounted for by the already reduced sleep efficiency seen in those with ADHD as compared to those without [168].

25.4.2 Nonstimulants

Nonstimulant medications have become available as an alternative treatment to improving symptoms of ADHD. They work as norepinephrine reuptake inhibitors, increasing synaptic neurotransmitter concentrations through alternative pathways than do stimulants. These medications, such as atomoxetine (ATX), have had elevated results in decreasing core ADHD-related behavior in children and adults, where the increase in synaptic neurotransmitters has been associated with a reduction in inattentive and hyperactive symptoms [169–173].

ATX has shown minimal signs of sleep disturbances among the ADHD population and is less likely than MPH to exacerbate disordered sleep [174]. Side effects of ATX include somnolence reported in 15–17% of individuals with ADHD [175]. Insomnia and fatigue are also more commonly reported while using ATX as compared to MPH [176, 177].

Doses of 1–1.8 mg/kg/day of ATX were associated with a smaller increase in sleep onset latency of 12:01 min for ATX as compared to 39.2 min for MPH and had less decrease in total sleep time as compared to children on MPH. Parent reports indicated children found it easier to get up in the morning, and had less difficulty falling asleep [159].

25.5 Summary

In conclusion, individuals with ADHD frequently present with symptoms of sleep disturbances. Primary sleep disorders such as RLS, SDB, and DSPS have shown strong associations with ADHD, which could be accounted for by the pathophysiological pathways regulating sleep. The uses of medication to treat ADHD as well as the presence of a comorbid disorder have also been implicated in the exacerbation of sleep disturbances. Future treatment of ADHD should take into consideration the presence of sleep disturbances since the treatment of sleep disturbances frequently leads to improvements in ADHD symptoms.

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Sleep Disorders and Autism: Behavioural Correlates, Diagnostic Tools and Treatment Strategies

26

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Abstract

Disrupted sleep is a common complaint among children with autistic spectrum disorder (ASD). Disturbed sleep can be explained in three ways in this population—shared neurocircuitry and pathophysiological mechanisms, as a core symptom of the autistic spectrum disorder and thirdly, an effect of comorbid psychiatric disorder. A number of studies have shown that circadian rhythm is disturbed among patients with ASD. Sleep problems may be assessed using parent responded questionnaires, for example, children sleep habit questionnaire and objectively, using actigraphy and polysomnography. Literature regarding management of insomnia in this population is scarce with melatonin being most commonly investigated.

Keywords

Autistic spectrum disorder · Insomnia · Sleep disturbance · Melatonin · Sleep questionnaires

26.1 Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition with different and variable levels of severity, characterized by social communication impairment across different contexts and the presence of restricted, repetitive and stereotypical behaviours [1].

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The prevalence rate of sleep problems in ASD children is markedly higher (ranging from 40 to 80%) [2–4] compared to typically developing children (26–32%) and children with other neurodevelopmental disabilities [5–8].

In consideration of different autistic symptoms profiles, there is a considerable difference of sleep architecture in ASD population such as prolonged sleep latency, decreased sleep efficiency, reduced total sleep time, increased waking after sleep-onset (WASO) period, bedtime resistance and daytime sleepiness. Sleep problems in ASD include: insomnia, parasomnias, sleep-related breathing disorders (SRBDs) and sleep-related movement disorders (SRMDs) [8, 9]. In ASD population, insomnia represents one of the principal sleep concerns reported by parents, impacting negatively on children and their family daytime behaviour, parental stress and quality of life [3, 6]. Insomnia is classified into sleep-onset insomnia (SOI) and sleep maintenance insomnia (SMI) [8]. SOI consists of difficulty in initiating sleep, intended as increased sleep latency or time to fall asleep [8]. SMI can be related to decreased sleep duration, decreased sleep continuity and increased and early awakenings [8].

Although understanding the causes of sleep disorders in ASD is a clinical priority, the causal relationship between these two conditions remains unclear. The ongoing debate on the possible causes of sleep disorders in ASD is still open with three possible etiological explanations: (1) sleep problems are a consequence of biological and genetic abnormalities and disrupted sleep architecture present in individuals with ASD; (2) sleep problems are intrinsic to the clinical phenotype of ASD and (3) lastly, sleep problems represent a co-occurring condition completely independent from ASD [10, 11] (Fig. 26.1).

Consequently, the management of sleep problems in children with autism spectrum disorder represents a challenge for clinicians and families as ASD children may be more vulnerable to the consequences of a disturbed sleep.

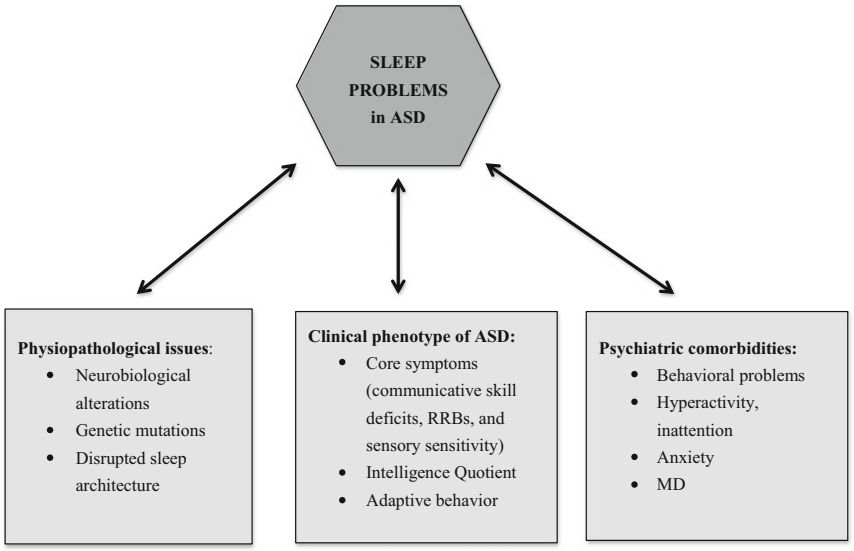
In this chapter, we review the main literature concerning sleep disorders and autism with a focus on: the potential relationships between sleep problems and autism, behavioural correlates, diagnostic tools and treatment strategies.

26.2 The Explanation of Sleep Disorders in Persons with Autism: A Conceptual Model of Interaction

A conceptual model of the potential relationships between sleep problems and autism and hypothetical scenarios of this association would be discussed.

26.2.1 Insomnia and Autism Could Share a Common Underlying Neurological Etiology?

Multiple factors are implicated in the etiology of ASD, such as genetic mutations, neurobiological mechanisms, neurotransmitter dysregulation, medical and psychiatric comorbidities, behavioural and environmental issues [6, 11].



RRBs = Restricted interests and repetitive behaviours; MD = Mood Disorders

Fig. 26.1 Possible etiological explanations of sleep problems in autism spectrum disorder (ASD). (1) Sleep problems are a consequence of biological and genetic abnormalities (involving serotonin, melatonin and GABA) and disrupted sleep architecture present in individuals with ASD; (2) sleep problems are intrinsic to the clinical phenotype of ASD and (3) sleep problems represents a co-occurring condition completely independent from ASD. *RRBs* restricted interests and repetitive behaviours; *MD* mood disorders [11]

Olivia J. Veatch et al. [9] highlighted overlapping and shared genetic and biological mechanism between sleep regulation and ASD. Numerous neurotransmitters including serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA) have a role in both sleep's homeostasis and ASD [9, 12, 13] (please refer to Chap. 1).

Any dysregulation of these neurotransmitters can modify regular sleep-wake cycles. It has been well established that abnormal serotonin synthesis and degradation are implicated in ASD and involved in sleep regulation [9]. Furthermore, serotonin is involved in the synthesis and production of melatonin. There is evidence of a connection among melatonin system, ASD and sleep, which includes altered synthesis and release of the melatonin hormone (altered circadian patterns: elevated diurnal melatonin and lower nocturnal level) and response to treatment (slow metabolizing alleles in CYP1A2) [2, 3, 14, 15]. Melatonin is a naturally occurring hormone involved in coordinating the body's sleep-wake cycle. Several studies have described abnormal melatonin regulation in ASD [15–18]. For example, Tordjman et al. [17] measuring levels of a major metabolite of melatonin (i.e. 6-sulphatoxymelatonin) in 49 children and adolescents with ASD and

88 age- and sex-matched controls found that nocturnal production of melatonin was significantly reduced in ASD. Similarly, genetic mutations in the melatonin pathways have been reported among subjects with ASD [19–22]. In more detail, the production of melatonin involves different enzymatic reactions, such as acetylserotonin O-methyltransferase (ASMT) enzyme which converts serotonin to melatonin. Melke et al. [21] have reported that a decreased expression of the ASMT transcript is correlated with decreased blood melatonin levels in individuals with ASD. These authors suggested that this deficit in melatonin might be responsible for sleep problems in ASD, and specifically circadian abnormalities. However, in a large sample, Toma et al. [19] did not find differences in ASMT variants in ASD compared to controls.

Moreover, in ASD children, an imbalance between neuronal excitation and inhibition has been described [2]. Dysregulation of GABAergic system (GABA-related genes and migration and maturation of GABAergic interneurons) is involved in ASD and insomnia [3, 8, 9]. Reduced spontaneous GABAergic neurotransmission has also been described in mouse models of idiopathic autism [23]. Furthermore, neurexins and neuroligins mutations, related with ASD etiology, influence the glutaminergic and GABAergic balance promoting sleep-wake disruption and abnormal EEG patterns [2, 24].

Sleep architecture represents the cyclical pattern of sleep as it shifts between the different sleep stages, including non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. It may change with age and can have an impact on the quality of life. For example, it is known that during physiological development, NREM sleep gradually increases while REM sleep decreases, resulting in a lighter sleep; thereby, it might become easier to awaken throughout the night and harder to fall and stay asleep at night. Disrupted sleep architecture, including increased REM density, reduction of REM sleep or longer sleep latency, has been also described in individuals with ASD [25–32]. For example, Bruni et al. [31] evaluated sleep architecture and NREM sleep alterations by means of cyclic alternating pattern (CAP) in 18 children with ASD compared to 12 controls, and found peculiar CAP modifications in children with ASD with a correlation of the quantification of sleep electroencephalographic (EEG) oscillations with the degree of mental ability. In another study, Miano et al. [33] showed alterations of NREM sleep in children with ASD. A recent prospective longitudinal study in 73 children with ASD found that sleep duration, evaluated with parental questionnaires, in children with ASD is reduced from 30 months of age and this reduction persists until adolescence [25]. However, another study showed that young adults with Asperger syndrome have a similar polysomnographic profile compared with controls [29]. Differences in methodology and samples can explain inconsistent results.

Future research in this area should use more rigid diagnostic criteria and definitions of sleep problems. For example, the use of both objective (i.e. polysomnography, actigraphy and videosomnography) and subjective measures (i.e. parent-report and sleep diaries) of sleep may reduce the discrepancy in the results [34].

26.2.2 Insomnia Can Be an Intrinsic Feature of the ASD

A possible hypothesis on the causes of sleep problems in ASD is that these may themselves be a core feature of autism. Restricted interests and repetitive behaviours (RRBs), the core diagnostic symptoms of ASD, include ritualistic behaviours, cognitive inflexibility, stereotypies, and insistence on sameness. Bed time routine represents one of the rituals ASD persons can be attached to. Not adhering to this routine can lead to significant distress, which, in turn, can delay sleep onset or cause insomnia [10, 35]. On the other hand, given that transition between activities are often difficult for children with ASD, not having an established bed time routine can lead to problem behaviours (e.g. noncompliance), which, in turn, can delay bedtime [36].

Individuals with ASD can also perseverate in activities (e.g. time-consuming rituals) before bed time, and perseveration in activities may delay bedtime as well. Accordingly, excessive and repetitive cognitive activities, including intrusive thoughts, may determine physiological hyperarousal and hyper-reactivity, contributing to sleep-onset delay [37, 38].

Moreover, arousal dysregulation and sensory reactivity may be involved in the complex and multifactorial etiology of sleep problems in ASD children [4, 36, 39]. Mazurek et al. [40] observed a correlation among anxiety, over-responsivity and sleep problems, identifying the hyperarousal as a shared underlying mechanism in patients with ASD. The authors found that both anxiety and sensory problems are positively related to bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety and night awakenings.

Furthermore, alteration of the sensory processing could be linked with their sensitivity concerning the sleep environment [40]. Sensory over-responsivity consisting "negative responses (e.g., distress, avoidance, or hypervigilance) to specific sensory stimuli, such as light, sound, and/or tactile experiences," which can be present in different context, may involve also sleep environment [36, 41, 42]. Thus, people with ASD are more disposed to insomnia because of different but overlapping behavioural and emotional issues [24]. Moreover, there is evidence from the literature of an association between sleep problems and severity of autistic symptomatology [43, 44]. In particular, night awakenings and sleep duration have been deeply correlated with maladaptive daytime behaviours impacting on their functioning [39]. Finally, it is possible that sleep problems can be exacerbated by deficits in communication skills. Specifically, these deficits can interfere with the child's ability to understand when parents ask children to go to bed or to fall asleep [11].

26.2.3 Insomnia Is More Frequent and Associated with Problematic Behaviours in People with Autism Spectrum Disorder?

A third possible scenario is that sleep problems are a condition completely independent from ASD. In this context, it is important to examine the relationship between

sleep disorders and associated psychiatric comorbidities in individuals with ASD. In fact, it is possible that sleep problems may worsen associated psychiatric symptoms, such as disruptive behaviours or aggression [26, 39, 45]. By contrast, it can also be possible that associated psychiatric features, such as attention deficit hyperactivity disorder (ADHD), may worsen sleep disorders present in individuals with ASD [9, 24, 36, 46, 47]. In more details, inattention, hyperactivity and oppositional behaviours may be associated with sleep disruption in a bidirectional relationship [40, 48, 49] (please see Chap. 25).

There have been many attempts to find a relationship between sleep problems and specific clinical characteristics of autism spectrum disorder, psychiatric comorbidities, cognitive abilities and level of functioning. Psychiatric conditions, including depression, anxiety and attention deficit hyperactivity disorder, can impact sleep patterns [9, 11, 50]. Disrupted sleep worsens behavioural problems (overactivity, disruption, non-compliance, aggression and irritability), increases ASD symptoms, such as restricted, repetitive stereotypical behaviours and social communication impairment, and negatively impacts neurocognitive function affecting daily functioning of both children and their families [48, 49, 51]. Research demonstrated a bidirectional correlation between sleep problems and maladaptive behaviours such physical aggression, hostility, inattention and hyperactivity [39, 40]. This reciprocal interaction suggests that treating a sleep disorder may improve daytime behaviour and family functioning [49, 52]. Underlying complex shared genetic, neurobiological and environmental factors are responsible for correlation between sleep and behaviour [53].

26.3 Measuring Sleep in Persons with Autism

26.3.1 Diagnostic Tools

In this chapter, we analyse the principal diagnostic tools commonly used for sleep disorders evaluation. Sleep problems assessment includes both subjective (parental questionnaires, parent report and sleep diaries) and objective measures (polysomnography and actigraphy) [54]. A correct and combined use of these instruments allow the clinician to make a valid and complete diagnosis.

26.3.1.1 Parent-Report Measures

An accurate evaluation of medical history with a focus on sleep history (sleeping habits, bedtime routines and associations), psychiatric comorbidities and underlying medical problems is necessary for a complete sleep assessment [54]. Standardized parent-report questionnaires represent non-invasive and not expensive methods, which should be used in order to obtain a reliable measure of sleep habits and potential maladaptive behaviours associated [55]. A recent review of the literature on the topic revealed the necessity of developing assessment tools with valid psychometric properties and more diagnostic power [55]. In the following sections,

common parent-reported questionnaires used for clinical sleep assessment in ASD population are discussed.

26.3.2 Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ is a parent-report sleep screening instrument designed for school-aged children, widely employed in the clinical assessment of ASD [40, 56–58]. CSHQ is a questionnaire constituted by 45 items administered to parents or caregivers, evaluating sleep habits and disruption [56]. The score is organized in a principal scale "Total Sleep Disturbance" and eight different subscales, evaluating the major domains of prevalent paediatric sleep problems: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night awakenings, parasomnias, sleep disordered breathing and daytime sleepiness [40, 56]. The items are evaluated on a 3-point Likert scale (1 = rarely; 3 = usually); a higher score indicates more sleep problems [59]. CSHQ is considered a reliable and valid instrument for sleep problems' clinical assessment in school-aged children [56] with typical development or affected by various neurodevelopmental disorders including ASD [60]. The CSHQ exists also in a more recent version for toddlers and preschool children (range of age 2.5–5 years) [61].

26.3.3 Family Inventory of Sleep Habits (FISH)

The "Family Inventory of Sleep Habits" (FISH) is a parent-report questionnaire created to evaluate sleep hygiene in children with autism spectrum disorders [62]. The 12 items assess daytime routine, pre-bedtime and bedtime routine, sleep environment and parental behaviours related to sleep moment [62]. Parents score the behaviour referring to the last month period on a Likert scale ranging between 1 and 5 (never—1; occasionally—2; sometimes—3; usually—4 and always—5); lower the score, worse the sleep hygiene [62].

26.3.4 Sleep Disturbance Scale for Children (SDSC)

SDSC is a 26-item, 5-point Likert scale, questionnaires for children aged 3–18 years [49, 63]. Questioning the last 6 months, it evaluates six principal sleep problems: disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorder, disorders of excessive somnolence and sleep hyperhydrosis. In a recent review, the SDSC together with the Sleep Disorders Inventory for students (SDIS)–children and adolescent, described below, has been considered a valid and reliable instrument, fulfilling the principal psychometric criteria [63].

26.3.5 Sleep Disorders Inventory for Students (SDIS)–Children and Adolescent Form

The SDIS is composed of four to five subscales: obstructive sleep apnoea syndrome, excessive daytime sleepiness, periodic limb movement disorder, delayed sleep phase syndrome and narcolepsy disorders. The subscales are scored on 7-point Likert scale, evaluating the last 6–12 months.

26.3.5.1 Objective Measures

- **Polysomnography (PSG)**
  PSG represents the gold standard for sleep problems' diagnosis and analysis of sleep architecture. Nocturnal polysomnography monitors and records continuously multiple physiological parameters during overnight sleep. PSG includes different measurements: electroencephalography (EEG), electro-oculography (EOG), skeletal muscle activity (EMG), electrocardiogram (ECG), pulse oximetry, oro-nasal airflow and pressure [3, 24]. Moreover, it helps in analysis of different sleep stages (NREM and REM) including their microstructure by using EEG parameters and eye movement detected with EOG.

  PSG is generally used for evaluating sleep-related breathing disorders, obstructive sleep apnoea, periodic limb movement disorder because it records oxygen saturation, oro-nasal airflow and muscle activity through multiple devices. Furthermore, PSG estimates night awakenings, sleep latency, sleep duration and sleep efficiency, hence, it is useful for the clinical assessment of chronic unexplained insomnia. Not being home performed, the PSG procedure may be hardly tolerated by ASD children because of poor adjustment to the new environment and sensory sensitivity, which is frequently described in this population [3].

  Several polysomnography studies have reported sleep anomalies in patients with autism spectrum disorders independently from the cognitive disability [10]. Limoges et al. [64] found longer sleep latency, increased night awakenings, less sleep efficiency and increased stage 1 among ASD patients. PSG studies observed that in ASD population, behavioural regression was correlated with longer sleep latency, less sleep efficiency, increased wake after sleep onset and longer REM latency [2, 32].
- **Actigraphy**
  Actigraphy gives an objective measure of sleep quality and pattern, using a device, an accelerometer generally located on the child's wrist, which records and monitors limb movements during sleep [3, 24]. Using the magnitude of the activity period, it is possible to estimate and differentiate the wakefulness from the sleep [24]. Furthermore, it also assesses the sleep latency and sleep efficiency typifying children as "poor sleepers" (prolonged initial sleep latency and decreased sleep efficiency) or "good sleepers" [57]. The actigraphy device can also record the level of light, sounds or noises as well, thus helping in studying not only sleep parameters but also the environment that can influence sleep onset. This method may be applied for a variable period of time, which can range from a

couple of days to a 2- to 3-week period giving more reliable and objective information [65]. Being performed at home, actigraphy represents a manageable instrument. It is easily employable also for children with sensory over-responsivity, anxiety and challenging behaviours [65].

Research on sleep in ASD people has demonstrated that subjective methods should be used in combination with actigraphy in order to have a complete evaluation of sleep patterns [10, 66]. Information provided by the parents can be validated and confirmed through actigraphy results not only in autistic children but also in typical development children, or children diagnosed with developmental delay [10, 61].

26.3.6 Recommendations and Strategies of Interventions

Management and treatment of insomnia in the ASD population involve both behavioural and pharmacological therapy [7].

In a practice pathway, behavioural strategies are recommended as the first-line intervention for sleep problems in children with ASD, considering the pharmacologic treatment as a second option only in cases of behavioural approaches failure or partial response [2, 3, 7]. However, the combination of pharmacological and behavioural intervention has resulted in a better response [2]. More evidence-based research studies are necessary to better establish the efficacy of both pharmacotherapy and parent-based sleep education programmes in ASD population [7].

26.4 Behavioural Intervention

Sleep hygiene and behavioural therapy have been demonstrated to improve sleep onset and maintenance in ASD children.

Major principles of good sleep hygiene are represented by appropriate and positive daytime/evening habits and bedtime routines. In particular, promoting exercise during the day, reducing daytime naps, limiting emotional and behavioural stimulation around bedtime, guaranteeing an appropriate individualized sleeping environment and minimizing exposure to electronic devices in the evening may implement sleep quality [2, 67, 68]. A visual support may be helpful to reinforce and remind the child of the bedtime [67]. Child's bedtime routine and sleep location should be customized, knowing that every ASD children may present different sensorial perception and tolerance to environmental stimuli (light, noise and temperature) [9]. Tactile sensitivity to linen or blankets should be also evaluated in the context of hypersensitivity to external stimuli in order to provide an optimal sleep location [2]. Weighted blankets have been considered helpful by parents of ASD children [2, 69].

The exposure to electronic devices should be restricted during evening hours because of the negative effect on the release of endogenous melatonin, essential for circadian rhythm regulation [9]. The management of insomnia requests parents'

involvement and training because behavioural approaches may also improve parental stress and their strategies to deal with their offspring sleep disorder [67, 70].

Among behavioural strategies "bedtime fading approach" (delaying bedtime hour and limiting sleep naps), "graduated extinction" (gradually learn to fall asleep alone) and "systematic ignoring approach" (ignore child's bedtime resistance) are described [2, 24, 67]. The behavioural approach has been considered more helpful for low-functioning ASD individuals with poor verbal language; however, wider and accurate studies are needed [2].

26.5 Pharmacological Treatment

Currently, there is no medication specifically approved for treatment of insomnia or other sleep disorders in infants. Except for melatonin, an over-the-counter drug, there is limited evidence for other medications for treating insomnia [67]. Other off-label pharmacological treatment is evaluated in case of inefficacy of both behavioural strategies and melatonin supplementation [9].

26.5.1 Melatonin

Melatonin is an endogenous hormone secreted during darkness by the pineal gland with chronobiotic and hypnotic functions [18]. A national survey revealed that in child psychiatrist practice, melatonin is the most frequently recommended in ASD individuals [71]. Due to defective rhythm of endogenous melatonin in ASD population, synthetic supplemental melatonin has been demonstrated as efficacious in improving sleep latency and sleep duration, however varied effects were observed in reducing night-time awakenings [7, 72]. Given its chronobiotic and hypnotic properties, it is necessary to administer melatonin at the right time and in the correct dosage [18]. For treating sleep-onset insomnia, ASD children generally respond to a dose range from 1 to 3 mg, taken 30 min before bedtime because of its short half-life (around 20–50 min) [67, 72]. Depending on the clinical response, the dosage may be increased up to 3 mg, rarely up to 6 mg or more [2, 32, 67]. However, clinical response has not been shown to be related to dose [73]. Treatment duration should be individualized and last at least 1 month [18]. Suspending too early an effective treatment correlates with a relapse of insomnia.

In case of inefficacy of the melatonin treatment, the possibility of an altered metabolism (CYP1A2 poor metabolizer) should be considered [18]. Treatment with melatonin has been shown to be well tolerated and safe in the paediatric population. Any or minimal adverse side effects were described, such as morning sleepiness, increased enuresis, headache and diarrhoea [7, 18, 72, 74]. Lowering the seizure threshold has a controversial adverse effect with the use of melatonin [75].

Recent review on the treatment of sleep-onset insomnia with melatonin in ASD population identified multiple methodological issues with the available studies,

namely small sample size, non-homogeneous population, deficiency of controlled trials and limited use of objective measures [72, 76, 77].

- **Ramelteon**
  Some evidence for the use of ramelteon (2–8 mg at bedtime), a synthetic melatonin receptor agonist (MT1, MT2), is emerging among ASD population, where it has shown to be effective at lower doses compared to typical developing children [78–80].
- **Other Pharmacological Approach**
  There is little evidence in literature concerning the use of off-label insomnia drugs in ASD population [67]. Medications with sedative properties may have potential applications in ASD children [2, 81].

In clinical practice, first-generation **antihistamines** (trimeprazine, niaprazine and diphenhydramine) are frequently recommended in paediatric insomnia because of their sedative properties, being H1-subtype receptor agonists in the central nervous system [78]. Sedation, paradoxical effects, ataxia and dizziness have been described as frequent side effects in children [18]. No specific trials on ASD individuals are reported in literature.

Clonidine, an alpha-2 adrenergic agonist, used in ASD children for hyperactivity, impulsivity and aggressiveness, has been reported to be well tolerated and efficacious in reducing sleep latency and night-time awakenings at the dosage of 0.1 mg/day for at least 6 months [82].

The lack of evidence-based trials on the use of **benzodiazepines** (clonazepam), hypnotic drugs promoting the GABA inhibitory properties, for paediatric insomnia, restricts its use in paediatric population given also the side effects profile (risk of addiction, cognitive impairment and rebound insomnia) [71]. No specific trials on ASD individuals are reported in literature.

The use of **zolpidem,** a non-benzodiazepine short-acting hypnotic, specifically developed for insomnia, is not approved for paediatric insomnia. There is little evidence in literature for attention—deficit and hyperactivity disorder (ADHD) children, none in ASD [18, 71].

Gabapentin (3–15 mg/Kg) has shown promise in treating refractory insomnia in children by improving sleep quality, increasing slow-wave sleep and sleep efficiency [83]. Gabapentin was found to be safe and well tolerated also in children affected by neurodevelopmental disorders at a lesser dosage compared to the one administered for epilepsy [83].

Mirtazapine (7.5–22.5 mg at bedtime), a drug with noradrenergic and serotoninergic properties, may improve maladaptive behaviours of ASD and insomnia [24, 84].

A successful pharmacological treatment of psychiatric comorbidities through **antidepressants** or **atypical antipsychotics** can improve sleep and the general outcome [2, 24, 67]. Owens et al., evaluating the percentage of psychiatrists prescribing medication for insomnia, showed higher values for sedating

antidepressants, alpha agonist, trazodone (12.5–25 mg) and atypical antipsychotics in ASD population [24, 71].

26.6 Discussion and Conclusion

Reviewing the literature on the relationships between autism and insomnia, we outlined some critical points concerning the assessment tools, behavioural and, in particular, pharmacological treatment.

Management of insomnia in people with autism represents one of the principal concerns and management challenge for clinicians. A prompt and valid assessment of sleep disorders is necessary in order to avoid negative consequences on children's behaviour and functioning and parental quality of life and stress. In this context, we propose a diagnostic flow chart schematizing a possible procedure, which may guide the clinician when a child with autism refers for insomnia (Fig. 26.2). An accurate assessment, using subjective and objective measures, excluding psychiatric and medical comorbidities, leads to an opportune treatment.

Given the importance of parental questionnaires for diagnosing sleep problems in children with communicative difficulties, assessment tools with more valid psychometric properties should be established for ASD children specifically, evaluating features such as sensory over-responsivity.

Further characterization of sleep profiles and behavioural correlates, investigating the role of environmental stimuli may be helpful in order to design better targeted and tailored intervention.

Given the impact that insomnia may have on family well-being, studies evaluating the frequency, duration and efficacy of parent-based sleep education program and the combination with pharmacological treatment are essential. Currently, there are no drugs specifically approved for sleep disorders in paediatric population, either in typical developing or ASD children. Additional evidence-based trials in ASD population are urgently needed to establish the efficacy of pharmacological treatment.

Future controlled clinical trials should better clarify the efficacy, dosage, tolerability and safety of hypnotic medications and which population should more benefit from these treatments.

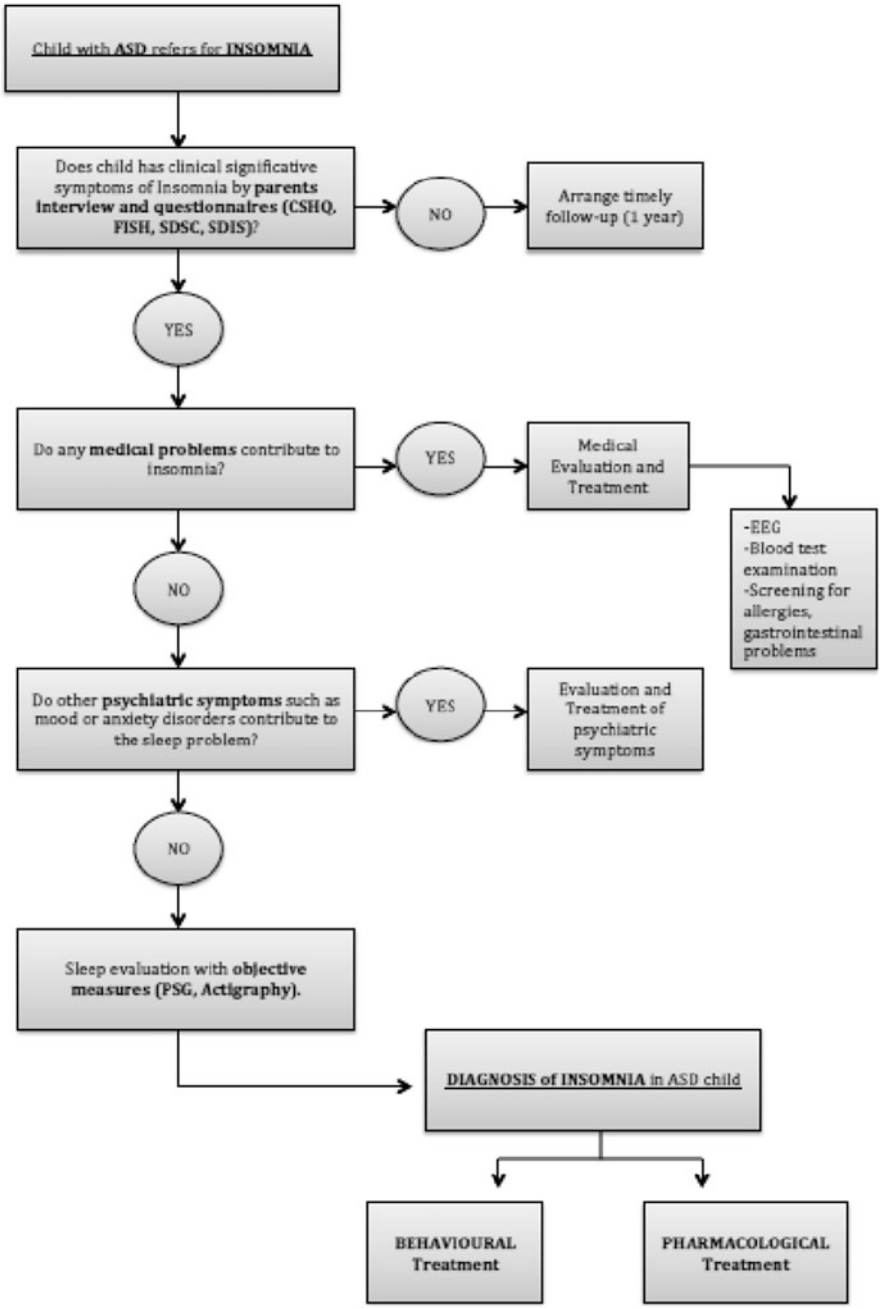


Fig. 26.2 Clinical flow chart

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Sleep in Dementia

27

Charles Pinto and Kirti Yeshwant Tandel

Abstract

The ability to initiate and maintain sleep is reduced with normative ageing. Recent researches have also proven that age-related sleep impairment has an underlying neurobiological mechanism. These changes are believed to reflect the neuronal degeneration in mechanisms that are responsible for an optimum sleep physiology. Neurodegeneration is augmented in dementia. These patients often present with a wide spectrum of sleep disturbances like circadian rhythm disturbances, insomnia, hypersomnia, periodic leg movements and restless legs syndrome (RLS), REM sleep behaviour disorder, nocturnal agitation and wandering. This chapter discusses the diagnosis of management issues of sleep disturbances among patients with dementia.

Keywords

Dementia · Insomnia · OSA · RLS · PLMD · REM sleep behaviour disorder

27.1 Introduction

Sleep is a complex yet an elaborate process. Lesions in strategically placed neuroanatomical areas can result in sleep disturbances that are commonly seen in the elderly population with neurological disorders like dementia. These disturbances can lead to irritability, impaired cognition, hypersomnia and also may cause depression

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and other psychiatric disorders. The sleep disturbances found in patients with dementia can have direct or indirect mechanisms. Specific lesions in neuroanatomical regions responsible for maintaining a normal sleep physiology and neurochemistry constitute the direct mechanisms, whereas the indirect mechanisms usually include environmental factors like insufficient light exposure or excessive noise. Traditionally, sleep disturbances are interpreted to represent consequences of neurodegenerative diseases like Alzheimer's dementia (AD); however, a causal relationship between sleep disturbances have also been researched by investigators, which may be of critical importance in prevention of AD.

27.2 Normal Sleep and Sleep Architecture

The normal ageing process is accompanied by various non-pathological changes in sleep [1]. Human sleep patterns can be quantified in brainwave activity through electroencephalography (EEG). These wave patterns are categorised into two types: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Fig. 27.1). The NREM sleep is divided into stages 1, 2, 3 and 4, which represent the transition from light to deep sleep [2]. Stage 1 NREM sleep begins while transitioning from wakefulness to falling asleep. The largest portion of sleep is comprised of the stage 2 NREM, whereas stages 3 and 4 represent the deep sleep, distinguished majorly by 'slow wave' sleep on EEG. The REM sleep occurs in bursts and comprises of an EEG pattern resembling wakefulness-like vivid dreams, rapid eye movements and muscle atonia. Normal sleep has cycles that switch from deepening stages of NREM sleep followed by REM sleep episodes that occur every 90–120 min throughout the night. The REM sleep episodes increase in frequency,

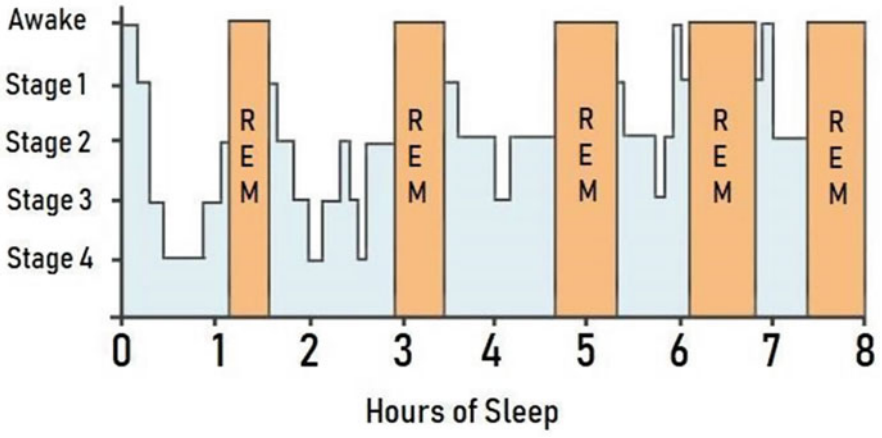

Fig. 27.1 Different stages of Sleep. Non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM)

especially in the latter half of the sleep [3]. The function of sleep is, thus, believed to be primarily restorative [4].

27.3 Sleep and Ageing

The ability to initiate and maintain sleep is reduced with normative ageing. The geriatric age group is associated with increase in deficits in the physiology of sleep such as non-rapid eye moment sleep and associated neural oscillations [1]. Recent researches have also proven that age-related sleep impairment has an underlying neurobiological mechanism. These changes are believed to reflect the neuronal degeneration in mechanisms that are responsible for an optimum sleep physiology [5]. Older individuals tend to take longer to fall asleep as compared to younger adults and their sleep is usually characterised by sleep fragmentation and stage shifts resulting in frequent arousals [6]. The elderly population also have increased light sleep and reduced deep sleep. Despite spending longer time in beds, they have less total sleep time (TST) [7]. The endogenous circadian rhythm also shows changes, possibly due to the deterioration of the suprachiasmatic nucleus (SCN) in the hypothalamus [8]. These changes weaken the circadian entrainment as well as flatten the circadian amplitude, which makes them more susceptible to a disturbed circadian timing and also to shift work disorders or jet lag. The early morning awakening seen in the elderly can be explained by the forward shift in the sleep phase caused due to the age-related circadian changes [9] (Fig. 27.2). Thus, overall it is common to see a deterioration of the night-time sleep pattern as the age advances, though it is not a rule. Hence, the normal ageing can be a predisposing factor for sleep changes in elderly but not sufficient for causing sleep disorders. Besides physiological changes

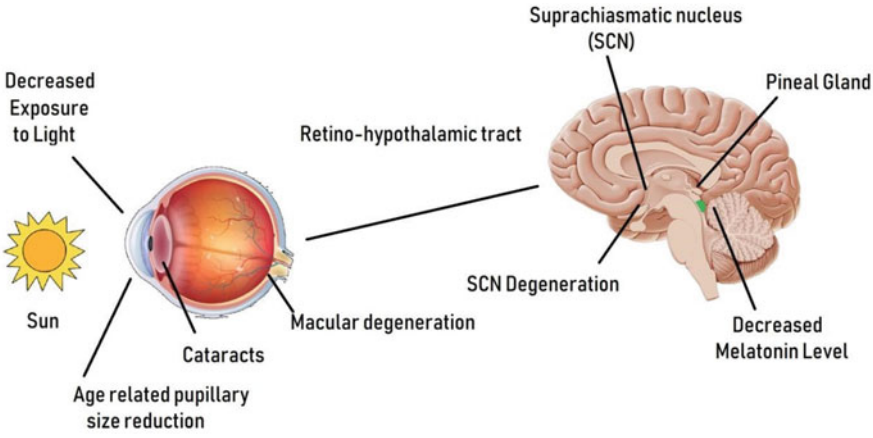

Fig. 27.2 Pathophysiology of sleep disturbances in patients with dementia including environmental and intrinsic factors

Table 27.1 Etiology of sleep difficulties in the elderly

Sleep disorders
• Insomnia
• Obstructive sleep apnoea
• Restless legs syndrome (RLS)
• Circadian rhythm disorders
• Periodic limb movement disorders
• Narcolepsy
• Parasomnia
Medical conditions leading to sleep disorders
• Cardiovascular diseases
• Chronic pain
• Medication side effects
• Cerebrovascular events
• Gastroesophageal reflux disease (GERD)
• Chronic obstructive pulmonary disease (COPD)
• Visual impairment
• Nocturia
Neuropsychiatric disorders
• Anxiety disorders
• Depressive disorders
• Bipolar affective disorder
• Post-traumatic stress disorder
• Psychosocial stressors (bereavement, retirement, isolation from family, etc.)
Lifestyle factors
• Lack of physical or social activity
• Poor sleep hygiene
• Substance misuse
• Poor sleep environment during institutionalised care

associated with ageing and consequent neurodegeneration, a number of other factors also contribute to sleep disturbance (Table 27.1).

27.4 Dementia and Sleep

Dementia is defined as a syndrome characterised by progressive deterioration of neurocognitive function. The prevalence and incidence of dementia increase exponentially after the age of 65 years [10]. Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 50–75% of all cases. AD is followed by vascular dementia (VD) (20%), dementia with Lewy bodies (DLB) (5%) and fronto-temporal dementia (FTD) (5%) (Table 27.2). Apart from cognitive decline, patients with dementia also suffer from psychiatric symptoms such as irritability, agitation, apathy and depression. Gradually, the course of the

Table 27.2 Subtypes of dementia

• Alzheimer's disease (AD)
• Lewy body dementia (DLB)
• Fronto-temporal dementia (FTD)
• Vascular dementia (VD)
• Parkinson's disease dementia
• Progressive supranuclear palsy
• Huntington's disease
• Creutzfeldt-Jakob disease (CJD)

illness robs the individual's independence and necessitates institutionalised care where prevalence of sleep disturbances is high. These patients often present with a wide spectrum of sleep disturbances like circadian rhythm disturbances, insomnia, hypersomnia, periodic leg movements and restless legs syndrome (RLS), REM sleep behaviour disorder, nocturnal agitation, wandering, etc. [11].

27.4.1 Sleep Architecture in Alzheimer's Disease (AD)

AD is characterised by circadian rhythm abnormalities. The neurodegeneration occurring at the suprachiasmatic nucleus, which is the neuroanatomic substrate of circadian physiology, is at the centre stage of pathophysiology of sleep disorders in AD [8]. Studies have also shown accompanying age-related macular degeneration, reduced melatonin levels, environmental factors as well as increased incidence of cataracts in this population (Fig. 27.3) [12]. There is strong correlation between severity of dementia and the severity of circadian rhythm disturbances. Sleep disordered breathing (SDB) and other respiratory dysrhythmias seen in AD are caused due to the neurodegeneration occurring in the supramedullary respiratory pathways and brainstem respiratory neurons [13]. Similarly, degenerative changes in a myriad of nuclei-nucleus basalis of Meynert, the norepinephric neurons in the brainstem, laterodorsal tegmental nuclei and pedunculopontine tegmental nuclei may be responsible for the reduced REM cycles seen in patients with AD [14]. Sleep in AD may also be disturbed due to adverse effects related to medications given for underlying psychiatric disorders like mood disorders, agitation, periodic limb movement disorders, accompanying cardiovascular diagnosis, respiratory problems and other medical diseases. Environmental factors like excessive noise and low exposure to light in long-term care nursing homes can also indirectly contribute to etiology of sleep disturbances in elderly [15].

Sleep in patients with AD is characterised by decrease in sleep efficiency, increased arousal and awakening frequency, increase in stage 1 NREM sleep stage, reduced total sleep time and less number of K complexes and sleep spindles on EEG [16]. During onset of the disease process, the sleep-wake rhythmicity is usually disturbed and accompanying sleep fragmentation leads to nocturnal awakening, insomnia, hypersomnia and wandering during night-time. Some individuals also report increased daytime naps along with increased time spent awake in bed,

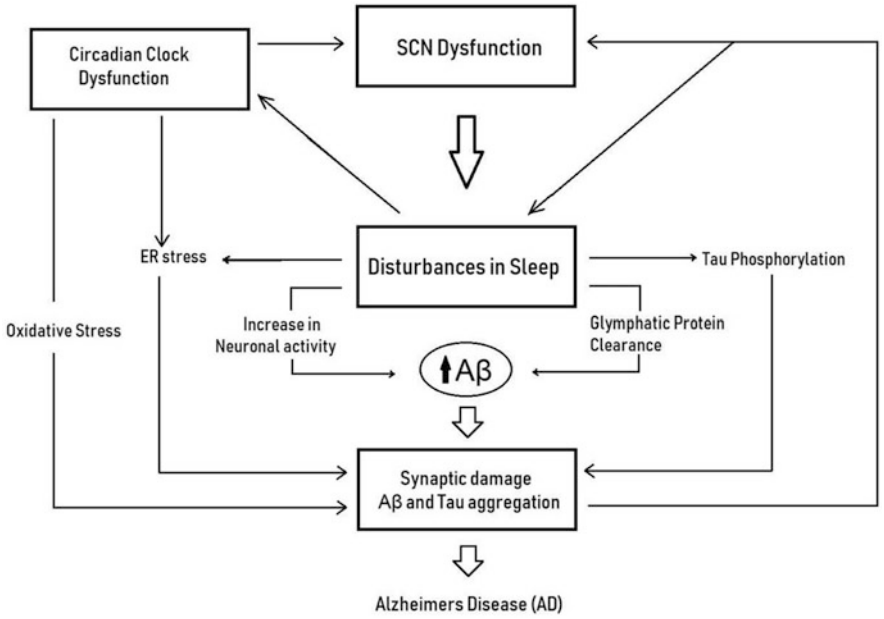

Fig. 27.3 Mechanisms that link Alzheimer's disease, circadian dysfunction and sleep deprivation

confusional state and disorientation. As described earlier, sleep changes are age dependent and, hence, as AD advances, there is disturbed circadian rhythmicity, reduction in REM sleep duration and increase in REM sleep latency; all resulting in significant daytime sleepiness in patients with AD [17].

Recent hypothesis also directs towards role of orexinergic system in AD pathophysiology. Orexin is a neurotransmitter in the hypothalamus responsible for wakefulness and decrease in REM sleep duration, thus altering the sleep-wake cycle [18]. Higher CSF orexin levels are associated with a more fragmented sleep pattern in patients with AD. It is also shown that there is an interaction with the tau proteins and amyloid beta, the CSF biomarkers in AD, due to orexinergic signalling overexpression [19]. A recent Chinese study has shown that Aβ and tau function by regulating the expression levels of orexin A and adenosine A1 receptor and may be considered as novel biomarkers of sleep disorders in AD [20].

27.4.2 Sleep and Lewy Body Dementia (DLB)

Sleep disturbances are more common in patients with DLB than AD. Sleep is usually characterised by movement-related arousals and excessive daytime sleep [21]. Sleep laboratory studies show reduced sleep efficiency, sleep disordered breathing consistent with obstructive sleep apnoea (OSA) and periodic limb movements [22]. Most of them have restless legs syndrome with sleep fragmentation, insomnia and

nocturnal awakenings. EEGs may show slowing with increased theta activity and loss of alpha activity. Temporal regions may show transient sharp waves. Frontal intermittent rhythmic delta activity (FIRDA) have long been considered as an abnormal variant in the EEG of older patients and might represent the intrusion of sleep-related elements of the EEG into the waking state.

27.4.3 Sleep and Fronto-Temporal Dementia (FTD)

Fronto-temporal dementia is characterised by executive dysfunction, early personality changes, language difficulties and behavioural problems such as loss of insight, disinhibited behaviour, hyperorality, apathy and lack of social awareness. Sleep disturbances are very common in FTD but less marked as compared to AD. The sleep-wake rhythm is very fragmented with phase advancement, which results in an early onset and offset of sleep. EEG shows increased delta and theta activity in fronto-temporal region with generalised slowing [23].

27.4.4 Sleep and Vascular Dementia

The cognitive impairment in vascular dementia (VD) is secondary to recurrent vascular injury. Sleep disturbances in VD are as a result of disturbed sleep-wake cycle and decreased quality of sleep. OSA is commonly associated with vascular dementia. In the immediate post-stroke period, the prevalence of central sleep apnoeas is very high [24].

27.4.5 Sleep and Creutzfeldt-Jakob Disease (CJD)

CJD is a rapidly progressive dementia characterised by accumulation of misfolded prion proteins, gliosis and vacuolation. It is associated with ataxia and myoclonus. EEG typically shows sharp wave abnormalities with CSF studies showing raised *tau* levels. The mean survival rate is only 4–8 months. Sleep disturbance is common with at least 50% of patients, characterised mostly by insomnia, restless legs syndrome, somniloquy, somnambulism, dream-reality confusion and sleep-related breathing disorder characterised by central or obstructive sleep apnoea. Polysomnography studies show disorganised sleep patterns, decreased number of sleep spindles and K-complexes with decreased REM sleep duration. Awake EEG study shows hallmark periodic sharp wave patterns comprising of biphasic, triphasic and mixed spikes or slow waves and a generalised slow-wave pattern in the background [25].

27.4.6 Sleep and Other Neurodegenerative Disorders

Studies show that 80% of patients with Parkinson's disease (PD) develop dementia within 8 years. Dopamine agonists used for treatment in PD may cause REM sleep intrusion into wakefulness. EEG studies show slowing in temporal, occipital and frontal regions [26]. Progressive supranuclear palsy (PSP) is characterised by degeneration of the fronto-subcortical neuronal pathways. This type of dementia is accompanied by apathy, decreased executive functioning, impulsivity, postural instability, axial rigidity, downward gaze, etc. Patients with PSP have sleep dysfunction in the form of excessive daytime sleepiness and reduced REM sleep duration. EEG slowing is predominantly seen in the frontal region [27].

27.5 Bidirectional Relationship

Recent researches have concluded that there is a relationship between sleep-wake cycle and levels of amyloid-β (Aβ) peptide in brain [28]. Alzheimer disease (AD) is characterised by accumulation of the amyloid-β (Aβ) peptide in the brain. On the other hand, sleep deprivation is found to increase the concentration of soluble Aβ resulting in its accumulation [29]. Increased Aβ accumulation alters sleep patterns and increases wakefulness. Sleep abnormalities like OSA, dream enactment behaviour and frequent nocturnal awakenings have been reported even in the presence of normal cognitive function in individuals with early Aβ deposition. Thus, it is difficult to be stated whether Aβ deposition results from sleep disturbances or sleep disturbances are caused by its deposition. Till the picture becomes clear, it is best to be considered as having 'bidirectional' relationship. This fact has important implications in diagnosing and management of AD [30].

27.5.1 Pathogenesis of Sleep Disorders in AD

Accumulation of Aβ is the most important contributor to the severity of sleep disorders in AD. Also due to concomitant other physical medical and surgical disorders, physical activity is reduced, which results in deficient *zeitgebers* to entrain the circadian rhythm in such individuals [31]. Institutionalisation also decreases the exposure to daylight, thus decreasing the stimulation to the suprachiasmatic nucleus via the retinohypothalamic tract. This diminishes the circadian amplitude. AD is associated with obstructive sleep apnoea (OSA), which is known to impair the quality of sleep. OSA is intrinsically associated with sleep disruptions in the form of sleep architecture, oxidative stress, hypoxia as well as intrathoracic and hemodynamic changes along with cardiovascular comorbidities. OSA also contributes to cognitive impairment, thus affecting executive functioning adding to the risk of developing AD. Medications for comorbidities like cardiovascular diseases, depression, hypertension and diabetes also disrupt sleep-wake cycle. A study involving mouse models of AD showed that there is a causal relationship between disturbed sleep pattern and AD pathology. The data suggested that Aβ aggregation disrupts the sleep-wake cycle and diurnal fluctuation of Aβ [32].

27.5.2 Sleep Disruption and Risk of AD

Sleep durations less than 5 h or more than 11 h, have been associated with an increased risk for developing cognitive impairment [33]. Cognitive decline is also found in individuals with poor sleep quality, prolonged latency of sleep, increased daytime napping, low sleep efficiency and prolonged latency of sleep onset. Sleep disturbances and long sleep duration (> 9 h) were associated with non-amnestic and amnestic incident cognitive impairment [34]. Cross-sectional studies conclude that fragmentation of sleep is associated with cognitive performance in elderly population [35]. Sleep deprivation increases the Aβ concentrations initially, whereas chronic pattern of sleep disturbances accelerates the Aβ deposition into insoluble amyloid plaques. This is also conversely demonstrated that the amount of interstitial fluid levels of Aβ significantly reduced with infusion of a dual orexin receptor antagonist [36].

Studies have also pointed towards an increased risk of AD associated with clinically significant sleep disordered breathing defined as apnoea plus hypopnea index or AHI more than 15 per hour [37]. Both mice and human studies have shown that the soluble Aβ levels fluctuate with the sleep-wake cycle in a diurnal pattern, which, thus, concludes that the sleep disruption does increase the risk of developing AD. A meta-analysis done recently also looked for a possible dose-response association of duration of sleep and subsequent cognitive impairment. The study found that the lowest incident risk of cognitive disorders was found in subjects with sleep duration of at least 7–8 h in a day [38]. Advanced circadian timing also results in subjective memory complaints. Sleep fragmentation is associated with lowered perception of cognitive decline and less concern about memory failures [39]. Sleep disturbances-induced increase in systematic inflammation is associated with increased β-amyloid burden and is thought to drive AD pathogenesis [40]. A multicentre study investigating 3210 individuals suggested that sleep disturbances (insomnia, nightmares and general sleep problems) in earlier life can result in late-life cognitive disturbances [41].

Thus, all these prospective studies in humans support the bidirectional relationship between sleep and dementia. More research is, however, warranted to confirm the data that sleep disruptions tend to accelerate the pathophysiology of AD (Fig. 27.4).

27.6 Common Sleep Disorders in Dementia

27.6.1 Sleep Disordered Breathing (SDB)

Sleep disordered breathing is commonly associated with cognitive decline and also associated with AD onset. Obstructive sleep apnoea (OSA) is one of the common sleep-related breathing disorder that affects people with AD. The severity of AD is proportional to the severity of OSA and studies have demonstrated a causal relationship between SDB and AD [42]. The neurodegeneration in the brainstem respiratory

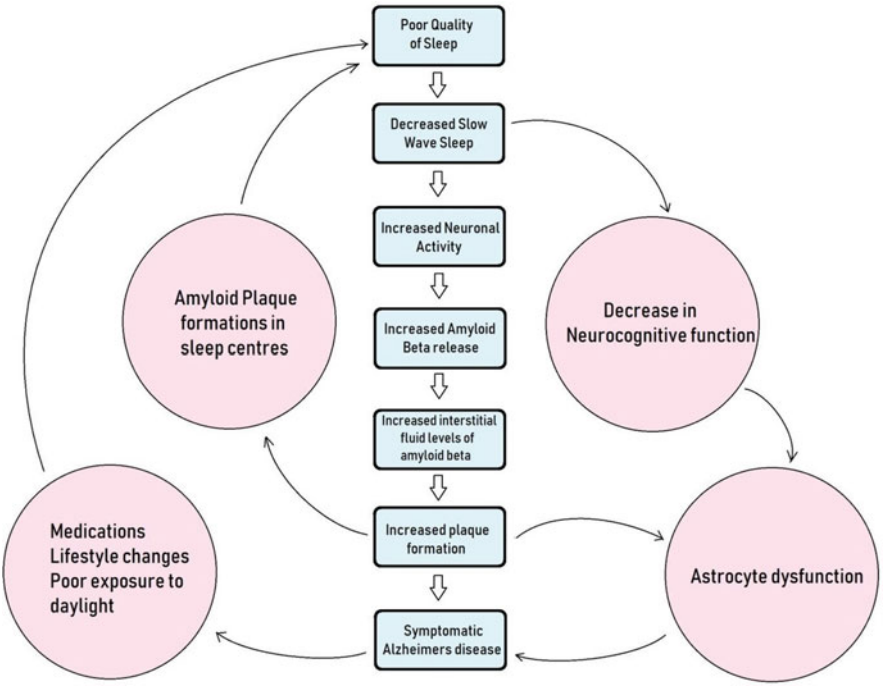

Fig. 27.4 The bidirectional relationship between Alzheimer's disease and sleep

centre that accompanies the pathophysiological course of AD is considered to be the main cause for sleep apnoea. These changes are further accelerated by the intermittent cerebral hypoxemia that usually occurs during the night-time in patients with OSA. Recent literature also points towards an association between OSA and APOE epsilon 4 allele, which is one of the key genotypic markers for AD [43]. Another reason for higher comorbidity between AD and OSA could be greater prevalence of risk factors for OSA with increasing age. Obesity and snoring are risk factors for OSA and they are seen increasingly as the age advances, especially after 40 years. In general, OSA is more prevalent in men, whereas in women risk increase significantly after menopause [44].

27.6.2 Insomnia

Insomnia is characterised by difficulty in initiating and/or maintenance of sleep. Patients with insomnia may also report unwanted early morning awakenings along with significant functional impairment during daytime. The mechanism underlying the association between dementia and insomnia is unclear. A meta-analysis found that insomnia is associated with an increased risk for dementia. Five studies of 5242 retrieved references were included in the meta-analysis. The pooled risk of dementia

in older adults with insomnia was calculated and showed that insomnia was associated with a significant risk of all-cause dementia with evidence for significant heterogeneity in the analysis [45]. Insomnia also leads to an accumulation of amyloid β deposits, which triggers cognitive decline. Also amyloid deposits in the preclinical stage of AD are associated with poor quality of sleep [46].

27.6.3 Circadian Rhythm Disorders

These disorders are characterised by a disparity between endogenous sleep-wake system and the sleep-wake schedules that the individual are required to follow [47]. Circadian rhythm disturbances (CRDs) affect as many as a quarter of Alzheimer's disease. Alterations in the suprachiasmatic nucleus and melatonin secretion are the major factors linked with the cause of CRDs [48]. Individuals suffering from circadian rhythm disorders present with difficulty in sleeping at a desirable time and frequent sleep disruptions. These are mostly seen in cases where there are frequent changes in daily routines, for example, shift work duties and jet lag. Such disturbances can also be seen in people who fail to maintain the endogenous rhythmicity relative to daily desired sleep schedule, for example, multiple daytime naps.

27.6.4 Sleep-Related Movement Disorders

27.6.4.1 Restless Leg Syndrome

The restless legs syndrome is characterised by unpleasant sensations in the lower limbs [49]. This leads to an irresistible urge to move around, which helps to relieve the sensations momentarily. Patients often complain of difficulty in initiating sleep. The higher prevalence of medical co-morbidity in patients with dementia and concomitant use of medications, especially diuretics, antidepressants, antihistamines, caffeine and bronchodilators, are responsible for increased incidence of RLS in this population. Diabetic neuropathy, anaemia and chronic renal failure are often associated with RLS.

27.6.4.2 Periodic Limb Movement Disorder (PLMD)

Another sleep-related movement disorder often accompanying RLS is the periodic limb movement disorder, characterised by stereotypic leg movements every 20–40 s during sleep, causing sleep disruption and frequent arousals. Patients often present with excessive daytime sleepiness and unrefreshing sleep as they are mostly unaware of these repetitive twitches occurring during sleep [50]. Patients with dementia often have vascular, metabolic and other neurological factors that lead to the occurrence of this movement disorder. Venous insufficiency in the lower limbs is said to be the most common cause of PLMD. Other causative factors are osteoarthritic changes, deficits in dopaminergic transmission and cycles in arterial blood pressure.

27.6.4.3 REM Behavioural Disorder

REM behavioural disorder is distinguished by the muscle tone restoration and activity, especially during the REM phases of sleep. These movements can range from punching, kicking, talking, moving out of bed, jumping, etc., thus enacting the underlying dreams. Due to this, patient or the caregiver often complains of injuries to self or the bed partners rather than a disrupted sleep pattern [51]. The patient typically can be aroused rapidly with full dream recall with absence of any confusion. Common precipitating factors for this disorder are alcohol intoxication or withdrawal, use of TCAs or MOIs, excessive caffeine consumption, etc.

27.6.5 Secondary Sleep Disorders

27.6.5.1 Medical Disorders

Age-dependent medical conditions are often associated with dementia and can disrupt the sleep architecture due to physiological mechanisms of the medical diseases itself, its symptoms or the medications used for the treatment of these disorders. Chronic pain, cerebrovascular disease, diabetes, renal disorders, rheumatoid arthritis, gastrointestinal disturbances and nocturia are often responsible for an impaired sleep [52]. Patients with concomitant medical conditions usually present with insomnia alone or a mixture of insomnia and hypersomnia.

27.6.5.2 Psychiatric Disorders

Sleep in AD also shows a progressive deterioration in circadian rhythmicity and sleep architecture. Other psychiatric disorders accompanying dementia include depressive disorders, bereavement, anxiety, delirium, adjustment disorders, etc. [53]. Depression is usually characterised by reduced total sleep time (TST) and slow-wave sleep (SWS), decreased sleep efficiency, increased awakenings and REM density. Bereavement is very common in this population and sleep disturbances may in turn give rise to depression and subsequent cognitive impairment [54]. Social isolation, inactivity, boredom along with retirement, financial stress, dependency, health issues and institutionalisation are very common in this age and can impair sleep pattern in these patients.

27.6.5.3 Medications and Substance Misuse

Old age is often accompanied by various neurodegenerative disorders like dementia and Parkinson's disease apart from the other medical disorders. Thus, polypharmacy is very prevalent in elderly. These medications can directly affect the sleep architecture or indirectly through their side effects. Common medications that are responsible for sleep impairment are antidepressants (SSRIs), antihypertensives, diuretics, beta-blockers, corticosteroids, bronchodilators, etc. The irrational use of sedatives and hypnotics is often accompanied by a number of adverse side effects. Also there are increased incidences of patients with dementia receiving inappropriate medications with unwarranted use of psychotropics for agitation and psychosis [55]. The common substances that impair sleep are alcohol, nicotine and caffeine.

The types of sleep disorders seen in patients with dementia secondary to medications or substance misuse can range from insomnia, hypersomnia, parasomnia or a mixture of all of these. Alcohol increases the severity of sleep disruptive behaviours and is a known culprit for sleep fragmentation. Similarly excessive use of stimulants like caffeine and nicotine is responsible for difficulty in maintaining sleep and also increasing the onset of sleep latency [56]. Nicotine also causes sleep fragmentation especially during discontinuation [57].

27.6.6 'Sundowning'

Several times people with dementia present with agitation and disruptive behaviour, especially during night. Commonly called as 'sundowning' over years; this phenomenon is thought to occur in a large number of people with dementia at some point in their illness. Most studies suggest that the time of maximal agitation occurs between 5 pm and 9 pm, whereas some report slightly late onset in the night [58]. The nighttime worsening of behaviour in patients with AD is explained by the increased incidence of sleep disorders. Studies have put forth few hypothesis such as REM sleep disturbances, sleep apnoea and dysregulation of SCN for a possible physiological explanation of sundowning [59]. The rest-activity cycle disturbances are caused due to the neuronal degeneration of cholinergic nucleus basalis of Meynert (NBM) which is responsible for the modulation of SCN and also induction of non-NREM sleep, thus increasing sundowning in patients with AD [60].

Patient-related factors that may cause sundowning include confusion occurring upon awakening from sleep leading to agitation, delirium induced by nocturnal hypoxia after sleep apnoea, dream enactment behaviour following awakenings from REM sleep phase, etc. Sundowning may also primarily be due to external factors like staff interruptions and expectations and timing of antipsychotic medications. A Korean study has concluded that the prevalence of sundowning in patients with AD as up to 27.8%. It also showed an association among presence of APOEε4 allele, RBD and more severe dementia with an increased risk of sundowning in AD [61].

27.7 Assessment

The etiology of sleep disturbances in patients with dementia is multifactorial and, hence, a thorough assessment is needed to understand the causative factors. A detailed assessment should include a comprehensive clinical interview, physical examination, psychological evaluation and if needed even a sleep laboratory testing that can assist in diagnosis.

27.7.1 Comprehensive Clinical Interview

Since patients with dementia will not be able to recall accurately, a collateral history from the caregiver becomes very important. It is important to elicit any problems in duration, severity, frequency and the course of the sleep in patients with dementia. Any responses to previous interventions, exaggerating and alleviating factors, daytime impairment and any poor sleep hygiene practices along with family history of sleep disturbances should be carefully elicited. Disruptive environmental influences on sleep, a disturbed sleep schedule and wrong beliefs about sleep should also be assessed. It is also important to ask for any major life stressors correlating with the sleep disruption, history of any medical illness like rheumatologic, pulmonary, cardiac, gastrointestinal, neurological or any chronic pain disorders, psychiatric disorders, substance misuse or use of any self-medications like melatonin, alcohol, antihistamines, etc. Apart from this, individuals should be asked about hallucinations, injurious parasomnias, sundowning, night-time wandering, etc.

Interviewing the bed partner for evidence of snoring, any nocturnal movements and disordered breathing pattern also helps in diagnosis. The data provided about circadian activity patterns and overnight sleep help in diagnosis and assessing response to treatment.

27.7.2 Neuropsychological Evaluation

One of the most common co-morbid disorders in patients with dementia are depression and anxiety spectrum disorders. A mental status examination (MSE) should be routinely carried out as a part of the preliminary assessment to screen for cognitive deficits. Screening through scales like Beck Depression Inventory, etc. can be done easily and can help identify the severity that might not be evident in clinical interview [62]. Some cases, however, may also warrant a detailed and more thorough clinical assessment in form of Minnesota Multiphasic Personality Inventory-2 (MMPI-2) [63]. Epworth sleepiness scale (ESS) or Pittsburgh sleep quality index (PSQI), though not validated specifically for dementia, can be filled by caregivers of the patients and can be used from prognostic point of view. Sleep Disturbance Inventory (SDI), developed to assess caregiver burden due to sleep disturbances, and the Behaviour Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) are more dementia specific [64].

27.7.3 Polysomnography (PSG)

Polysomnography comprises of physiological measurements of electroencephalography (EEG), electro-oculography (EOG), electrocardiography (ECG), chin electromyography, oxygen saturation, respiration and leg muscle activity recorded during a normal sleep episode in an individual. It is considered to be the gold standard test for diagnosing sleep disorders. It is helpful in diagnosing SDB, PLMD and RBD

[65]. Another recent study showed the importance of PSG variables in sleep alterations as potential biomarkers for diagnosis and prognosis of early-phase cognitive impairment [66]. However, its extensive nature of assessment may limit its use in patients with dementia.

27.7.4 Other Methods

Actigraphy uses non-invasive wearable motion sensors and helps in assessment of circadian rhythm disorders. Total sleep time and sleep efficiency can be calculated by objective measurements using the actigraphy data through validated sleep scoring algorithms [35]. It is recommended by the American Academy of Sleep Medicine (AASM) for assessment of irregularities in sleep-wake rhythms in patients with dementia [67]. The Multiple Sleep Latency Test (MSLT) is used to evaluate the daytime sleepiness. It is usually carried out by offering the patient with a total of five 20 min nap periods every 2 h throughout the day. The sleep latency is recorded and also checked for any REM phases. Excessive daytime sleepiness is diagnosed if the mean sleep latency is less than 8 min [21].

27.8 Treatment of Sleep Disorders in Dementia

The approach to treatment for sleep disorders in dementia is similar as that for general population. A mix of pharmacological and non-pharmacological treatment along with the use of objective measurements obtained from actigraphy and polysomnography is to be followed.

Obstructive sleep apnoea (OSA) is characterised by sleep fragmentation during night-time, daytime hypersomnia, low mood, insomnia and cognitive dysfunction. Recently, a clinical trial with CPAP adherence (4 h or more per night over 1 year) in older adults with mild cognitive impairment significantly improved cognition and slowed the trajectory of cognitive decline [68]. The non-PAP devices such as mandibular advancement devices have good scope in future as a reasonable alternative in patients who may not be able to use PAP.

Polysomnography studies show REM sleep without atonia in REM sleep behaviour disorder. Management includes precautionary measures such as placing furniture away from the bed, moving the bed away from the window, keeping a rug on the hard floor, etc. In situations where the bed partner is at risk of injury, melatonin and clonazepam are effective for decreasing oneiric behaviours. Melatonin is preferred in view of cognitive side effects of clonazepam [69].

In Lewy body dementia (LBD) and Parkinson's disease with dementia (PDD), restless leg syndrome and periodic limb movement disorder are common. Medications usually include iron supplementation along with a rational and balanced use of dopamine agonists in view of motor symptoms [70].

Narcolepsy may be found in some dementia patients, particularly in LBD. Stimulants, sodium oxybate and anticataplectic agents may be tried with care to

minimise the adverse effects especially in co-morbid cardiac disorders and cognitive dysfunction [71].

27.8.1 Non-pharmacological Treatment

27.8.1.1 Physical and Social Activity

Building muscle mass, reducing falls, mood optimisation and improving strength are some of the benefits of a regular daily physical routine. Studies have shown that exercise also helps in phase shifting of circadian rhythms and, thus, promotes restful sleep in older adults [72]. Social interaction along with some physical activity improves daytime alertness and night-time sleep in the elderly population [73]. Such routine increases slow-wave sleep (SWS) due to physical exertion, psychological factors and stronger circadian zeitgebers. Recently, a new concept of caregiver being trained as 'exercise coaches' has come up. Research says that participating in non-strenuous daytime activities improves sleep architecture in residents with dementia [74]. There is decrease in wake time overnight on actigraphic measurement in the starting phase. Another study, however, did show a decreased wake time at night by 36 min after 2 months of treatment that included a combination of sleep hygiene, bright light therapy for 1 h at night and walking for 30 min daily [75].

Researchers have done studies where patients with AD and PD had a multimodal exercise program that included exercise sessions for 1 h, 3 times in a week for 6 months, which were designed to target 60–80% of maximal heart rate [76]. Those who were able to maintain this structured physical routine showed a significant decrease in sleep disturbances and reduction in instrumental activities of daily living (IADL) deficits.

Social activities help in providing *zeitgebers* and, thus, decrease the sleeping pattern during daytime. Richards et al. (2005) showed that in a nursing home with 147 residents with dementia, individualised social activities for 2 h daily reduced actigraphically measured daytime sleep and also increased the night-time total sleep time. Similarly, another study demonstrated an improved nocturnal sleep, measured by polysomnography after intervention in the form of a structured social activity and physical activity (high-intensity physical resistance strength training 3 days a week and walking for up to 45 min on 2 days, social activity for 1 h daily and 5 days a week) [77].

There are, unfortunately, no standardised programs for a structured social activity combined with physical routine so far. Hence, patients should be advised to exercise vigorously and regularly (at least 3–5 times per week for at least 30–40 min), with a target heart rate in mind. Patients with dementia should be encouraged to have regular social interactions.

27.8.1.2 Bright Light Therapy

Bright light therapy (BLT) is an intervention to entrain the circadian phase. It involves exposure to light, thereby activating the retinohypothalamic tract to the

suprachiasmatic nucleus (SCN). The light delivered close to bedtime delays the circadian phase, whereas when it is delivered close to the wake time, it advances the circadian phase [78]. There are, however, mixed results as far as the effect of BLT in patients with dementia is concerned. A Cochrane meta-analysis aimed to review the effectiveness of light therapy in improving cognition, sleep, activities of daily living, challenging behaviour and psychiatric symptoms in dementia. Seven out of ten studies in the meta-analysis delivered BLT through a light box (2500–10,000 lux) for 1–2 h. It was administered in the morning, evening, both or all day for a duration ranging from 10 days to 10 weeks. The pooled data showed a significant decrease in night-time awakenings, especially where BLT was administered in morning. However, there was no effect of BLT on nocturnal total sleep time. Also the data was not conclusive enough to recommend any specific dose, timing or duration for the BLT modalities [79].

However, another meta-analysis concluded that light therapy was effective for sleep problems particularly for insomnia symptoms and circadian outcomes like total sleep time, time in bed, sleep onset latency and sleep efficiency [80]. Thus, we can conclude that despite the mixed results, morning time BLT can be recommended for patients with dementia who have a delayed circadian phase, particularly combined with melatonin therapy. Dowling et al., similarly showed that nursing home residents receiving BLT in morning (>2500 lux) plus 5 mg of melatonin at night for 10 weeks had greater daytime activity along with improvement in the day-night sleep ratio when compared to those receiving only BLT [81].

27.8.1.3 Sleep Hygiene

Sleep hygiene comprises of various behaviours which help in sleep consolidation at night. They include minimising daytime naps, adequate and regular night-time sleep periods, regular vigorous physical activity, a fixed bedtime routine, reducing sleep disrupting substance misuse (e.g. alcohol, tobacco, caffeine, etc.), having a sleep conducive environment with a dark, cool and quiet bedroom, avoiding excessive light during bedtime and using bed exclusively for sleep only. A study showed that sleep hygiene education given to patients with dementia in group homes resulted in increased total sleep time during night (9.6 h as compared to 7.8 h in controls) [82]. The study also demonstrated that sleep efficiency and the percentage of time spent asleep in bed improved in the sleep hygiene group (84%) as compared to that in controls (75%). Eliminating caffeine intake in afternoon and evening also helps in significant improvement in sleep and apathy [83]. Interestingly, another Japanese study concluded that a nap for short time (<30 min) and a light physical exercise was effective in adjusting the sleep-wake rhythm in patients with mild-to-moderate dementia [84]. In the absence of any adverse side effects, sleep hygiene education should be promoted in insomnia treatment for patients with dementia.

27.8.1.4 Alternate Medicine

Different alternative medicines have been tried for treating sleep disturbances in dementia. Kwok et al. (2013) and Simoncini et al. (2014) have tried to show some improvement in sleep in patients with AD after acupressure and acupuncture

[85, 86]. Slow-stroke back massage (3 min) may be an effective nursing intervention by improving the total sleep time [87]. Tai Chi in patients with vascular dementia showed improvement in sleep quality and depressive symptoms [51]. A human-like communication using a child-like robot for elderly women who were living alone showed significant improvement in total sleep time as compared to a mechanical robot [88]. However, more effective double-blind, randomised controlled trials are required to establish the role of these alternative interventions in sleep disturbances for patients with dementia, if the patient or the caregiver wishes to pursue a non-pharmacological intervention, without excessive cost and adverse effects.

27.8.2 Pharmacological Treatment

27.8.2.1 Melatonin

Melatonin is responsible for mediation of the relationship between circadian clock and sleep. It is secreted from the pineal gland in dim light, especially during evening hours. The levels of melatonin are decreased in patients with AD [89]. Melatonin administered exogenously has circadian phase-shifting effects which are opposite to that of light. It also exerts a soporific effect and improves cognitive performance, sleep-wake patterns in MCI as well as emotional performances. Recent studies have shown an equivocal data while looking for a possible beneficial role of melatonin in improving sleep quality in patients with dementia. Different doses of melatonin have been used with or without an additional modality treatment ranging from 5 mg for 10 weeks (with BLT) [81], 6 mg slow-release melatonin for 2 weeks [90] to 10 mg or 2.5 mg for 8 weeks [91]. Only melatonin with BLT showed a benefit. A meta-analysis found a benefit of melatonin use by increasing the total sleep time by 24 min along with improved sleep efficiency but without any cognitive benefits [92]. Asayama et al. showed improvement in total sleep time with 3 mg of melatonin when given at 10.30 pm [93]. Wade et al. used 2 mg prolonged-release melatonin preparation for 24 h in 80 persons with dementia (mild to moderate) and concluded that there was less cognitive decline (MMSE Scores) and less impairment in IADL as compared to controls [94]. Thus, in individuals not responding to behavioural interventions, it is advisable to use a low dose of melatonin (2–5 mg) along with BLT while looking for any increase in depressive symptoms.

27.8.2.2 Melatonin Receptor Agonists

Ramelteon is a melatonin receptor agonist which simulates the action of melatonin. A case report study in four patients with DLB showed improvement in Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) scores after using ramelteon for 8 weeks [95].

27.8.2.3 Benzodiazepine Receptor Agonists

Benzodiazepines have been notorious in causing inadvertent side effects especially in the elderly population [96]. The long-acting ones have been associated with anterograde amnesia, risk of falls, confusional states, cognitive decline, daytime

sleepiness and also risk of dependence or abuse. A study done in 1796 people with first diagnosis of AD concluded that benzodiazepines were associated with an increased risk of AD [97]. The risk of AD was increased irrespective of the dose and half-life of benzodiazepines, especially the long-acting ones. Hence, benzodiazepine receptor agonists (BRAs) like zolpidem and zaleplon are usually preferred. BRAs have a shorter half-life with a better tolerance and less risk for dependence or abuse. However, morning sedation and incidence of parasomnias warrant cautious use of BRAs and can be used in patients with safe living conditions and attentive caregivers.

27.8.2.4 Other Hypnotics

Memantine was found to decrease probable REM sleep behaviour disorder in patients with DLB and PDD. There is less nocturnal activity with memantine [98]. Yin et al. assessed the 5-year effect of nocturnal sleep disturbances on the long-term outcome in patients with AD [99]. A total of 93 patients with AD and concomitant sleep disturbances were given treatment with atypical antipsychotic risperidone (0.5–1 mg), melatonin (2.55 mg), zolpidem (5–10 mg) and no drug treatment. The study concluded that low-dose risperidone improved the 5-year outcome in AD patients with SD with improvement of nocturnal sleep problems and also bringing better emotional stability for the caregivers.

27.8.2.5 Antidepressants with Sedative Property

Antidepressants with sedative property are used in sleep disorders in dementia due to their soporific effect. Camargos et al. studied the effect of 50 mg trazodone at bedtime for 2 weeks and found that there was improvement of 43.5 min in total sleep time without any adverse cognitive side effects [100]. Trazodone, a slow-wave sleep enhancer, is associated with a delayed cognitive decline [101]. However, antidepressants with anticholinergic properties are known to worsen cognition in AD and also worsen RLS. Hence, antidepressants like trazodone and tricyclic antidepressants (TCAs) should be used cautiously. Romeo et al. carried out a meta-analysis of cost-effectiveness of antidepressant treatment in dementia and their effects on carer outcomes [102]. The study used sertraline and mirtazapine and found no cost-benefit to either of the two compared to no treatment. However, the investigators concluded that caregiver hours reduced in the mirtazapine group (6.7 vs. 12.3 h) due to improved sleep with mirtazapine.

27.8.2.6 Stimulants

DLB is associated with daytime hypersomnia. Role of modafinil in such hypersomnia is debatable as few studies have shown reduction in physical fatigability, whereas others have not shown any benefits [103, 104]. There are not many studies so far demonstrating the role of methylphenidate in hypersomnia in patients with dementia except for addressing apathy.

27.8.2.7 Recent Advances and Research

Suvorexant, an orexin receptor antagonist, with better tolerability and lesser adverse effects is one of the first in the newer class of drugs used in treatment for insomnia. It is unique in its mechanism helping in natural transition from wakefulness to sleep by inhibition of the orexin neurons of the arousal system that promote wakefulness [105].

27.9 Conclusion

Sleep disorders are commonly seen in patients with neurodegenerative disorders. The demographical shift towards geriatric population will in near future give rise to the number of people with dementia suffering from sleep disorders as well [106]. The bidirectional relationship between sleep and neuropathological hallmarks of cognitive disorders particularly AD has been explained in detail in Sect. 27.5 and diagrammtically respresented in Fig. 27.4. But there is a need for more research. An evaluation of cognitive impairment in any individual also demands a detailed history regarding the persons' sleeping patterns. Sleep is often ignored during health evaluation and, hence, an early evaluation and interventions for sleep impairment in such individuals may slow the disease progression and lead to a greater quality of life for patients as well as caregivers. Lifestyle factors like sleep could, thus, potentially improve healthcare utilisation efficiency and help in future interventions [107].

27.9.1 Future Research

In coming years, it is concluded that researchers should aim at electrophysiological studies in order to find early signs of development of AD and develop procedures that can result in overall improvement of sleep structure. There is a need for more data aiming towards establishing a relationship between cognitive deterioration and oxidative stress, hypoxemia, inflammatory states, vascular pathology and other neurological signs and symptoms in AD and production of tau protein.

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Sleep in Delirium

28

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Abstract

Sleep disturbances are very common among patients with delirium, and evidence suggests that sleep deprivation is one of the important precipitating factors for development of delirium. Sleep architecture in patients with delirium is characterized by predominance of light sleep phases of non-rapid eye movement sleep (NREM) and relative lack of rapid eye movement sleep (REM) and deeper phases (N3 phase) of NREM sleep. The role of sleep deprivation in patients with delirium is hypothesized to be mediated by melatonin, an endogenous hormone secreted by the pineal gland, which plays an important role in maintaining the 24-h circadian rhythm cycle and various stages of sleep. Keeping this in mind, exogenous melatonin and ramelteon have been evaluated in prevention and management of delirium. Role of melatonin in prevention of delirium has been evaluated in some of the randomized controlled trials and there is a lack of consensus with respect to its role in prevention of delirium. Data on role of melatonin in management of delirium are limited to case reports and case series and there is a lack of prospective randomized controlled trials. Studies have also evaluated the role of non-pharmacological measures, focusing on restoring or ensuring sleep in management of delirium and suggest the beneficial effect of the same. Accordingly, it can be said clinicians managing patients with delirium should evaluate the role of sleep deprivation in causation of delirium and should ensure adequate sleep, especially the proper sleep architecture.

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Keywords

Delirium · Sleep · Melatonin

28.1 Introduction

Sleep is one of the most important physiological functions which ensure rest and emotional well-being [1]. Sleep disturbance can be triggered by many stimuli, with physical illnesses and hospitalizations being some of the most important triggers for sleep disturbance. Hospitalization is associated with disruption of sleep architecture and hospitalized patients often report disturbance in sleep initiation, maintenance of sleep, early morning awakening and reduction in total sleep time [1]. Other factors which influence the sleep architecture include pain, scheduled or unscheduled nursing care activities at night, environmental factors like artificial light and noise of the machines, other patients in the ward and medications being received for sleep [1].

One of the important complications of some of the illnesses includes delirium, which is understood as an acute-onset neuropsychiatric condition, often considered to have a fluctuating course, is reversible and short lasting. It increases mortality, lengthens duration of hospital stay, worsens functionality, increases treatment cost, increases cognitive decline and risk of developing dementia, imposes significant distress due to symptoms of delirium even after recovery, induces significant distress among the caregivers taking care of the patients during the experience of delirium [2] and lastly, increases post-discharge sleep disturbances [3]. Prevalence of delirium in patients with various disorders varies depending on the treatment setting and assessment method. In some settings, prevalence rates are reported to be as high as 82% [4, 5], with significantly higher prevalence reported among patients admitted in the intensive care units (ICUs), especially those who require mechanical ventilation [6].

Besides the cognitive and non-cognitive symptoms, sleep disturbance is considered as an important symptom of delirium. Further, sleep disturbance is also understood as a precipitating factor for delirium. Sleep disturbances in delirium include sleep fragmentation with poor night-time sleep with frequent short naps during the day and overall poor quality of sleep [7]. Accordingly, it can be said that sleep disturbance has both causative and outcome relationship with delirium.

28.2 Sleep Disturbance as a Symptom of Delirium

Sleep disturbance is understood as a well-known symptom of delirium. Sleep disturbances in delirium may include difficulty in sleep during the night, interrupted sleep, daytime napping and reversal of sleep-wake cycle [8]. International Classification of Disease tenth revision (ICD-10) [9] mentions sleep disturbances in patients with delirium may present in the form of insomnia, reversal of sleep-wake cycle, daytime drowsiness and disturbing dreams or nightmares. Further, according to

ICD-10, sleep disturbances are essential for definitive diagnosis of delirium. On the other hand, ICD-11 draft does not mention sleep disturbances as essential criteria for diagnosis of delirium but mentions that the sleep disturbances may manifest as sleep-wake cycle disturbances (reduced arousal of acute onset or total sleep loss with reversal of the sleep-wake cycle). Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [10], mentions sleep disturbances to be very common in patients with delirium and considers that their presence supports the diagnosis but are not essential for core diagnosis of delirium. According to DSM-5, sleep disturbances may manifest as disturbance in sleep-wake cycle (daytime sleepiness, night-time agitation, difficulty in falling asleep, excessive sleep during day or wakefulness throughout night). Studies which have evaluated the sleep disturbances in patients with delirium by using Delirium Rating Scale–revised 98 version in patients referred to the consultation-liaison services and various intensive care units have reported the prevalence of sleep disturbance in 94.7–100% of patients. Studies which have evaluated the factor structure of symptom profile of patients with delirium suggest that sleep disturbances usually load on the factors, which also include non-cognitive symptoms such as motoric disturbances, delusions, hallucinations and fluctuation of symptoms [2].

28.3 Sleep Disturbance as a Precipitating or Etiological Factor Associated with Development of Delirium

Co-occurrence of sleep disturbance and delirium in hospitalized patients, especially those admitted to ICUs, suggests that both disorders may either have common pathophysiological pathways or may have a potential cause-effect relationship. Among the various neuropathogenesis etiological models of delirium, diurnal dysregulation or melatonin dysregulation hypothesis is one of the important hypotheses [11], which asserts that alteration in the sleep physiology among the medically ill patients may be causative factor for delirium. According to this hypothesis, there is disruption of 24-h circadian rhythm cycle and various stages of sleep in medically ill patients, which leads to disturbance in the normal integrity of the sleep and alters sleep architecture in the form of difficulty in falling asleep, maintaining sleep, alteration in the sleep-wake cycle and disruption in usual stages of sleep [11, 12]. The evidence for this hypothesis comes from various spheres. Data accumulated over the last four decades have time and again demonstrated that hospitalized patients often experience marked alteration in sleep-wake cycle, which is characterized by insomnia, difficulty in initiating sleep, fragmented sleep and disorganization of sleep cycle [11, 12]. The factors which have been linked with poor sleep in these patients include noise, pain, artificial light, pain, severity of the critical illness, use of multiple medications and use of mechanical ventilators [13–16]. These environmental factors influence secretion of melatonin and disrupt biological clock, resulting in development of delirium. Available data suggest that there is disruption in the circadian rhythm of melatonin secretion in patients with delirium and melatonin levels decrease before the emergence of delirium [17]. Sleep

architecture in patients with delirium is characterized by predominance of light sleep phases of non-rapid eye movement sleep (NREM) and relative lack of rapid eye movement sleep (REM) and deeper phases (N3 phase) of NREM sleep. Additionally, patients with delirium have disorganization of circadian timing [18]. Some of the commonly used medications in patients admitted to ICUs include use of opioids and benzodiazepines, which are known to suppress slow-wave sleep. Propofol, often used for sedation among intubated patients, is known to suppress the REM sleep and worsen the overall quality of sleep [19]. Other agents which have been reported to suppress REM sleep include corticosteroids, vasopressors, antidepressants and lipid soluble beta-blockers [20]. Sleep deprivation has been shown to influence lung mechanics, balance between sympathetic and parasympathetic system, lead to immune suppression, impaired endocrine responses and impairment in cognitive functions [21]. All these factors increase risk for development of delirium (Fig. 28.1).

Evidence also suggests that patients who are sleep deprived have higher chance of developing cognitive symptoms in the form of poor attention, memory deficits and emotional imbalance, which are well-recognized symptoms of delirium. Among patients admitted to ICUs, available data suggest that compared to patients, who are not sleep deprived, those patients who experience sleep deprivation are more likely to develop delirium [11, 12]. However, it is important to note that these studies only report about association of sleep deprivation and delirium and it is not clear whether sleep deprivation is a cause of delirium or both are an outcome of admission to the ICU [19, 21]. Other studies have also shown abnormalities in the plasma concentration and urinary metabolites of melatonin among patients with critical illnesses [22–26]. Studies have also evaluated melatonin levels among patients with delirium and these suggest reduction in the melatonin levels as early as 3 days prior to the diagnosis of delirium [17]. Studies have also shown alteration in melatonin secretion among patients undergoing surgeries [27–30]. However, it is important to note that these findings are confounded by use of opioids during the perioperative period [21].

Melatonin, which is a naturally occurring endogenous hormone, primarily secreted by the pineal gland, plays a key role in managing multiple bodily functions, which are affected in patients with delirium. Besides pineal gland, melatonin is also synthesized at retina, testis and the gastrointestinal tract, but secretions from these sources contribute a small amount to the circulating levels of melatonin [21]. It is primarily secreted during the darkness and the secretion is primarily controlled by suprachiasmatic nucleus (SCN) of hypothalamus through the release of norepinephrine. The binding of norepinephrine to the adrenergic receptors leads to activation of adenylate cyclase and resultant expression of adenosine monophosphate (cAMP), and synthesis of rate-limiting enzyme involved in the melatonin synthesis. The melatonin synthesized is not stored, and hence, the levels are reflective of the synthetic activity of the pineal gland [31]. In the presence of light, signals from melanopsin-containing retinal ganglion cells suppress the synthesis of melatonin [31]. The synthesis of melatonin is also influenced by clock genes (CLOCK and BMAL1) by producing heteromeric complexes of Period and Cryptochrome

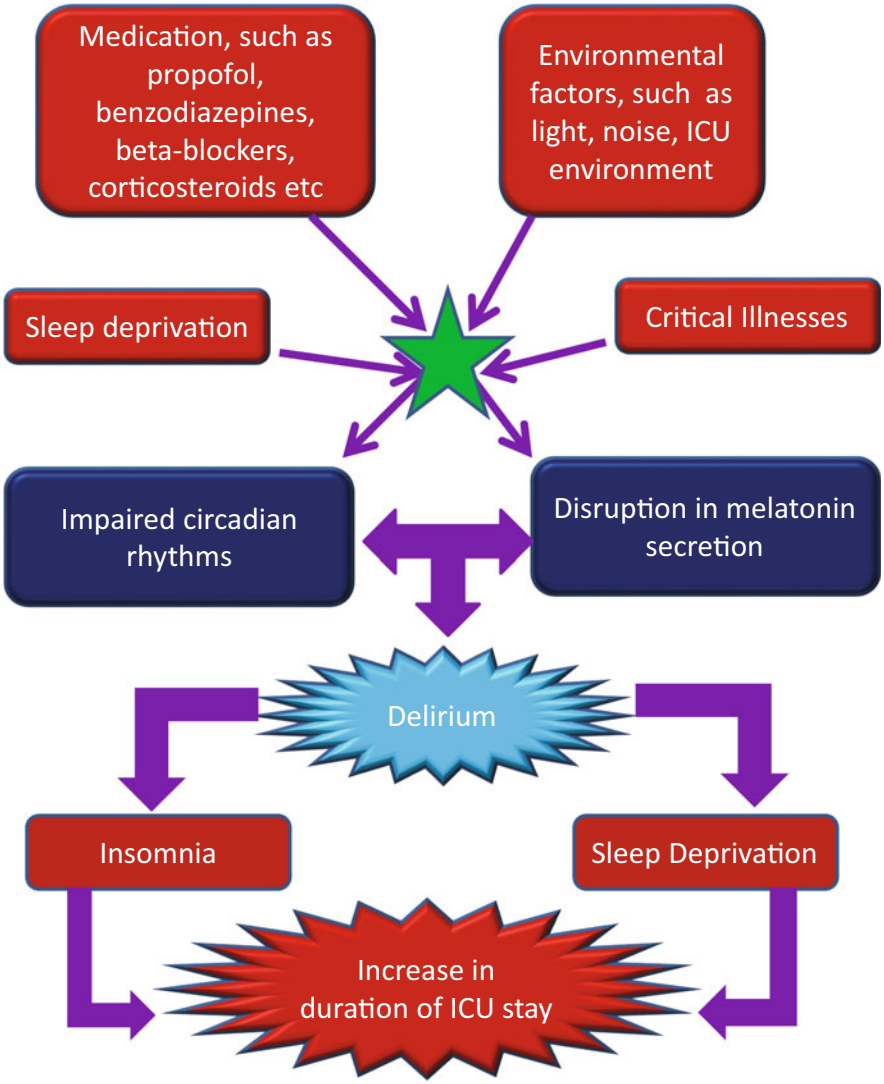

Fig. 28.1 Role of Sleep disruption in pathophysiology of delirium

proteins respectively. These proteins complete the negative feedback and lead to gene suppression [21]. The secretion of endogenous melatonin typically starts around 9.00 PM with a peak between 2.00 and 4.00 AM. The melatonin release is inhibited between 7.00 and 9.00 AM, which coincides with the peak levels of endogenous cortisol. The major metabolite of melatonin is 6-sulphatoxymelatonin (MT6), which closely reflects the plasma concentrations of melatonin [21].

The various physiological roles of melatonin include managing the chronobiologic cycle of the body, resetting the circadian rhythm, antioxidant properties at the

level of mitochondrial and nuclear deoxyribose nucleic acid (DNA), strong antiapoptotic activity, anti-inflammatory activity and analgesic properties. Melatonin also reduces the impact of glucocorticoids-induced neurotoxicity and apoptosis and resultantly act as a protective factor for development of learning and memory [11, 12]. Melatonin also acts as an antioxidant, pro-oxidant effect against microbials, helps in adaptation to the changes occurring in the environment, adaptation to the changes in the neuroendocrine system, delay in progression of various hormone-dependent malignancies, immune regulation, neuroprotection and sleep regulation [21].

Reduction in melatonin levels has been shown to be associated with development of post-operative delirium and sleep deprivation. Studies which have longitudinally evaluated the melatonin levels in patients undergoing surgery suggest that compared to the baseline levels, the post-operative melatonin levels are significantly lower among patients who develop delirium [32]. Other studies have shown association of significantly lower melatonin levels with mechanical ventilation [24] and association of abnormal melatonin release and sepsis [22], which are well-known risk factors for development of delirium.

Further association has been observed between irregular melatonin circadian rhythm and development of delirium. Studies have also shown that use of exogenous melatonin is associated with reduction in the incidence of new-onset delirium, and management of delirium [33–47]. Melatonin has also been linked with the clinical manifestation of delirium, with patients with hyperactive delirium exhibiting reduction in the level of metabolites of melatonin in the urine and patients with hypoactive delirium showing the reverse association [11, 13]. Further, there are data to suggest that there is reduction in the melatonin secretions with ageing, which can explain the higher risk of developing delirium among elderly [11, 13].

28.4 Evidence of Sleep-Related Interventions for Management of Delirium

As altered biological rhythm, disturbance of melatonin secretion and sleep deprivation are considered as important contributors for development of delirium; researchers have evaluated the efficacy of pharmacological measures and non-pharmacological measures in prevention and management of delirium. A recent review evaluated the role of melatonin and ramelteon in prevention and management of delirium. According to this review, the data on role of melatonin in prevention of delirium are limited to five randomized controlled trials (RCTs), two retrospective studies, one non-randomized observational study and one case report. On the other hand, data on management of delirium with melatonin and ramelteon are limited to 11 case series or case reports with lack of randomized control trials [33]. Studies which have evaluated the role of melatonin in prevention of delirium have come up with mixed results, with some of the studies reporting no therapeutic benefit with melatonin when compared to placebo [34–36], whereas others suggest that this may be of some benefit [37–40]. One of the studies compared melatonin with other agents

and suggested that the incidence of delirium was lower in the melatonin group, not only compared to placebo but also to no sedation, midazolam and clonidine [37]. In these trials the researchers used melatonin in the doses of 1–3 mg in the evening time and majority of these trials were limited to patients undergoing some kind of surgery. Similarly, studies which have evaluated ramelteon have also come up with mixed results, with some reporting lower incidence with ramelteon when compared to placebo [41] or tranquilizers [42] or the control group [43]. A meta-analysis, which included data for 669 elderly patients from four RCTs for use of melatonin in prevention of delirium, concluded that compared to the control group, use of melatonin had no influence on the incidence of delirium (relative risk: 0.41; confidence interval: 0.15–1.13). In the sub-group analysis, which was limited to elderly patients, use of melatonin was associated with 75% reduction in incidence of delirium in patients in medical wards (relative risk: 0.25; confidence interval: 0.07–0.88; p value 0.03), but not in sleep-wake disturbances (relative risk: 1.24; confidence interval: 0.5–3.00; *p* value 0.64). However, among patients in surgical ward, no significant difference was found. Resultantly, the authors concluded that use of melatonin has preventive effect for delirium in patients admitted in medical wards but not among those admitted in surgical wards [44]. Reports which have evaluated the role of melatonin and ramelteon in the management of delirium suggest that use of these agents is associated with reduction in severity of delirium and reduction in agitation [33]. Overall, it can be said that there is a lack of high-quality data on evaluation of role of melatonin and ramelteon in the prevention and management of delirium.

With respect to the non-pharmacological measures, studies have evaluated the beneficial effects of light therapy and noise reduction in prevention of delirium [45]. Some of these studies have used these interventions together, which are labelled as sleep promotion bundle that include bundling care, minimization of noise and light and the use of eye masks and ear plugs. These studies suggest that use of sleep promotion bundle interventions is associated with reduction in incidence of delirium [46].

28.5 Management of Delirium

Management of delirium involves proper detection, identification of the cause, addressing the cause and use of pharmacological and non-pharmacological measures to address the symptoms of delirium. One of the most important issues in the management of delirium includes identification of the etiological agent and addressing the same. This may involve review of medication history, detailed physical examination, assessment for contributory environmental factors and carrying out investigations to look for possible etiological factors. Upon identification, the underlying cause must be addressed. More often than not, delirium is often an outcome of alterations in more than one factor, with one of the factors acting as the main offending agent with multiple contributory factors [48]. Depending on the offending factor, the management of underlying cause may also involve treatment of

underlying infections, use of antidotes for poisoning and intoxication and use of benzodiazepines and thiamine.

The management of delirium requires unambiguous, supportive environment to improve the orientation and maintain the competence of the patients. Accordingly, the non-pharmacological measures should include providing support and orientation, providing unambiguous environment, measures for maintaining competence and providing other supportive measures. In terms of pharmacological measures, antipsychotics are considered as preferred agents for management of hyperactive delirium, with no medications recommended for management of hypoactive delirium [48].Among the various antipsychotics, haloperidol has been recommended as preferred agent, although in recent times, evidence has accumulated for atypical antipsychotics too. There is some evidence for use of cholinesterase inhibitors (donepezil, physostigmine and rivastigmine) and highly selective α-2 receptor agonist (dexmedetomidine). It must be remembered that pharmacotherapy should be considered when non-pharmacological measures have failed or there are specific indications for its use. The common indication for use of pharmacological agents in patients with delirium includes severe agitation or severe anxiety causing significant distress to the patient or placing the patient at risk to harm themselves or others. Lack of cooperation for essential investigations or treatment procedures may be other indications for use of pharmacotherapy [47].

From the sleep perspective, earlier it was believed that sedation was beneficial in preventing delirium. But with time, it has been realized that not only total sleep duration is important but preservation of sleep architecture is also important from the perspective of prevention and management of delirium. In terms of non-pharmacological measures, reduction in noise and light exposure during the night, clustering the nursing care activities scheduled at the awake time and reducing stimuli at night to protect patient's sleep cycles can help in preventing sleep deprivation and ensuring good sleep.

Accordingly, all efforts must be made to prevent sleep deprivation and ensure normal duration of sleep, in which normal sleep architecture is maintained. Some of the measures in this regard involve avoidance of medications which reduce REM sleep, slow-wave sleep or lead to alteration in the sleep architecture or parasomnias [48]. Some of these agents that are associated with one or more sleep-related disturbances include opioids, non-steroidal anti-inflammatory agents, anaesthetics, anticholinergics, anticonvulsants, anti-Parkinson's agents, cardiac drugs (such as β-blockers, clonidine and digitalis), corticosteroids, tricyclic antidepressants, selective serotonin reuptake inhibitors and sedative/hypnotics (i.e. benzodiazepines). Hence, use of benzodiazepines must be limited to delirium associated with alcohol or benzodiazepine withdrawal.

As melatonin has an important role in regulating circadian rhythm, melatonin may be of some benefit in preventing delirium. However, at present, data are limited to make any recommendations for use of melatonin in the management of delirium.

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Sleep Disturbances and Functional Gastrointestinal Diseases

29

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Abstract

Sleep is largely regulated by the light-dark cycle and associated circadian rhythms. Poor health outcomes are known to be associated with poor sleep quality and sleep deprivation. Sleep quality and sleep disorders affect symptom manifestation and have been implicated in increasing risk of medical conditions like hypertension, obesity, stroke, and heart disease and increased overall mortality. Recent studies have suggested that there is a strong association between sleep disturbances and gastrointestinal diseases like gastroesophageal reflux disease, peptic ulcer disease, irritable bowel syndrome, etc. It is important for gastroenterologists as well as sleep physicians to be aware of the relationship between sleep disorders and gastrointestinal illnesses to ensure good care for patients. Currently, most literature on sleep disorders in GI diseases is based on subjective parameters, and limited information is available on objective criteria like polysomnography.

Keywords

Sleep · Circadian rhythm · Gastrointestinal disorders · Irritable bowel syndrome · Inflammatory bowel disease · Chronic liver disease

29.1 Introduction

Sleep is a physiological state characterized by changes in the level of consciousness, unresponsiveness to the surrounding environment, and inactivity of voluntary muscles. Sleep restores people physically, mentally, and emotionally.

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Polysomnographic criteria classify sleep into rapid eye movement (REM) sleep and non–rapid eye movement (NREM) sleep. NREM sleep constitutes 75% to 80% of total sleep time, whereas REM sleep accounts for the remaining 20% to 25% of the sleep time [1]. REM sleep is characterized by the random rapid movement of the eyes, low muscle tone throughout the body, and the occurrence of dreams. Patients with sleep deprivation experience a reduction in productivity and quality of life, leading to an increase in accidents and errors in the workplace [2]. Sleep disorders have been linked to neurocognitive effects such as impaired attention, slower response time, and an increased likelihood of falling asleep at work [2]. Certain disease conditions like diabetes, hypertension, stroke, and obesity have been found to be associated with long-term sleep deprivation [1]. More significantly, long-term sleep deprivation has been associated with an overall increase in morbidity and mortality. Recent studies have suggested a strong association between sleep disturbances and gastrointestinal diseases [3–6]. Poor sleep has been shown to result in the worsening of gastrointestinal symptoms. Conversely, many gastrointestinal disorders affect the sleep-wake cycle and lead to poor sleep.

29.2 Sleep Cycle and Its Role in Human Physiology

Sleep exists as part of a 24-h cycle that is primarily regulated by the light and dark periods of a 24-h day. Periodic light and dark changes provide the basis for physiological clocks, ubiquitous in human physiology and behavior. The alignment of sleeping and waking with the circadian cycle is crucial for establishing a healthy sleep cycle. Circadian rhythms are 24-h cycles that are part of the body's internal clock, running in the background to carry out essential functions and processes. One of the most essential and well-known circadian rhythms is the sleep-wake cycle. Misalignment of these environmental changes (e.g., occurring among shift workers like factory workers and nurses) in association with other etiological factors that are specific to a given sleep disorder frequently causes sleep disturbances and may precipitate sleep-related symptoms such as insomnia [7].

The circadian rhythm is regulated by the suprachiasmatic nucleus (SCN), a tiny region located in the anterior hypothalamus just above optic chiasma and functions as a person's master biological clock. The SCN receives inputs from ganglion cells of the retina via the retino-hypothalamic pathways. The SCN regulates secretion of melatonin, cortisol, and core body temperature. Alterations of the SCN lead to abnormalities in the circadian rhythm and changes in a person's sleep-wake cycles [8].

A broad range of vital functions display circadian in the human digestive tract. For example, there is a variation in volume of salivary secretion with decrease in secretion at night [9]. There is evidence of changes in peristaltic movements of the gut with circadian rhythms. Gastric emptying rates are longer in the later part of the day than in the morning, nocturnal propagation velocities of the migrating motor complex are slower, and colonic motor activity is minimal during sleep [10]. There are also changes in secretion of mucous and digestive enzymes with decrease in

secretion during nighttime [11]. Circadian regulation also has an impact on hepatic metabolism. Plasma glucose, regulation of lipids, including triglycerides, cholesterol, and free fatty acids, and bile acids follow circadian rhythms [12].

Because circadian rhythms have apparent central and local influences, alterations in sleep-wake cycling are likely to affect the pathogenesis of digestive diseases.

29.3 Gut-Brain Axis

The connections between the gastrointestinal system and the brain are essential in regulating the digestive tract and maintaining the gut immune system. This bidirectional network involves the central nervous system (CNS), neuroendocrine and neuroimmune systems, and autonomic nervous system including enteric nervous system (ENS). The autonomic network incorporates sympathetic and parasympathetic nervous activity, which drives afferent signals through enteric and vagal pathways to the CNS and efferent signals from the CNS to the intestine [13]. Neuroendocrine activity allows the brain to modulate the actions of intestinal cells such as interstitial cells of Cajal, also known as pacemaker cells, enterochromaffin cells, and smooth muscle cells. This relationship between the brain and the gastrointestinal system involves feedback loops, which also influence the circadian rhythm and sleep regulation pathways.

29.4 Digestive Diseases and Sleep Disorders

The GI diseases that most frequently impair sleep are acid-related (gastroesophageal reflux disease and peptic disease), functional bowel diseases like irritable bowel syndrome, inflammatory GI disorders (ulcerative colitis and Crohn's disease), and liver diseases. These disorders and the impact of sleep disorders on these conditions are briefly described below.

29.4.1 Gastroesophageal Reflux Disease and Sleep

An international consensus group has defined GERD as a condition that develops when reflux of stomach contents causes troublesome symptoms with or without complications [14]. Typical symptoms that lead to the diagnosis of GERD are regurgitation and heartburn. As much as 16% of the US population complains of regurgitation, and 6% report clinically troublesome heartburn [15]. GERD symptoms can worsen with lying recumbent, especially after meals. During sleep, there is a decrease in swallowing, reduction in salivary volume, and reduced frequency of peristalsis, leading to increased gastric acid reflux. This, in turn, makes the esophagus more susceptible to gastric acid injury. The normal daily production of saliva varies between 0.5 and 1.5 L. The whole unstimulated saliva flow rate is approximately 0.3–0.4 ml/min. This rate decreases to 0.1 ml/min during

sleep and increases to about 4.0–5.0 ml/min during eating, chewing and other stimulating activities [16]. Swallowing rate decreases to 5 times per hour during sleep from approximately 25 times per hour during wakefulness [17]. These physiological changes during the sleep results in prolonged acid exposure, leading to an increased risk of mucosal damage and esophagitis [18].

There is a bidirectional relationship between gastro-esophageal reflux disease (GERD) and sleep. GERD may adversely affect sleep by awakening patients during the night because of acid reflux or, more commonly, causes multiple short amnestic arousals with resultant sleep fragmentation [19]. Poor sleep might adversely affect GERD by heightened perception of painful intraesophageal stimuli, such as gastric acid (centrally mediated sensitization), and an increase in the exposure of the esophagus to gastric acid [20, 21]. Multiple studies have shown that around 65% of patients with gastroesophageal reflux disease have both daytime and nocturnal symptoms [22–25]. Only about 13% of patients with gastroesophageal reflux disease experience only nocturnal symptoms. Patients with 47–57% of gastroesophageal reflux diseases have both daytime and nocturnal symptoms [25–27]. By contrast, 25% of the general population reported having heartburn symptoms during sleep time [25]. Nocturnal reflux can be associated with insomnia, snoring and nightmares. Gastroesophageal reflux disease can also affect a patient's sleep experience by causing nocturnal cough, choking, wheezing, sore throat, and breathlessness [28, 29].

Obstructive sleep apnea (OSA) is characterized by repetitive narrowing or collapse of the upper airway during sleep with the development of large negative intrathoracic pressures. Gastroesophageal reflux (GER) appears to be a particular problem for patients with OSA, as they exhibit an increase in GER symptoms and events during waking and sleep compared to individuals without OSA [30–33].

The precise mechanism underlying the increase in nocturnal GER in OSA patients is an area of active research. The role of obesity in the link between OSA and GER remains unclear. Obesity is a risk factor common to both OSA and GER and, therefore, represents a potential mechanism for the link between the two conditions. Shepard et al., in a recent study, found that rather than OSA it was obesity which was contributing to nocturnal reflux events [34].

29.5 Functional Dyspepsia, Ulcer Disease, and Sleep

29.5.1 Functional Dyspepsia

Functional dyspepsia (FD) refers to troublesome upper gastrointestinal symptoms including inability to finish a meal (early satiety), postprandial fullness, and epigastric pain or burning [35]. Some patients also complain of nausea, heartburn (although this is not the predominant complaint), and even weight loss (few patients with functional dyspepsia are obese). Peptic ulceration, reflux esophagitis, and gastric cancer may present with identical complaints but the vast majority of patients with these symptoms have functional dyspepsia. There are two subtypes of FD, although

these often overlap in practice [35]. The largest group (70%) have early satiety or postprandial fullness, termed postprandial distress syndrome. The other group experience ulcer-like pain or burning, termed epigastric pain syndrome. Functional dyspepsia is considered an idiopathic disorder, however, various factors have been implicated in its pathogenesis. *Helicobacter pylori* is a recognized cause of functional dyspepsia. Most patients with *H. pylori* do not develop functional dyspepsia; however, in a minority, eradicating the infection cures dyspeptic symptoms [36].

Gastroduodenal motility disturbances have also been observed in FD. Slow gastric emptying, failure of the gastric fundus to relax normally after eating, hypersensitivity to distension of the stomach or duodenum (visceral hypersensitivity) have been described [37].

People with postprandial distress have increased duodenal eosinophils that may degranulate. Duodenal eosinophils have been linked to increased mucosal permeability, submucosal neuronal structural and functional changes, and symptoms [38].

Currently, there are limited data on sleep abnormalities in FD patients. Lacy et al. [39] studied sleep disturbances in FD patients. The authors used Pittsburgh Sleep Quality Index (PSQI) scores to assess sleep quality in FD patients. PSQI scores were higher in FD patients with more severe symptoms, and the difference in PSQI scores between FD patients with severe symptoms and mild symptoms was statistically significant. They also found that FD was associated with symptom severity and higher anxiety levels. Seventy percent of FD patients noted problems in falling asleep or staying asleep. The authors hypothesized that patients with FD might suffer from disordered sleep due to their dyspeptic symptoms, and this sleep loss may exacerbate FD symptoms due to the hyperalgesic effect of sleep loss. Another study by Miwa et al. [40] has also reported that the percentage of subjects who thought they got enough sleep was significantly lower for the FD subjects than for control subjects. In a study from China, the authors evaluated sleep quality and mood symptoms in patients with FD, assessing the associations of FD severity, disordered sleep, and psychological symptoms. Rome III criteria were used to evaluate FD symptoms; sleep disorder was assessed with the Pittsburgh Sleep Quality Index (PSQI), and Symptom Checklist–90-revised (SCL-90R) was utilized to determine the status of depression, anxiety, and other psychological symptoms. PSQI scores and nine symptomatic dimensions of SCL-90R were significantly higher in FD patients than in controls [41].

In conclusion, sleep disturbance is common in patients with FD. Impaired sleep is an independent risk factor for FD and both FD subgroups, and may play a role in symptom expression.

29.5.2 Peptic Ulcer Disease

Peptic ulcer disease (PUD) is defined as peptic injury of the digestive tract leading to a mucosal break reaching the submucosa that usually occurs in the stomach and/or proximal duodenum [42]. During deeper sleep stages, defensive factors against PUD development and recurrence, such as gastric bicarbonate secretion, and gastric

mucosal blood flow were found to increase, while aggressive factors like gastrin secretion decreased [43, 44]. These protective systems can be impaired by sleep disturbaces [45, 46].

Data on the relationship between sleep disorders and the risk of development of peptic ulcer disease (PUD) are currently limited. A Japanese survey by Segawa and colleagues noted a higher prevalence of gastric ulcers for shift workers than the day workers (2.38% vs. 1.38%, respectively). Similarly, for duodenal ulcers, the prevalence was 1.37% in shift workers and 0.69% in day workers [47]. The relative risk for peptic ulcers was 2.18 for shift workers compared with day workers [31]. The authors of the study hypothesized that the possible reasons for the higher risk of PUD in shift workers might be unpredictable meal timings, sleep dysfunction due to working in shifts, work-related stress, and concomitant use of nonsteroidal antiinflammatory drugs.

A recent study by Fang and colleagues from China examined whether perceived poor sleep quality predicted subsequent recurrence of PUD in older patients with mild cognitive impairment following *H. pylori* eradication and whether social engagement status altered this association. The results showed that PUD recurrence was more prevalent in poor as compared with good sleepers and increased and continued social engagement reduced the proportion of PUD recurrence in poor sleepers [48].

To summarize, currently there are limited data on association between sleep and PUD; however, above-mentioned studies show higher incidence of PUD in patient with poor sleep and some association is emerging for recurrence of PUD after *H pylori* eradication in patients with poor sleep.

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29.6 Irritable Bowel Syndrome and Sleep

Irritable bowel syndrome (IBS) is a common disorder that affects a significant percentage of the general population. Globally, IBS is estimated to affect about 10% of the general population, but prevalence rates are highly variable [49, 50]. IBS is one of the most common functional GI disorders seen in clinical practice. IBS is defined as abdominal discomfort or pain associated with changes in bowel frequency [51]. The exact pathophysiology of IBS is currently not known; however, multiple etiologies have been suggested, including bowel dysmotility, small bowel bacterial overgrowth (SIBO), autonomic dysfunction, visceral hyperalgesia, and microscopic inflammation [52].

Adults IBS patients report difficulty in falling asleep, decrease in sleep time, frequent nocturnal arousal and awakenings, or non-restorative sleep [53–56]. In a population-based study with 2269 participants, Vege et al. reported 33% prevalence of IBS among the participants with sleep disturbances. The risk of having IBS was 1.6 times greater in people with sleep disturbances as compared to those without sleep disturbances, even after adjusting for age, gender, and somatization scores [57].

Although several studies have documented subjective sleep disturbance in patients with IBS, objective polysomnographic studies have produced variable results. Elsenbruch et al. used the Pittsburgh Sleep Quality Index (PSQI) to measure subjective sleep quality, and polysomnography was performed to obtain objective measures of sleep quality, including sleep efficiency, sleep latency, number of arousals, and percentage of slow-wave sleep. The authors found significantly increased global PSQI scores as well as significantly higher scores on several subcomponents of the PSQI (i.e., sleep quality, sleep latency, habitual sleep efficiency, and daytime dysfunction) [54]. There was no objective difference between the two groups when using polysomnography as a marker of sleep quality. Both groups had a similar number of arousals, amount of slow-wave sleep, and REM sleep [54]. The results of this study suggested that patients with IBS may have exaggerated response to external or internal stimuli in the absence of objective sleep abnormalities.

Another study from Orr et al. also showed a significant increase in rapid eye movement (REM) sleep in patients with IBS using objective polysomnographic measures [58].

In a systematic review by Tu et al., there was a consistent evidence to link subjectively reported sleep disturbances with GI symptoms, but less conclusive evidence of objective sleep disturbances. There was evidence of positive correlation between subjectively reported sleep disturbances and GI symptom exacerbation among people with IBS [59].

In a recent meta-analysis from China by Wang and colleagues that involved 36 studies, the prevalence of sleep disorders was 37.6% (95% CI: 31.4% to 44.3%) [60].

Overall, patients of IBS have subjective evidence of poor sleep quality, however, more objective data are needed in this group of patients.

29.7 Inflammatory Bowel Disease and Sleep

Inflammatory bowel disease (IBD) is a group of inflammatory disorders of the large and small bowel. Crohn's disease (CD) and ulcerative colitis (UC) are the two principal types of inflammatory bowel disease [61]. Crohn's disease affects any part of the GI tract from mouth to anus, whereas ulcerative colitis primarily affects the colon and the rectum. During the active phase, patients suffer from symptoms such as fecal incontinence, abdominal pain, bloody diarrhea, arthritis, and fatigue [62]. Apart from physiologic complications, patients describe a series of extraintestinal manifestations such as high psychological distress [63, 64] and low quality of life [65]. The relationship between IBD and disturbed sleep is an area of active research. Interplay of poor sleep resulting in an increased inflammatory burden and worsening disease activity causing poor sleep quality has been suggested. Hypersomnia and decreased sleep duration have been linked to the development of ulcerative colitis [66]. Poor sleep quality has been described in several studies in IBD subjects with both inactive and active disease

[67, 68]. Moreover, there is an increasing evidence to suggest poor sleep quality is associated with an increased risk of flares in CD and may serve as a marker for subclinical inflammation [6, 69].

Various etiologies have been proposed regarding the etiology of sleep dysfunction in patients with IBD. Typical symptoms of abdominal pain, rectal urgency, and diarrhea can result in sleep disturbances. Medications involved in IBD management, including corticosteroids, can lead to sleep disturbances. A recent review by Qazi et al. suggested a bidirectional association between poor sleep and IBD. The study suggested that an interchange where poor sleep quality may increase severity of inflammation and risk of relapse, in turn, elevated inflammatory markers, and active disease may contribute to poor sleep [70].

Few polysomnography studies have been done in patients with IBD. In studies that examine IBD, sleep disturbances are most often measured by subjective instruments rather than polysomnography. Ranjbaran and colleagues [4] evaluated sleep disturbance via the PSQI in a large population of patients with IBD. They found that patients with IBD reported sleep disturbances (prolonged sleep latency, frequent sleep fragmentation, higher rate of using sleeping pills, decreased daytime energy, increased tiredness, and poor overall sleep quality) more often than did participants in the healthy control group and that there was a correlation between sleep disturbance and severity of the disease.

In another study, Ali and colleagues conducted a prospective observational cohort study looking for quality of sleep and disease activity in IBD patients using the PSQI scale [3]. Hundred percent of patients with active disease had an abnormal PSQI score, while only 54% of patients with inactive histology had sleep abnormalities. An abnormal PSQI score had a positive predictive value for the histologic inflammatory activity of 83%.

Recently, a systematic review and meta-analysis on sleep quality and disease activity in patients with IBD was published. Six studies were included for the analysis. Sleep quality was measured using subjective questionnaires in six studies and objective methods in three studies. Disease activity was diagnosed following standard guidelines. A significant association between subjective sleep quality and disease activity was observed (pooled OR ¼ 3.52, 95%CI: 1.82, 6.83, $P < 0.001$). A significant association between sleep efficiency and disease activity was observed as well (pooled OR ¼ 4.55, 95% CI: 1.92, 10.75, P ¼ 0.001). Findings from that meta-analysis indicated that both subjective and objective poor sleep quality were associated with an increased risk for disease activity in IBD patients.

To summarize, there is definite association between IBD and sleep disorders, however, larger studies with an experimental design are warranted to confirm the effects of sleep quality on intestinal pathological changes in IBD patients [71].

29.8 Chronic Liver Disease and Sleep

The leading causes of chronic liver disease (CLD) and cirrhosis include harmful alcohol consumption (ethanol-associated liver disease), chronic viral hepatitis B and C, metabolic disorders, and nonalcoholic fatty liver disease. Clinical

manifestations of cirrhosis are highly variable and can lead to the development of ascites, jaundice, gastrointestinal bleeding, and hepatic encephalopathy (HE).

Sleep disturbances in liver cirrhosis are closely associated with the presence of HE. HE has a broad spectrum of clinical severity, ranging from covert to overt HE with coma seen in severest grade [72]. In patients with HE, sleep disorders are described as a panel of sleep-wake abnormalities [73]. The most common abnormalities include difficulty falling asleep or maintaining sleep, or unrefreshing sleep, excessive daytime sleepiness (EDS), and sleep-wake inversion (disturbances of circadian rhythmicity).

Sleep disturbances have also been noted in compensated cirrhosis. Bajaj et al. have observed EDS and poor quality of sleep in compensated cirrhotic compared to healthy controls [74].

Prevalence estimates of sleep disturbances in liver cirrhosis based on questionnaires, such as the Pittsburgh Sleep Quality Index (PSQI) [75–80], and hospital-specific questionnaires [8] range from 48% to 81%. This is much higher than the prevalence observed in the general population [81]. Findings in cirrhotic patients include increased sleep latency (SL), reduced total sleep time (TST), and frequent awakenings [8].

As shown by actigraphy, objective measurements have confirmed the altered sleep quality in cirrhotic patients in the form of reduced sleep latency and frequent awakenings [82–84]. PSG has also been performed, establishing the presence of short TST, decreased sleep efficiency (SE), frequent awakenings, and lower amounts of slow-wave sleep (SWS), and rapid eye movement (REM) sleep in cirrhotic patients [85].

29.9 Conclusions

Sleep disturbances are frequently seen in patients with gastrointestinal diseases. The relationship between GI disorders and sleep is bidirectional, with each having an impact on the other. GI physicians and sleep specialists should be aware of this association to improve patient outcomes. More objective studies are required in the future for a better understanding of this association.

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Quality of Life in Patients with Sleep Disorders

30

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Abstract

Sleep disorders affect an individuals' mental and physical health leading to impairment in the level of perceived life satisfaction. Most common sleep disorders, that is, insomnia, obstructive sleep apnoea and restless leg syndrome, have been found to impair physical, social and psychological well-being leading to impairment in quality of life (QOL) as compared to healthy population. An improvement in QOL has also been observed with certain treatment modalities for these disorders. This chapter discusses effects of sleep disorders and their treatment on QOL of an individual.

Keywords

Sleep disorders · Quality of life · Satisfaction · Well-being

30.1 Introduction

Sleep is defined as a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment. It is also true that sleep is a complex amalgam of physiologic and behavioural processes. Behaviourally, sleep is typically (but not necessarily) characterised by postural recumbency, behavioural quiescence and closed eyes [1]. It is a biological process that is essential for life and plays an important role in brain and body activities including the metabolic activities, immune, hormonal and cardiovascular systems [2, 3]. A healthy sleep is characterised by adequate duration, good quality, appropriate timing and rhythm, absence of sleep disturbances and disorders and daytime vigilance and productivity.

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According to the National Sleep Foundation, most adults on an average need about 7–9 h of restful sleep each night, though some may be short sleepers or long sleepers [4, 5]. Numerous factors contribute to problems with sleep that range from lifestyle, environmental factors, medical and psychiatric disorders to sleep disorders. Vice versa, sleep problems may have a negative impact on the above-mentioned factors leading to a vicious cycle.

Sleep disorders involve issues with the quality, timing and quantity of sleep, which cause impairment with functioning and distress during the daytime [4]. Sleep disorders are classified in around hundreds of ways by different organisations; however, they are typically manifested in one of the following ways: failure to obtain the necessary amount of sleep even when more sleep is desired (sleep deprivation), an inability to maintain sleep continuity (disrupted sleep, also called sleep fragmentation, difficulty maintaining sleep and middle insomnia) and events that occur during sleep (e.g. sleep apnoea, restless legs syndrome) and increased sleep [2, 6]. The International Classification of Sleep Disorders' (ICSD) recent publication in 2014 is the third edition, built on the basic foundation of ICSD-2 and is a revised version of American Academy of Sleep Medicine's manual of sleep disorders nosology. It divides sleep disorders into seven major categories, provides reviewed sensitive and specific criteria for each disorder and coding as per International Classification of Diseases ninth and tenth edition [7].

The seven major categories are:

1. Insomnia.
2. Sleep-related breathing disorders.
3. Central disorders of hypersomnolence.
4. Circadian rhythm sleep-wake disorders.
5. Parasomnias.
6. Sleep-related movement disorders.
7. Other sleep disorders.

30.2 Epidemiology

30.2.1 Insomnia

It is the most common sleep disorder among adults and elderly [8, 9]. More than 50 epidemiological studies [8, 9] of insomnia have been conducted worldwide and between 10% and 18.1% of the population studied report themselves to be poor sleepers or suffering from insomnia [1]. Indian studies report a prevalence ranging from 4.7% to 33% [10–12].

In general population, symptoms of insomnia are more common than clinical insomnia disorder. Different studies have suggested that one-third to half of the population report symptoms of insomnia in past year while 6–20% population suffer from diagnosable clinical insomnia [13–17].

In *primary care settings*, approximately 10–20% of adults complain of significant sleep impairments leading to functional impairments, productivity reduction and increased healthcare services' utilisation [13].

The prevalence of insomnia varies across different studies due to different definitions/criteria considered in each study. According to NIH State-of-the-Science Conference held in June 2005, the addition of a diagnostic criteria of perceived daytime impairment or distress as a function of the insomnia symptoms has reduced prevalence of insomnia to approximately 10% [18]. And, the application of diagnostic criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* [19], which gives duration criteria of 1 month and exclusion of other primary disorders, gave prevalence estimates of only approximately 6% [20, 21]. Problem appears to have increased over the years as studies using recent DSM-5 criteria (duration criteria for 3 months, including early morning awakening) [22] were used in college students and psychiatric outpatients, prevalence was found to be 9.5% and 31.8% respectively [23, 24].

30.2.2 Obstructive Sleep Apnoea (OSA)

Various studies have been conducted to study the prevalence of OSA. In most of the studies, the prevalence of OSA in general population, for a cut-off of Apnoea-Hypopnoea Index (AH I) $\geq$5 ranges between 9% and 38% [25, 26]. In fact, in some countries, the prevalence exceeds 50% of the general population [27]. Studies also confirm a higher prevalence in males, those having obesity and advanced age [25, 26].

According to studies conducted in India, the prevalence of OSA and OSAHS ranges from 9.3% to 13.7% and 2.8–3.6%, respectively, with higher prevalence in males [28–30].

30.2.3 Restless Leg Syndrome (RLS)

International RLS Study Group (IRLSSG) 2003 criteria describe four characteristics for the diagnosis: An urge to move the legs usually accompanied with unpleasant sensations in legs; worsening at rest; symptoms are partially or totally relieved by movement; and symptoms occur or are worse in evening or night [31]. A fifth clause that rules out that symptoms arise from any of the common conditions that can mimic RLS was included in 2014 [32].

Most of the studies for the prevalence of RLS have been conducted before 2014. These studies have used various methods to diagnose RLS that range from using IRLSSG 2003 criteria, Cambridge Hopkins diagnostic Questionnaire, extraction of information through questionnaires to studies used clinical interviews. All these issues add to variability in prevalence rates of RLS over different studies. According to a review conducted by Koo et al. [33], RLS/WED prevalence was estimated to be higher in North America and Europe where it ranges between 5.5% and 11.6% while

it was lower in Asia ranging between 1.0% and 7.5%. Women are affected more than men and are threefold more common in pregnant females as compared to non-pregnant females with a highest prevalence during the third trimester [34]. RLS usually runs a chronic course and worsening has been seen with advancing age.

Studies conducted in Indian subcontinent show that approximately 2% of Indian population suffers from RLS [35, 36] with a higher prevalence (around 11%) in higher altitudes [35].

This chapter is limited to the impact of QOL of these three most common sleep disorders.

30.3 Quality of Life

The *World Health Organization (*WHO) defines 'Quality of Life' as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad concept influenced in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to the environment [37].

According to Aaronson [38], there are two common threads in the structure and content of measures that carry the QOL label. First, thread reflects a multidimensional conceptual approach incorporating four broad health dimensions:

1. Physical health, that is, somatic sensations, disease symptoms, treatment side effects.
2. Mental health, ranging from a positive sense of well-being to non-pathological forms of psychological distress to a diagnosable psychiatric disorder.
3. Social health, including assessment of both quantitative and qualitative aspects of social contacts and interactions.
4. Functional health, including both physical functioning in terms of self-care, mobility and physical activity level and social role functioning in relation to family and work.

Apart from these core dimensions, disease-specific measures incorporate variables that are specific to a given disease, treatment or research situation [38].

Multiple models have been given to describe dimensions of QOL like Dijkers's model, Wilson and Cleary's model and PROMIS conceptual model [39]. None of the models clearly delineate the scope of the term 'Quality of Life' as it has diverging definitions, operationalisation and measures. Hence, the term 'quality of life' is used as an umbrella for any aspect of living with illness or disability [39].

30.4 Assessment of Quality of Life in Sleep Disorders

There are limited numbers of instruments designed to assess quality of life in sleep disorders. The available instruments are divided into two types: generic and disease specific [40, 41]. These instruments are tabulated in Table 30.1.

30.4.1 Generic Scales

Generic QOL scales are based upon the WHO definition of Health-'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [55]. This definition covers the presence of positive aspects as well as the absence of negative aspects. Perfect QOL considers health in all the three domains—physical, mental and social [56]. Generic quality of life measures are those which have been developed to assess QOL in a broad range of population irrespective of the illness status. They permit cross-disease QOL comparisons, generate normative data (in healthy population), allow comparison between healthy and diseased population and thus, facilitate meta-analysis. Disadvantage of these scales is that they tend to lack sensitivity to detect changes in QOL related to a specific illness and with specific treatment outcomes [40, 41].

Generic scales with sleep-related dimensions are Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), SF-12 and SF-8; Nottingham Health Profile; Sickness Impact Profile, EQ-5D (EuroQol Group); Health Utilities Index etc. All these measures have acceptable psychometric qualities [40].

30.4.2 Disease-Specific Scales

Disease-specific instruments assess concerns relevant to a particular illness. These instruments can measure changes in QOL over time and treatment outcomes, which

Table 30.1 Instruments to assess quality of life in sleep disorders

Generic QOL scales	Sleep disorder-specific QOL scales
Short Form-36 [42], short Form-12 [43]	Functional outcomes of sleep questionnaire (FOSQ) [44]
Nottingham Health Profile [45]	Calgary sleep Apnoea quality of life index (SAQLI) [46]
Sickness Impact Profile [47]	Hotel-Dieu-16 (HD-16)- for insomnia [48]
World Health Organization quality of life—Brief form (WHOQOL-BREF) [49]	Quality of life of insomniacs questionnaire [50]
The quality of life enjoyment and satisfaction questionnaire short-form (Q- LES-Q) [51]	Insomnia Severity Index [52]
QOL Inventory [53]	Restless Leg Syndrome Quality of Life Questionnaire-Abetz [54]

is not possible with generic measures. Scales specific to sleep disorders include Ferrans and Powers Quality of Life Index: Narcolepsy version, Functional Outcomes of Sleep Questionnaire (FOSQ), Calgary Sleep Apnoea Quality of Life Index (SAQLI), to name a few [40].

30.5 Scales Commonly Used for Assessment of QOL in Sleep Disorders

30.5.1 Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) [42] and SF-12 [43]

They are the most commonly used generic measures of QOL. They measure health-related QOL under eight dimensions—physical functioning, role functioning in physical domain, role functioning in emotional domain, mental health, social functioning, bodily pain, vitality and general health. SF-36 has an additional item comparing health 1 year ago. SF-36 is most widely used, and its psychometric properties have been tested extensively in more than 40 countries. There is no total scoring. Physical and mental health component summary scores are measured. Higher scores reflect the better QOL. Vitality which is scored in the mental health component is the dimension related to sleep. It correlates with both mental and physical components. SF-12 is a shorter version and assesses QOL on the same eight dimensions [40].

30.5.2 The Nottingham Health Profile (NHP) [45]

The NHP reflects the effects of ill health perceived by a lay man. It has two parts. Part 1 assesses six domains—physical abilities, pain, sleep, social isolation, emotional reactions and energy level. Part 2 assesses seven domains—occupation, ability to do jobs around the house, social life, home relationships, sexual life, hobbies and holidays [40]. Of the 38 questions in part 1, less than 50% are expected to be affected by sleep disorders [46].

30.5.3 Sickness Impact Profile [47]

It measures the amount of impact sickness has had in a person's life. It has 136 questions divided into 12 dimensions—sleep and rest, emotional behaviour, body care and movement, home management, mobility, social interaction, ambulation, alertness behaviour, communication, work, recreation and pastimes and eating. Sickness Impact Profile generates an individual score for two dimensions of physical and psychosocial score along with a total score. It lacks face validity for those who consider themselves as healthy [40].

30.5.4 World Health Organization Quality of Life—Brief Form (WHOQOL-BREF) [49]

It is a well-validated 26-item questionnaire covering four domains—physical health (7 items), psychological health (6 items), social relationships (3 items) and environment (8 items) with two additional items of overall QOL and general health [57].

30.5.5 The Quality of Life Enjoyment and Satisfaction Questionnaire Short-Form (Q-LES-Q) [51]

It is a 16-item questionnaire with a total score ranging from 0 to 100. It has been used in variety of psychiatric disorders including sleep disorders [58].

30.5.6 QOL Inventory [53]

It is a 31-item questionnaire with 17 domains. It assesses QOL by questions related to sleep, cognitive function, daytime performance, social and family relationships and health [58].

30.5.7 Functional Outcomes of Sleep Questionnaire (FOSQ) [44]

It assesses the impact of excessive sleepiness on physical, mental and social functioning. It is a 30-item questionnaire divided into five subscales—activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome. For each item, a person may answer 'did not engage in' and this option is one of the strengths of the instrument [40].

30.5.8 Calgary Sleep Apnoea Quality of Life Index (SAQLI) [46]

The original SAQLI is a respondent-driven, evaluative measure with 35 questions divided under four domains of daily functioning, social interactions, emotional functioning and symptoms. It also includes a fifth domain on treatment-related symptoms. A Short SAQLI is a self-report measure derived on the basis of responsiveness, repeatability, readability and representativeness from original SAQLI. The unique feature of original SAQLI of well-balancing quality of life benefits against treatment-induced symptoms has been retained in Short SAQLI [40].

30.5.9 Hotel-Dieu-16 (HD-16) [48]

Léger et al. [48] developed the Hotel-Dieu-16 (HD-16) scale in 2005. The HD-16 assesses five dimensions—physical, energy, cognitive, social and psychological under 16 questions. It was designed to control comorbid illness acting as a confounding factor in assessment of QOL in insomnia. This scale has some limitations like non-specificity of some items [48, 58].

30.5.10 Quality of Life of Insomniacs Questionnaire [50]

Rombaut et al. [50] developed the Quality of Life of Insomniacs questionnaire in 1990. It has been used only in few studies [50, 58].

30.5.11 Insomnia Severity Index (ISI) [52]

Morin et al. [52] developed ISI in 2011. It has self-rated seven items that assess the nature, severity and impact of insomnia over last month. This questionnaire is mainly used to assess the severity of insomnia, though item number 5 assesses noticeability of sleep problem by others in terms of impairing QOL and item number 7 assesses interference in daily functioning. All the items are rated on 5-point Likert scale [52].

30.5.12 Restless Leg Syndrome Quality of Life Questionnaire-Abetz [54, 59]

Abetz et al. [54] developed this scale in 2005. It is an 18-item self-administered scale and assesses the impact of RLS on daily life, emotional well-being, social life and work life [54]. This is the only scale that has been designated as 'Recommended' by Movement Disorder Society Task force in 2014 in cross-sectional assessments and treatment monitoring in the RLS population. This task force also highlighted the need of the development of paediatric RLS quality of life instruments [60].

It is important to decide which instrument of quality of life to be used according to the intended purpose. Generic scales are more of a discriminative type which help to assess QOL differences between two different diseased populations and between diseased and healthy populations. Whereas disease-specific scales are more of evaluative type which help in assessing changes over time in same population or effects of treatment.

30.6 Sleep Disorders and Quality of Life

As said by Thomas Dekker, 'Sleep is the golden chain that ties health and our bodies together'. Quality of sleep determines the quality of life. Disruption of sleep affects brain function and human physiology, in turn leading to multiple short- and long-term consequences over one's health and life, further leading to reduction in quality of life. Short-term consequences include drowsy driving-related motor vehicle accidents, impaired sexual life, increased stress responsibility, mood disorders, emotional disturbances, somatic symptoms, attention and concentration deficits, impaired work performance, disturbed social and personal life. Long-term consequences include a broad range of chronic medical illnesses like diabetes mellitus, hypertension, obesity, cardiovascular disorders, malignancies etc. [2].

30.6.1 Insomnia

It is an opinion and experience shared by both doctors and patients that insomnia has a negative impact on quality of life of an individual. Enough research evidence is available to support the shared opinion. A systematic review conducted by Ishak et al. in 2012 [15] included 58 studies over 25 years (1987–2012), revealed that insomnia adversely affects an individual's personal, social, occupational life, thereby impacting overall quality of life. Most of the studies included in this review used SF-36 to assess QOL and reported reduced QOL in all eight dimensions of QOL measured by SF-36. Using Nottingham Health Profile and Sickness Impact Profile, reduced QOL as a function of insomnia was found to be comparable to reduced QOL due to chronic medical illnesses. The review summarised that insomnia negatively affects and impairs quality of life of an individual and with increasing severity of insomnia, QOL may get impaired further. This impairment may be attributed to dysfunction in social and occupational areas as evidenced by reduction of work productivity, frequent absenteeism, impaired cognition and disturbed mood and increased morbidity of psychological and physical illness leading to a greater healthcare burden due to chronicity of illness and direct and indirect costs to society [15].

Clinical review conducted by Kyle et al. [58] on health-related quality of life (HRQOL) in insomnia populations with or without comorbidities highlighted the pervasive negative impact on HRQOL across not only domains of vitality and energy but also other mental, social and physical functioning domains of SF-36. This result holds to varying degrees even after controlling for comorbidities like breast cancer and Parkinson's disease. They also established an association between worsening HRQOL across all eight domains of SF-36 (physical functioning, role functioning—physical, role functioning—emotional, mental health, social functioning, bodily pain, vitality and general health) with increasing severity of insomnia, with such associations consistent even after controlling for both mental and physical comorbidities of insomnia [58].

30.6.2 Obstructive Sleep Apnoea (OSA)

Multiple studies have been conducted on quality of life in patients with OSA across the world. Most of the studies have reported significant reduction in physical, mental and psychological aspects of quality of life in these patients. Initially, QOL assessment in sleep apnoea was done only for research purposes, but with the advent of science, the importance of QOL assessment in clinical practice has been recognised. Impaired QOL may be an indication to start continuous positive airway pressure (CPAP) therapy in OSA patients. QOL can also be used to monitor treatment response.

According to a systematic review conducted by Moyer et al. [61], SF-36 demonstrated lower QOL repeatedly across multiple dimensions with 'vitality' demonstrating closest proximity with sleep-related disorders. Similar results have been replicated in studies on QOL in OSA in the last two decades. In a study conducted by Asghari et al. [57], QOL was assessed using WHO QOL-BREF on 502 patients and reported that QOL score in physical domain was significantly reduced in OSA patients as compared to normal healthy population data. Body mass index and Epworth sleepiness scale score negatively correlated with physical and mental domains of WHOQOL-BREF.

In a systematic review conducted by Dutt et al. [62] in 2016 including studies from 1990 to 2015, authors reported significant impairment of HRQOL in OSA. Mental health component, especially vitality, was found to be the best generic QOL instrument in this review as well.

Both the above-mentioned reviews interestingly revealed that impairment in QOL is not directly proportional to severity of OSA as given by Apnoea-Hypopnoea Index (AHI) that is currently considered as a measure for the severity. Even no other polysomnographic variable has been consistently found to be associated with QoL impairment. It appears that HRQOL deteriorates up to a certain extent with increasing Respiratory Disturbance Index (includes apnoeas, hypopnoeas, respiratory event-related arousals), but later plateaus [62].

30.6.3 Restless Leg Syndrome

Multiple scales have been developed to assess QOL in RLS patients like RLS-QOL questionnaire [59], RLS-QLI (RLS-QOL Instrument) [63], but are not widely used. RLS has an impact on quality as well as quantity of sleep due to disruption in sleep structure and sleep fragmentation. A review article by Zucconi et al. concluded that moderate to severe RLS has a detrimental effect on QOL with prominent reductions in scores on scales measuring vitality/energy and limitation of work and activities [64].

RLS has been found to affect all domains of SF-36 and impairment in QOL is to a similar degree as with chronic illnesses like depression, diabetes mellitus (type 2) and osteoarthritis. Sleep disturbances have been implicated as one of the important

contributors to impairment in QOL in RLS patients. Sleep disturbances also affect cognition which may further reduce QOL [65].

In a study conducted in Spain, the QOL in adult cases of RLS was found to be poorer in comparison with controls, especially in women. In the same study, RLS was found to be associated with depression-anxiety, with a significant impact on sleep, on social and work relationships. Around 11% of the cases were so impaired that RLS made it difficult for them to work [66].

In a study conducted by Sander et al. [67] in 2016, 24 children and adolescents of 383 were diagnosed as a case of RLS according to criteria for definite RLS in children recommended by IRLSSG. Both the groups were assessed on paediatric QOL inventory which is a 23-item self-report scale with four subscales—physical, emotional, social and school functioning; and a total score. QOL was found to be significantly less in RLS children as compared to controls with physical, emotional and overall functioning being affected.

30.7 Effects of Treatment on Quality of Life in Patients with Sleep Disorders

30.7.1 Insomnia

As mentioned above, insomnia affects almost all the domains of QOL and impairs a person's personal, social and occupational life. So it appears that improvement in insomnia should also improve the QOL of an individual. Adequate data on this are not available till date. In most of the studies, generic instruments have been used to assess change in QOL over time which are although specific to detect impaired QOL as compared to healthy population and as compared to other illnesses but not sensitive enough to assess changes with time and treatment response. Research using disease-specific scales sensitive to detect changes over time and treatment response is the need of the hour.

Literature review conducted by Krystal et al. included 19 treatment studies of insomnia and its effects on deficits in QOL in patients of insomnia. The review concluded that treatment modalities, both pharmacological and non-pharmacological, lead to improvement in at least one of the affected domains of QOL as compared to placebo and can improve the perceived QOL and functioning of the patient [68].

According to a review by Kyle et al. [58], successful treatment of insomnia may have a positive impact on the functioning of an individual and his quality of life. A review that included studies conducted over 25 years (1987–2012) concluded that sleep restoration methods, both pharmacological and non-pharmacological, improve health-related QOL (HRQOL); however, medication-related side effects may affect the QOL negatively. But generalisation of these results is still questionable due to dearth in the research in this field [15].

30.7.2 Obstructive Sleep Apnoea

As mentioned earlier, disease-specific scales are sensitive to measure changes in QOL over time and treatment outcomes. But SF-36 has been found to be sensitive in assessing treatment outcomes as replicated in various studies that CPAP therapy for OSA may increase HRQOL scores in SR-36 scale, almost in range of population norms [61].

The effect of treatment on QOL in OSA patients is still a debatable topic and has not been worked up convincingly. Disparate results have been obtained in various studies with some studies showing improvement in QOL with CPAP (continuous positive airways pressure) treatment to an extent that it reaches at the levels of healthy controls whereas no improvement in QOL was seen in other studies. In a number of studies, the issue of compliance has not been taken into consideration adequately neither the adjustments to consider compliance have been made nor, hence, the results do not answer the question in hand adequately and appropriately. A review conducted in 2016 suggested that CPAP treatment improves QOL at least in moderate to severe OSA patients [62]. A meta-analysis conducted in 2017 [69] suggested that both CPAP and Mandibular Advancement Device improve health-related QOL in OSA, whereas meta-analysis of 13 RCTs conducted in 2019 [70] concluded that CPAP may impact physical symptoms of OSA, but has no significant impact on psychological QOL.

A Cochrane review conducted in 2006 which included randomised trials of minimum intervention period of 2 weeks of nocturnal CPAP with an inactive control or oral applications in adults with OSA concluded that CPAP is effective in reducing daytime sleepiness and improves QOL in people with moderate to severe OSA [71].

A systematic review was conducted by Merino et al. in 2016 impact of CPAP therapy on HRQOL in elderly patients with OSA. Only two studies were included with 69.6% adherence (over 3-month follow-up) in one study and 35% adherence (over 12-month follow-up) in another. They concluded that use of CPAP in elderly can have a positive impact on HRQOL with remarkable differences in domain of vitality or energy and improvement in both diurnal and nocturnal symptoms [72].

30.7.3 Restless Leg Syndrome

Treatment of RLS with L-dopa and dopaminergic agonists (DAs) ameliorates symptoms of RLS both during sleep and wakefulness. Looking at effect of RLS on QOL, we may presume that treatment of RLS should have a positive impact on QOL, but the effect may take several weeks to appear. To assess the effects of treatment on QOL, long-term studies are required. Most of the studies conducted on treatment of RLS are short term and hence are unable to assess the impact of treatment on QOL. Very few long-term studies have been conducted to assess effect on QOL as one of the important outcomes of studies. According to a review conducted by Zucconi et al. [63], dopaminergic treatment was found to improve QOL, when QOL was measured using disease-specific scales—John Hopkins

RLSQoL, QOL RLS questionnaire; and generic scale—mental health, social functioning and vitality domains of SF-36 [64].

A randomised controlled trial compared efficacy and tolerability of ropinirole (up to 0.5 mg/day), bupropion (300 mg/day) and combination of elemental iron (150 mg) and folic acid (500 μg). Patients were followed up to 6 weeks. This study demonstrated improvement in RLS-related QOL in all three groups across time but did not show any differences in QOL across groups implicating that all the three modalities are equally effective in terms of improvement of QOL in RLS patients [73].

According to Kalloo et al. [74], patients QOL is impacted by pharmacological treatment of RLS, but these medications have various adverse effects which may have a negative impact on QOL. But to derive conclusions about the overall impact of treatment on QOL and to generalise the conclusions, further long-term research studies are warranted.

30.8 Conclusions

Sleep disorders involve multiple areas of an individuals' life and have an impact on cognitive performance, work, education, sexual life, interpersonal relationships, leisure activities, general physical and mental well-being. Impact of sleep disorders has been known even before the advent of specific QOL measures for sleep disorders. Impact of an illness and impact of treatment of an illness on QOL have become an important clinical marker today which helps a clinician to decide the need for starting and continuing treatment taking care of the impact treatment modalities have on QOL. Hence, QOL in sleep disorders is a research question which is inadequately answered till date but also an important clinical measure which needs further development and assessment.

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Part IV

Sleep and Neurological Disorders

Sleep in Parkinson's Disease

31

Anjali Gera and Cynthia Comella

Abstract

Parkinson's disease (PD) is a neurodegenerative condition that can present with a constellation of other symptoms that are defined as "non-motor." Sleep problems are one of the prominent and frequently (nearly 64%) reported non-motor symptoms. Sleep fragmentation may arise because of pain, dystonia, bradykinesia, and neurodegeneration. Similarly, excessive daytime sleepiness (EDS) can be multifactorial in etiology in PD, including being a result of sleep fragmentation at night and primary sleep disorders that are often seen in PD (including periodic limb movement, obstructive sleep apnea, and circadian rhythm disorders). Few genome-wide association studies have been done among patients with PD having sleep disorders. Thus far, there is no association for genetic predisposition to PD and OSA, EDS, and RLS or PLMS, although additional studies are needed. This chapter discusses these issues in detail along with management strategies for the sleep disorders in PD.

Keywords

Parkinson's disease · Pathophysiology · Insomnia · RLS · Genome-wide studies · OSA · Daytime sleepiness

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31.1 Introduction

Parkinson's disease (PD) is a neurodegenerative condition which is diagnosed by its clinical presentation with bradykinesia as the key feature and including at least one of the following: tremor, rigidity, and postural instability. However, PD also includes—and can present with—a constellation of other symptoms that are defined as "non-motor." These include fatigue, anxiety, depression, constipation, pain, autonomic dysregulation, and disturbances in sleep. Some studies have suggested that the presenting symptoms of PD can be non-motor. Non-motor symptoms can present in the absence of the cardinal features of PD, and one study of 433 PD patients found that 21% of patients with PD presented with non-motor symptoms [1].

Disturbances of sleep in PD were first described by James Parkinson over 200 years ago. Sleep disturbances are now recognized as one of the most frequent non-motor symptoms of PD and can occur in up to 64% of patients with PD [2, 3]. Table 31.1 includes some of the sleep disorders that can be seen in PD. Sleep disorders, along with other non-motor symptoms, have the propensity to become increasingly disabling with a significant impact on quality of life with greater severity and duration of disease.

31.2 Sleep Fragmentation

Difficulty with sleep maintenance, or sleep fragmentation, is one of the most common problems with sleep in PD, occurring in 81% of PD patients in one study involving 689 participants [4]. The most common cause of sleep fragmentation in patients with PD is due to the motor and non-motor symptoms—which often increase in severity—at night. Patients can be awakened due to their tremors reappearing in the earlier stages of sleep. Bradykinesia and rigidity can make it very difficult for patients to turn in bed or get out of bed at night in particular, when their dopaminergic medications wear off a few hours after their last dose of the day. Pain can disrupt sleep, which is another non-motor symptom that can accompany motor symptoms of PD, including dyskinesias, dystonia, or be a result of rigidity, including shoulder pain due to chronically reduced arm swing and rigidity. Several

Table 31.1 Sleep disorders in PD

Sleep fragmentation
Excessive daytime sleepiness
Obstructive sleep apnea
REM sleep behavior disorder
Restless legs syndrome
Altered sleep-wake cycle
Periodic limb movements
Nocturia
Circadian rhythm disturbances

antiparkinsonian medications have stimulant properties which can contribute to sleep fragmentation, including the carbidopa-levodopa controlled-release formulation, intake of regular levodopa when nocturnal motor symptoms occur, dopamine receptor agonists, and the monoamine-oxidase type B inhibitor selegiline (which has a methamphetamine metabolite). Immediate release dopaminergic therapy should be avoided close to bedtime and selegiline should be given in the morning hours. Evidence regarding the impact of surgical options on sleep in Parkinson's disease patients, in particular deep brain stimulation of the subthalamic nucleus, is conflicting at this time.

Patients can also have disrupted sleep due to other non-motor symptoms that can be seen in PD, including anxiety and depression. Treatment of anxiety and depression as it contributes to sleep fragmentation in PD can include mirtazapine. In addition to treating anxiety and depression, mirtazapine has been reported to help parkinsonian symptoms including rest tremor and levodopa-induced dyskinesias, and can also help boost appetite, another non-motor symptom commonly seen in PD [5, 6].

Practicing good sleep hygiene and keeping an optimal sleeping environment are especially important for patients with PD. Exercise in the morning or late afternoon can help promote sleep, while vigorous exercise later in the day can disrupt sleep and should be avoided. Ensuring adequate exposure to light during the day, especially for elderly patients who may not be able to go outside on their own, is important for maintaining a healthy sleep-wake cycle. Television or use of electronic devices should be avoided prior to bedtime or when one has difficulty falling back asleep in the middle of the night, as the light from the screens can further disrupt the sleep-wake cycle. Light shining into the room (including from under the bedroom door or between the shades) and light from electronics must be minimized. This includes turning an alarm clock away from the face, turning off cell phones or placing them face down (with vibrations off), shutting off computers, and covering small but bright lights on surge protectors, fans, humidifiers, and air purifiers with dark tape or sticker scan all help darken the bedroom to optimize the sleep environment. If a caregiver or partner is working and waking up with an alarm before the patient, vibrating wristwatches can be used for silent alarms that will not also wake the patient. Sudden noises such as a semi or an ambulance passing by at night, or a snoring partner in bed can all be minimized with a white noise machine, a fan, or ear plugs. We also recommend to avoid taking naps during the day, exercising in the evening, or eating a heavy meal before bedtime. Caffeine, nicotine, and alcohol should also be avoided close to bedtime. If one has trouble falling back asleep for more than 20 min, then the patient should get out of bed and do a quiet, relaxing activity such as stretching or reading.

31.3 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) can be multifactorial in etiology in PD, including being a result of sleep fragmentation at night and primary sleep disorders that are often seen in PD (including periodic limb movement, obstructive sleep apnea, and circadian rhythm disorders). Patients with PD have been reported to have an increased need for sleep as well.

EDS can significantly impact quality of life for not only patients with PD but also their caregivers, as these patients are sleeping during the day and awake at night. EDS can be seen in about 16–55% of patients with PD [7], and its frequency increases with disease duration. In a study of 153 patients, the frequency of EDS increased from 12% at time of diagnosis to 23% at 5 years [8]. This is thought to be related to neuronal loss in the dopaminergic and nondopaminergic brain circuits in the midbrain that are involved in sleep regulation, which is a slowly progressive process that continues throughout the course of PD.

Antiparkinsonian medications can also be associated with EDS, with dopamine agonists more likely to be associated than levodopa [9]. Patients with PD developing dementia may be predisposed to more drowsiness following each dose of levodopa. Reducing the dose of levodopa or replacing with carbidopa-levodopa controlled-release (and therefore allowing a slower rise of levodopa levels) can help with this problem.

31.4 Obstructive Sleep Apnea

It is controversial if obstructive sleep apnea (OSA) is more prevalent in PD compared to the general population. In fact, while many patients with PD also have OSA, most trials suggest that the prevalence of OSA is the same in the PD and general population [10]. Some studies have suggested that the prevalence of OSA may be lower than in the general population, which has been attributed to a lower body mass index of the PD patients [11]. On the other hand, there are many factors in PD that can predispose these patients to OSA, including aging [12], upper airway obstruction and restrictive lung disease due to hypokinesia and rigidity [13, 14], and autonomic dysfunction [15].

31.5 REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is associated with the development of neurodegenerative diseases. RBD without atonia is primarily associated with the synucleinopathies including PD, multiple system atrophy, and Lewy body dementia [16, 17]. RBD can precede or follow the onset of motor symptoms of PD. RBD is characterized by the loss of atonia that normally occurs during REM sleep and therefore is defined as an REM sleep parasomnia, in which abnormal behaviors occur during REM sleep. Patients with RBD experience vivid, distressing, and often

violent dreams (including of being chased or attacked). Bed partners and caregivers may note that the patient appears to be acting out dreams, such as talking or shouting or having more aggressive behaviors such as kicking, punching, and sometimes falling out of bed. Patients often are unaware of these events. RBD can lead to injuries to both the bedpartner and the patient.

While the precise prevalence of idiopathic RBD is not known, it is estimated to be about 42% in patients with PD [18]. Increased age is significantly associated with primary RBD. A majority of these patients are male, although the reasons behind the significant difference in gender are not clear. In one study of 45 patients with PD, eight participants (or 17.8%) had RBD preceding the onset of parkinsonism [19]. Eighty-six percent of these 45 participants recalled having frightening dreams. Indeed, several reports suggest a high rate of conversion of RBD to a synucleinopathy (PD, multiple system atrophy, or dementia with Lewy bodies), with risk estimates ranging between 20–45% by 5 years and 40–65% by 10 years [20, 21]. Another longitudinal study conducted postmortem quantitative analyses for alpha-synuclein on 40 PD patients with RBD and 41 PD patients without RBD revealed that PD patients with RBD had greater density and range of alpha-synuclein pathology on autopsy [22].

Neurons that induce REM sleep paralysis are thought to be involved in the pathophysiology of RBD. These neurons play a role in inducing REM sleep paralysis by (1) sending inhibitory GABAergic and glycinergic inputs to spinal cord motor neurons, (2) sending excitatory glutamatergic projections to the spinal cord interneurons which then inhibit the motoneurons, and (3) decreasing activity in the red nucleus, resulting in atonia [23]. Animal studies of rodents and cats as well as postmortem studies in humans have suggested that RBD is caused by dysfunction of the subcoeruleus nucleus and nuclei in the ventral medial medulla [24–26]. The pathophysiology of RBD is thought to be due to impaired GABAergic and glycinergic neurotransmission from the ventral medial medulla and glutamatergic neurotransmission from the subcoeruleus nucleus and the ventral medial medulla. An alternate pathophysiology has also been described to be secondary to damage to pathways that connect the subcoeruleus nucleus and ventral medial medulla to the dorsolateral hypothalamus and the limbic system.

Treatment of RBD is dependent upon its severity and its impact on the patient and the patient's bedpartner. If the RBD symptoms are resulting in injury and/or are bothersome to the patient or family, it is important to first caution the patient and bedpartner about protective measures, including moving furniture away from the bed, and pillows or other protection for the bedpartner if they are in the same bed. There are no controlled studies of oral pharmacologic agents. Initial treatment is melatonin starting at 3 mg, to be taken 60 min prior to bedtime [27]. Melatonin can be slowly titrated upward to 12 mg every evening. Usually, the patient is advised to gradually increase the dose at 1- to 2-week intervals, and should be attempted for at least 4–6 weeks. If no improvement with melatonin, clonazepam is used starting at 0.25 mg at bedtime, with slow uptitration to 2 mg at bedtime under close guidance by the physician. It is reasonable to reach the highest tolerable dose of either drug that reduces symptoms while minimizing side effects. Importantly, the physician should

set reasonable expectations for the patient and family that neither drug is likely to completely resolve RBD. Other drugs that have been reported to be of some benefit include the cholinesterase inhibitors donepezil or rivastigmine, although data are limited and conflicting, and therefore, these medications should be considered a third line after melatonin and clonazepam [27].

31.6 Restless Legs Syndrome and Periodic Limb Movements

Restless legs syndrome (RLS) is characterized by an urge to move the lower limbs, which is commonly (but not always) accompanied by uncomfortable and unpleasant "crawling" sensations in the lower limbs. The urge to move the legs and/or the unpleasant sensations can begin or worsen during periods of rest or inactivity and are partially or completely relieved by movement. The sensations are worse in the evening or night in comparison to the day, thus disturbing sleep onset [28].

RLS occurs fairly commonly in patients with PD. In a cohort of 113 patients with PD, 24% had RLS [29]. However, the association between RLS and PD is controversial. Some studies have suggested that RLS is more common in PD patients, while others have suggested its frequency is similar to the general population [30]. Although dopaminergic treatment can help with both RLS and PD, data suggest different pathophysiologic mechanisms. Postmortem examination in a small study of four patients with idiopathic RLS did not reveal Lewy bodies or alpha-synuclein [31]. Iron levels in the substantia nigra are reduced in RLS but increased in PD [32]. Neuroimaging studies using sonography have detected increased echogenicity of the substantia nigra in PD patients but not in RLS patients [33].

Treatment of RLS depends on its severity and if symptoms impair quality of life, daytime functioning, or sleep. Iron levels can be low in RLS and should be evaluated. Low or low normal ferritin levels suggest iron deficiency and can initially be treated with iron supplementation. Iron levels below 45 ng/ml should be treated with iron supplementation orally. If the patient cannot tolerate the iron or if the iron levels do not improve after 3 months, intravenous iron supplementation should be considered. There are two formulations of intravenous iron, namely iron dextran and low-molecular weight iron dextran, the latter of which has a better safety profile and lower risk of anaphylaxis compared to iron dextran.

In the setting of low ferritin levels, the severity of RLS correlates with the degree of ferritin reduction and first-line therapy is the replacement of iron, which has been shown to improve symptoms of RLS if iron deficiency is present [34, 35]. The cause of iron deficiency should also be evaluated. Gabapentin is a reasonable first-line medication and has been shown to be efficacious for the treatment of RLS at a dose of 800 mg and at 200 mg for patients on hemodialysis. Pregabalin is also efficacious for RLS when given at doses between 150 and 450 mg/day, 1–3 h before bedtime. Dopaminergic medications including levodopa, ropinirole, rotigotine, pramipexole, and cabergoline can be used and are likely to be helpful for the patient's PD symptoms. Levodopa is very effective in treating RLS and of course patients with

PD are likely to be on dopaminergic medications. However, chronic use and taking higher doses of dopaminergic medications can lead to augmentation. Risk of augmentation is higher with pramipexole in comparison to the other dopaminergic medications, although augmentation can occur with any dopaminergic treatment including levodopa [36]. Augmentation is an iatrogenic worsening of RLS symptoms following treatment of dopaminergic medications. Augmentation is described by RLS symptoms beginning earlier in the day, having an increased overall intensity of symptoms, shorter latency of symptoms at rest, reduced duration of treatment benefit, or symptoms occurring in a previously unaffected body area. Rebound is another phenomenon that can occur during the night with dopaminergic medications on board. Oxycodone or naloxone can also be used for RLS and is efficacious in patients with severe treatment-resistant RLS; however, special monitoring is warranted in those with addictive tendencies and possible sleep-related respiratory problems should also be monitored.

Medications that can worsen RLS and should be avoided or minimized include serotonin reuptake inhibitors, venlafaxine, and antihistamines. Dopamine receptor antagonists such as antipsychotics and antiemetics (including metoclopramide) should be avoided.

Periodic limb movements (PLMs) are movements that occur during sleep and are characterized by a stereotyped and repetitive pattern. PLMs may or may not co-exist with RLS and might be indicative of genetic susceptibility to RLS. Indeed, up to 80% of RLS patients may also suffer from PLMs [37]. A polysomnogram may reveal PLMs that can occur in the absence of RLS. The prevalence of PLMs in PD patients is comparable to the general population [38]; however, PLMs have been reported to occur with increased severity of PD [39] and with degree of nigrostriatal degeneration [40]. Interestingly, one study has also suggested that patients with PD who undergo deep brain stimulation surgery may have worsening of their PLMs after surgery, which is thought to be secondary to reduction in dopaminergic therapy following surgery [41].

PLMs are difficult to treat. Patients with PLMs may respond to dopaminergic treatment similar to RLS. They can also respond to pregabalin, gabapentin, or duloxetine.

31.7 Nocturia

Nocturia is characterized by a higher than average need to urinate during the night. Nocturia significantly impacts the continuity and therefore the quality of sleep in patients with PD, as patients can have difficulty with falling back asleep after waking up (often multiple times) at night to urinate. In fact, nocturia is one of the most common non-motor symptoms in PD patients and can affect 60–80% of patients with PD [42–44]. The odds of developing nocturia in PD are higher with increasing disease stage [45], increasing age and with male gender [46]. One cross-sectional study of 70 patients with a diagnosis of PD found an association between taking dopaminergic agonists and a lower presence of nocturia in comparison to patients on

levodopa [47]. This finding was initially thought to be due to the patients with PD who are on dopamine agonists being younger in age and having shorter disease duration in comparison to those on levodopa; however, when patients were subdivided according to whether they were on dopamine agonists as a monotherapy or combined therapy, the patients who were on combined dopamine agonist therapy had a lower presence of nocturia compared to those on levodopa as monotherapy despite being of an older age and having a longer disease duration [47].

The initial approach to nocturia should begin with investigating for the cause of nocturia (in addition to PD). Neurogenic detrusor overactivity is the most common cystometric abnormality in PD patients [48]. However, nocturia can be due to other causes in patients with PD. For example, patients with OSA have greater risk to develop nocturia [49] and patients with OSA who used continuous positive airway pressure had a statistically significant decrease in the number of nocturia episodes, with good to complete elimination of nocturia in 75% of the 97 patients in one study [50].

Nonpharmacologic treatment should be the first line of therapy in PD patients with nocturia. Evening alcohol and caffeine should be avoided. Water intake should be limited for 2–3 h prior to bedtime. However, it is important to emphasize to keep well hydrated during the morning and afternoon hours as patients with PD tend to be more sensitive to postural changes and are more predisposed to orthostatic hypotension, but to limit fluid intake closer to bedtime. Anticholinergics, alpha blockers, and 5-alpha reductase inhibitors may be attempted although with great caution given patients with PD are more prone to side effects from these medications given the autonomic dysfunction (including orthostatic hypotension, erectile dysfunction, and dry mouth) that can occur with PD. Referral to a urologist would be advisable in those with persistent or refractory nocturia.

Neuromodulation, including sacral nerve modulation, has been used as a treatment for detrusor overactivity in patients with PD; however, long-term efficacy still needs to be determined for patients with PD [51]. In addition, one study reported improvement of detrusor overactivity with stimulation of the posterior tibial nerve [52]. Interestingly, deep brain stimulation of the subthalamic nucleus has been reported to improve urinary symptoms in PD [53], with stimulation of the subthalamic nucleus having effects of inhibiting micturition [54].

31.8 Genetic Association Between PD and Sleep Disorders

Few genome-wide association studies have been completed in sleep disorders. Thus far, there is no association for genetic predisposition to PD and OSA, EDS, and RLS or PLMS, although additional studies are needed. However, there is convincing data of at least a partial genetic association between PD and RBD. Given that a majority of patients who develop RBD also develop a neurodegenerative synucleinopathy, a genetic association between PD and RBD is unsurprising. The strongest genetic association reported thus far is associated with mutations in the *glucocerebrocidase* (*GBA*) gene [18, 55]. Both *GBA* and RBD are associated with autonomic

dysfunction [56], more severe motor disease [56, 57], and more aggressive cognitive decline [58]. *GBA* mutations have been reported to be specifically associated with the RBD subtype of PD more so than with idiopathic RBD. From a pathophysiological point of view, both RBD-associated PD and *GBA*-associated PD likely have a more diffuse spread of alpha-synuclein accumulation [22, 59]. The *GBA* mutation is indeed currently in the spotlight and studies thus far are strongly suggestive [60], but more studies are needed to confirm the association between *GBA* and RBD.

On the other hand, *LRRK2* mutations have not been found to be associated with RBD in PD patients [61]. Patients with PD due to LRRK2 mutations tend to have a less aggressive course with a less rapid cognitive decline, less autonomic dysfunction, and less RBD [62, 63].

31.9 Circadian Disruption in PD

Recent literature suggests that there may be a disruption in circadian rhythm in PD [64]. This disruption is not surprising given the role of dopamine on the circadian regulation and may be a result of differences in neuronal firing in the suprachiasmatic nucleus found in animal models of PD [64]. Compared to healthy controls, the circadian rhythm of hormonal markers including melatonin is blunted in PD patients [64], which can contribute to excessive daytime sleepiness in PD patients.

There exists a growing literature on treatments focused on circadian rhythm in PD, namely light therapy. Light therapy is a noninvasive and nonpharmacologic treatment that is becoming increasingly utilized for sleep dysfunction (and even motor symptoms and other non-motor symptoms such as mood) in PD [65, 66]. Light therapy (LT) is administered most commonly as a bright light, but green and blue light therapy are also used. LT should be given on a scheduled basis and timing is important to avoid phase advances or delays of the circadian rhythm. LT, therefore, should be administered right after usual wake time or around the time of usual sleep time.

31.10 Conclusion

Problems with sleep are a very common non-motor symptom of PD and can be caused by multiple different sleep disorders that are seen with PD, including sleep fragmentation, excessive daytime sleepiness, obstructive sleep apnea, REM sleep behavior disorder, restless legs syndrome, altered sleep-wake cycle, periodic limb movements, and nocturia. Circadian disruption also likely plays a major role in contributing to several of these sleep disorders. All of the sleep disorders seen in PD can cause significant disability in these patients as their disease progresses. Both pharmacologic and conservative, nonpharmacologic therapies are available for all of these sleep disorders, prompting early evaluation and diagnosis of sleep disorders in PD patients. A growing body of literature reveals several genetic associations

between sleep and PD. Knowledge about genetic mutations and their association with sleep in PD is likely to help with prognosis and set expectations for disease course including the development of sleep disorders and will hopefully lead to individualized therapeutic approaches such as gene therapy in the future.

Key Points

1. Sleep disorders in patients with PD have the propensity to become increasingly disabling with a significant impact on quality of life with greater severity and duration of disease.
2. Pharmacologic and nonpharmacologic treatments are available for all of the sleep disorders seen in patients with PD; hence, an early evaluation and diagnosis of sleep problems in PD patients is warranted.
3. Increasing our knowledge regarding genetic associations with sleep in PD is likely to help predict specific types of sleep disorders seen with specific genetic mutation carriers and allows an individualized therapeutic approach in the future.

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Sleep After Traumatic Brain Injury

32

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Abstract

Changes in the quality and structure of sleep have been recognized as a manifestation of alterations in functioning of neurons and their synapses due to traumatic brain injury (TBI). Recent developments in research methodology, electroencephalography, and brain imaging techniques are helping to confirm these changes. Clinical and epidemiological studies also starting to clarify the impact of changes in sleep quality and structure on daytime functioning of persons with TBI, making sleep disorders widely regarded as an important focus for clinical assessment. This chapter provides a deeper look into sleep disorders in TBI and their sophisticated taxonomy engendered by advances in sleep medicine.

Keywords

Traumatic brain injury · Sleep quality · Sleep disorders · Hypersomnia · Insomnia · Sleep-apnea

32.1 Epidemiology of Traumatic Brain Injury

Traumatic brain injury (TBI) is among the most disabling injuries affecting many individuals in the prime of their life [1–3]. Concern about TBI related to expansion of industrialization and armed conflict has led to increased interest in the

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epidemiology of TBI in civilians and among service members [2]. Published estimates of TBI vary worldwide, though when estimates from studies with comprehensive data collection methods are extrapolated internationally, reports suggest that 50–60 million persons are affected annually [3]. The pooled international incidence rate of TBI (excluding TBI with no overt pathologic features) is reported to be a staggering 349 (95% confidence interval (CI) 96–1266) per 100,000 person years [4]. A majority of the TBIs sustained are mild in severity (mTBI), occurring at an annual incidence of 224 (95% CI 120–418) per 100,000 person years, almost 10 times higher than the incidence of moderate TBI and 17 times higher than that of severe TBI [4].

The epidemiology of TBI is largely dependent on the definition used. Definitions of TBI vary, but all describe structural and/or physiological disruption of brain function as a result of an external force [1–3]. The most common means of defining injury are clinical classification systems, the Glasgow Coma Scale [5], and the American Academy of Neurology grading system [6], which define severity of TBI based on the duration of altered mental state and posttraumatic amnesia. Pathological classification is based on classic pathophysiological findings (e.g., brain contusion, concussion, diffuse axonal injury, hematoma, etc.) as well as physiological processes after the primary impact or secondary pathological processes that follow [7]. The mechanistic classification of TBI is based on the cause of injury (e.g., fall, struck by or against and object, exposure to explosion, etc.) and site of impact (e.g., force loading) [7]. These classification systems point to the complexity of TBI and the value of looking beyond acute presentation and presence/absence and durations of phenomena and taking into account accelerating/decelerating forces that can cause mechanical strain; the direction of the force that can pinpoint the site of impairment and suggest site of potential shear-induced tissue damage as a result of rapid head and upper body rotation, and the complex metabolic and neurochemical cascades occurring in neurons following stretch and compression [8]. Table 32.1 highlights the mechanisms of neuronal damage in TBI and measures and techniques used in neuropsychiatric assessment.

Another obstacle in the study of TBI and its consequences has to do with the time at which signs of injury appear or symptoms develop [10]. Diagnosis of TBI by a healthcare professional most often occurs when the signs and symptoms are present early after the injury [10]. However, it is known that some signs of a TBI, especially as it concerns mild TBI/concussion [9], do not appear immediately, but can present days or even weeks after the injury [11]. Such delayed manifestations of injury can include psychiatric disorders that come about as a result of injury to the brain, including sleep disorders, which may not be recognized as stemming from a brain injury either by the person experiencing them or by the healthcare professional assessing that person [12]. The long-term manifestations of injury depend on a number of different factors that are unique to an injured person. These factors are related to the injury itself (e.g., severity, mechanism of injury, location of injury, or concurrent injuries), the sociodemographic (e.g., age or race) [1], and socioeconomic (e.g., employment or income) characteristics of the person affected, the number and types of comorbid disorders that may be affecting the person at the time of injury or

Table 32.1 Measures/techniques often used in assessment of traumatic brain injury

Clinical assessment	Assessment based on mechanism of neuronal damage
Severity of injury based on: • Loss of consciousness (LOC) • Alteration of consciousness/mental state • Posttraumatic amnesia PTA) • Brain imaging findings (CT, MRI with FLAIR, fMRI, rCBF, PET, DTI, MRS) • Electrophysiological assessment (EEG, BEAM) • Neuropsychological assessment Behavioral assessment: • Glasgow coma scale (GCS) (eye opening (E), best motor response (M), verbal response (V); coma score = E + M + V) • Rancho Los amigos cognitive scale • Brain injury screening questionnaire • Rivermead post-concussion symptoms questionnaire • Neuropsychiatric inventory • Galveston orientation and amnesia test	Mechanistic assessment based on: • Site of impact; penetrating injuries • Force loading and direction • Cause of injury (struck by or against an object, falls, assaults, exposure to explosion, etc.) Primary effects: • Contusions; concussions • Diffuse traumatic axonal injury (shearing lesions) Secondary effects: • Hematomas (epidural, subdural; acute, and chronic) • Cerebral edema • Increased intracranial pressure • Hydrocephalus • Hypoxia • Inflammatory response • Neurotoxicity and other cellular responses

Abbreviations: *CT* computed tomography, *MRI* magnetic resonance imaging, *FLAIR* fluid-attenuated inversion recovery, *fMRI* functional magnetic resonance imaging, *SPECT* single-proton emission computed tomography, *rCBF* regional cerebral blood flow, *PET* positron emission tomography, *MRS* proton magnetic resonance spectroscopy, *DTI* diffusion tensor imaging, *EEG* electroencephalography, *BEAM* brain electrical activity mapping

after the injury (e.g., substance use and addictions), as well the person's sex/gender [13–17]. As such, this chapter will adopt the view of TBI as a disease process triggered by injury to the brain rather than an event, with the understanding that the course and duration of the recovery process depend on the interaction of a number of factors unique to each person [18].

32.2 Sleep and Psychiatric Disorders After TBI

TBI of any mechanism and severity at least temporarily disrupts processes within the brain circuits involved in sleep and wake regulation through interruption of neuronal inputs and outputs [19]. These disruptions may involve homeostatic (e.g., drive to sleep after a prolonged period of wakefulness) [20] or circadian processes (e.g., via a master pacemaker of an organism, which is driven by the light-dark cycle) [21], or most likely both because they are tightly linked [22]. Current hypotheses suggest that sleep and wakefulness are generated by activity in the axial core of neurons extending from the brainstem to the basal forebrain and that sleep-promoting neurons are spatially intermingled with wake-promoting neurons [23]. Consequently, the external forces involved in TBI, producing either local or diffuse disruptions in

these sleep- and wake-regulating circuitries [24], can produce a range of clinical manifestations.

Of the essential human functions most frequently compromised by TBI are those related to emotional, drive-related, and motivated aspects of behavior [25], which are functions of the limbic system (i.e., the hippocampus, amygdala, and septal nuclei). These brain structures are highly interconnected among themselves, the associated areas of the cortex (particularly prefrontal cortex) and the hypothalamus, which plays a key role in neuroendocrine, autonomic, and homeostatic functions including the sleep-wake cycle [26]. An external force to the head generates a sudden movement of the brain within the cranium, with rotation of the cerebral hemisphere on the relatively fixed brainstem, and such force has been shown to initiate complex metabolic changes within various structures of the brain and their endogenous substances (e.g., serotonin and dopamine among others) [27–29], believed to be essential in the regulation of sleep, mood, and behavior. Disruption of the brain regions regulating sleep, mood, and behavior after TBI underlies a wide range of post-injury comorbidities (e.g., sleep disturbance, mental disorders, and abnormal behavior) [30]. This observation is quite remarkable and has important implications for TBI research and practice, because it points to the conceptual unity of post-injury sleep disorders, psychopathology, and behavioral disorders. The emerging work on the interrelationship of these systems in TBI is providing potential avenues for the development of clinical approaches that are directed toward sleep and wakefulness pathology after TBI.

32.3 Presentation and Classification of Sleep Disorders

Broadly, TBI patients may present with concerns related to sleep as either inability to sleep adequately at night, excessive daytime sleepiness (fatigue, cognitive impairment, etc.), and/or behavioral abnormalities arising from sleep itself [31]. These disturbances may occur singly or in combination, and may be transient or long term [32]. A careful history taken from a patient and a significant other or family member that captures the duration, severity, and consistency of symptoms is essential in the evaluation of a TBI patient; all symptoms should be viewed as manifestations of underlying disorders, much like pain or fever (Fig. 32.1). Knowledge of classification of sleep disorders is essential for the differential diagnosis of sleep-related symptoms to identify the underlying disorder followed by targeted disorder-specific treatment, rather than nonspecific approaches. The International Classification of Sleep Disorders (ICSD) [33] describes and provides diagnostic criteria for all of the recognized adult and pediatric sleep and arousal disorders (right part of Fig. 32.1).

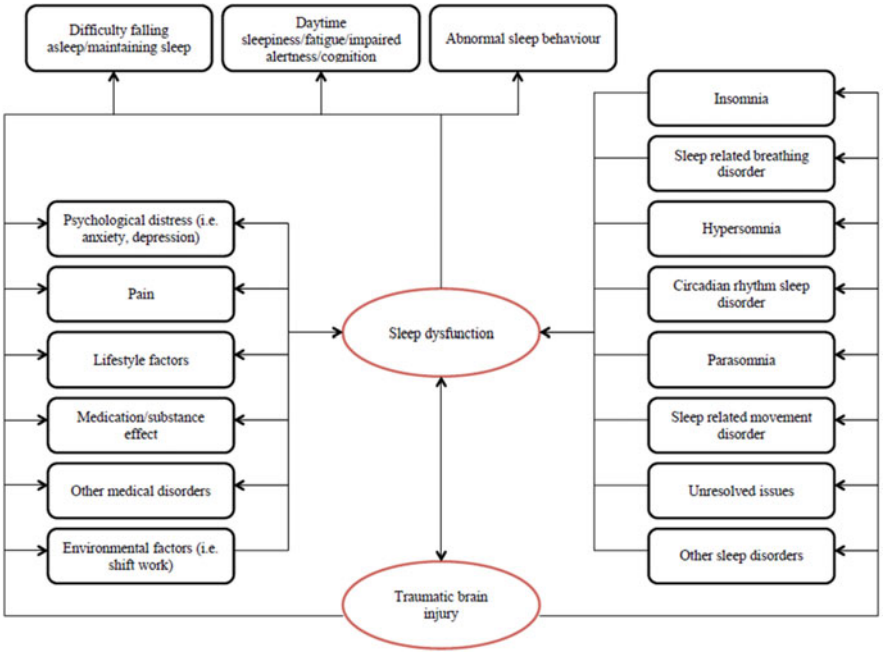

Fig. 32.1 Construct of sleep dysfunction in traumatic brain injury. Reprinted from sleep and psychosomatic medicine, Chap. 16, Mollayeva & Shapiro [32]

32.3.1 Insomnias

Insomnia is the complaint of persistent sleep difficulty despite adequate opportunity and circumstances for sleep, accompanied by daytime consequences [33]. Historically, the nature of insomnia provided important information about its possible etiology, which was central to the selection of specific and appropriate treatment. The most current classification system, ICSD-3 [33], has eliminated presumed etiology and employed a diagnosis of chronic insomnia disorder, which includes all insomnia of at least a 3-month duration, regardless of presumed etiology. Insomnia of less than 3 months is classified as short-term insomnia [33]. A recent diagnostic modeling study of middle-aged men and women with an established diagnosis of mTBI/concussion based on clinical history, neuroimaging results, and neuropsychological and multidisciplinary assessment [34], highlighted insomnia, as measured by the Insomnia Severity Index, as a nonhomogeneous construct, tightly linked to older age, bodily pain, depression, instability of bed time and wake time, napping during the day, and use of certain psychotropic medications [34]. It is important to note that insomnia severity was lower in the presence of previous head injury [34], potentially indicating person's adjustment to sleep difficulties, and therefore lower reactivity and reporting sleep difficulties during assessment, or a greater need for sleep [34]. Other studies of TBI patients support insomnia

increasing steadily with age [35] and being more prevalent in mTBI patients than in moderate to severe TBI patients [36], as well as those with low education and living in poverty, and in those with mental health disorders [34, 37, 38]. The latter is important to consider in a clinical setting when assessing a TBI patient with insomnia, because poverty, unemployment, low literacy, drug use, and mental illness are tightly linked to TBI, both in the preinjury and post-injury phases [37, 38].

32.3.2 Sleep-Related Breathing Disorders

All sleep-related breathing disorders (SRBDs) are characterized by disordered respiration during sleep and are categorized into four groups: obstructive sleep apneas (OSA), central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders [33]. In TBI patients, the prevalence of SRBDs is significantly higher than in the general population, ranging from 25% to 35% compared to approximately 10% in the general population across the lifespan [36, 39, 40]. According to an earlier report, the majority of the events affecting the authors' TBI participants were central in nature rather than obstructive [41], whereas in the general population, sleep apnea consists predominately of obstructive events (e.g., 90%) [42]. The immediate factor leading to collapse of the upper airway in OSA is the generation of subatmospheric pressure during inspiration that exceeds the ability of the airway dilator and abductor muscles to maintain airway stability [43]. Commonly prescribed sedatives, hypnotics, or muscle relaxants in patients with TBI [31, 44] may aggravate the inability to maintain airway stability. Alcohol intake is frequently an important cofactor [45] because of its selective depressant influence on the upper airway muscles and the lower arousal threshold to terminate an apnea episode [46].

The apnea event in CSA results from transient instability in central respiratory drive [47], leading to the abolition of drive to the respiratory muscles. Traumatic brain injury, especially severe cases involving centers in the medulla and pons that regulate vital functions, may produce defects in the metabolic respiratory control system and respiratory neuromuscular apparatus [49]. The clinical picture of CSA, due to instability of respiratory drive, resembles that of insomnia, including frequent awakenings, morning fatigue, and daytime sleepiness, but when CSA is part of hypoventilation syndrome, the clinical picture is dominated by daytime hypercapnia and hypoxemia, pulmonary hypertension, and right-sided heart failure [50, 51]. In diagnostic magnetic resonance imaging (MRI) examinations performed within 8 days of TBI in patients who had been unconscious for more than 24 h post-TBI, the brainstem was multiply affected in almost 60% of participants, with 46% of patients having lesions in the midbrain, 27% in the pons, and the rest in the medulla oblongata [52]. A recent multicenter, observational study of 7287 persons at up to 25 years after TBI who required inpatient acute rehabilitation reported post-injury obesity and overweight prevalence rates of 23% and 36%, respectively, with higher rates for obesity and being overweight associated with increasing time since injury, along with a history of hypertension, heart failure, or diabetes [53]. Obesity

frequently contributes to the reduction in size of the upper airway [54] by increasing fat deposition in the soft tissues of the pharynx or by compressing the pharynx with superficial adipose tissue in the neck, making the airway more prone to collapse and therefore playing a role in SRBDs [55].

32.3.3 Hypersomnia of Central Origin

Hypersomnia disorders primarily involve complaints of excessive daytime sleepiness where the cause is not disturbed nocturnal sleep or misaligned circadian rhythm [33]. Most of these conditions are caused by abnormalities or disorders of the central nervous system (CNS) or are the results of drug or substance effects [33]. Narcolepsy type 1 and type 2 disorders characterized by abnormal transition to rapid eye movement (REM) sleep and excessive daytime sleepiness (EDS) are included among these disorders. When cataplexy is present, the most frequent cause is an immune-mediated destruction of the hypocretin-producing neurons in the hypothalamus [56]. One early study showed damage to the hypothalamus in 42% of deceased TBI patients [57]. Another study of brains at autopsy from four patients who died 7–42 days after severe TBI showed a significant loss of hypocretin-producing neurons in addition to a partial loss of neurons producing melanin-concentrating hormone (MCH) and patchy gliosis throughout the hypothalamus [58]. These results support the hypothesis that severe injury to the brain involves the hypothalamus and suggest that reduced hypocretin signaling may contribute to the persistent sleepiness seen in TBI patients long after the injury. Loss of the MCH neurons may also contribute to the pathophysiology of posttraumatic sleep-wake disturbances because these cells are hypothesized to regulate REM sleep [59, 60]. Recently, new observations of increased sleep need after TBI not accompanied by excessive daytime sleepiness have been reported using the term "pleiosomnia" (i.e., a combination of the Greek word *pleion* [more] and the Roman word *somnus* [sleep]) [61]. A study of 36 patients with an increased need for sleep of more than 2 h compared to preinjury (64% moderate to severe TBI) at 32 months (standard deviation 18 months) post-injury, of whom 15 patients had their cerebrospinal fluid hypocretin 1 measured by radioimmunoassay (e.g., low cerebrospinal hypocretin levels observed in 20%), exhibited an increase in slow wave sleep (N3 sleep), as measured by polysomnography [61]. It is important to note that TBI patients underestimated their increased need for sleep [61]. N3 sleep is currently considered a reliable indicator of net changes in average synaptic density during the night and is a marker of sleep homeostasis [62]. Given the observed associations and considering that slow wave sleep allows for synaptic downscaling, safeguards energy reserves, restores neurotransmitter (and other biomolecular) supplies, and is required to maintain adequate levels of cognitive function, attention to N3 sleep amount [63], which could reflect recovery mechanisms or intrinsic consequences of diffuse brain damage, could be highly relevant to the study of TBI and associated disorders. This is also supported by another study, which identified relative change in stage 4 of N3 sleep in mTBI/concussed patients, in reference to age- and sex-specific normative

data, to be related to LOC and/or PTA at the time of injury, reflecting ongoing pathological processes in sleep [64].

32.3.4 Circadian Rhythm Sleep Disorders

Posttraumatic circadian disturbances are frequently underestimated because their manifestations mimic those of insomnia [65, 66]. In addition, because many behavioral and biological phenomena are influenced by the sleep-wake cycle and duration of preceding wakefulness, circadian rhythm studies must identify which portion in TBI patients' sleep variance is circadian and which is homeostatic, in addition to biologic metrics such as melatonin secretion and core body temperature, which do not have a stable identifiable point [67–69]. Taking into account these challenges, several preclinical and clinical studies attempted to understand both the acute and chronic implications of TBI on the circadian rhythm using newer monitoring techniques, such as gene sequencing [70–72]. The suprachiasmatic nucleus in the anterior hypothalamus serves as a CNS pacemaker, driving the circadian rhythm, including the sleep-wake cycle, hormonal secretion, and thermoregulation [73]. Within their cells, the CNS neurons have an intrinsic rhythm, which is produced by an autoregulatory transcriptional/translational feedback loop lasting approximately 24 h and thereby leading to an intracellular circadian rhythm. It has been proposed that a core feedback loop begins when two proteins, CLOCK and BMAL1, bind and drive the transcription of the PERIOD (Per) and Cryptochrome (Cry) genes [74–76]. One of the genes, Per3, regulates the circadian rhythm and is polymorphic [75]. Animal models suggest that TBI, even mild in severity, induces dysregulation of the circadian clock and modifies the expression of genes involved in immunity, inflammation, and glial function (e.g., chemokines and glial markers) linked to the circadian rhythm, synaptic activity/neuronal plasticity, neuroprotection, and cell death/survival [77]. A clinical study investigated the effect of Per3 polymorphism on sleep quality from 1 to 6 weeks post-injury in a sample of 96 mTBI patients, 24 of whom were heterozygous Per3 carriers, and the remainder noncarriers [78]. The results indicated that Per3 carriers exhibited shorter sleep duration at 6 weeks after mTBI compared with the baseline values. Among the poor sleepers, only the Per3 noncarriers exhibited a significant improvement in overall sleep quality at the follow-up assessment [78]. Whether or not this observation implies that specific interactions at the molecular level determine physiological outcome in TBI requires further study. Nonetheless, these results broaden our understanding of the means by which the molecular clock results in variable clinical manifestations after TBI.

32.3.5 Parasomnias

Parasomnias are defined as undesirable physical events or sensory experiences that occur with entry into, during, or arousing from sleep [33]. The ICSD-3 categorizes

all parasomnias into nonrapid eye movement (NREM), REM, or other parasomnias, which represent events that occur during the transition between wakefulness and sleep [33]. NREM parasomnias encompass disorders of arousal—sleepwalking, sleep terrors, and confusional arousals, as well as lesser known entities such as sleep-related sexual behaviors and eating disorders [79]. REM parasomnias include nightmare disorder, recurrent isolated sleep paralysis, and sleep-related painful erections, and are associated with neurodegenerative disorders such as Parkinson's disease, dementia, and multiple system atrophy [80]. NREM parasomnias seem to result from the co-occurrence of predisposing (genetic contribution), priming (sleep deprivation and various substances, including Z-drugs, lithium, and sodium oxybate), and precipitating factors, as well as from sleeping in an unfamiliar environment These factors include OSA, periodic leg movements, chronic pain, brain lesions or narcolepsy, fever, late physical activity, strong positive emotions before sleep, stress, and anxiety [80]. In an environmental risk factor study of more than 600 persons, those with REM sleep behavior disorder RBD (e.g., REM parasomnias) had previous head injuries, pesticide exposure, fewer years of formal schooling, and were smokers when compared to those without RBD [81]. The first study to use [18F]-fluorodeoxyglucose positron emission tomography to explore the potential long-term neurobiological effects of prior blast exposure/mTBI on wakefulness, REM sleep, and NREM sleep in the absence of concurrent post-concussive symptoms, and after adjusting for posttraumatic stress disorder (PTSD) symptoms severity, detected a decrease in relative cerebral metabolic rate of glucose during both wakefulness and REM sleep (but not NREM) in veterans with blast mTBI exposure compared to those without [82]. Reduced metabolism was detected in the right basal ganglia, amygdala, hippocampus, parahippocampal gyrus, culmen, visual association cortices, and midline medial frontal cortices, suggesting that a blast injury alters connections throughout the brain, especially those in deep subcortical structures that are densely packed with cholinergic axons and 5-HT1A receptor sites and known for their involvement in REM sleep [82]. REM sleep, a state of cholinergic and monoaminergic balance, may therefore be more sensitive to blast exposure compared to NREM sleep, with subsequent emergence of REM-related parasomnias. A case report of a 52-year-old male patient with a complaint of "restless sleep" and 10 years of intense and aggressive body movements and violent dreams highlighted a history of severe TBI at the age of 28, which left him in coma for 2 months, supporting the hypothesis of an association between cranial trauma and alterations in the dopaminergic pathways represented by periodic leg movements during sleep and RBD and proposes the possibility of hypothalamic hypocretin involvement in its pathophysiology [83]. Further research examined the spectrum of sleep disorders in patients with chronic TBI and reported complaints of parasomnia in 25% of the participants, with RBD being the most frequent parasomnia reported (13%). It has been proposed that the increased incidence of RBD relative to the general population is attributed to damage to brainstem mechanisms mediating descending motor inhibition during REM sleep [84].

32.3.6 Sleep-Related Movement Disorders

Sleep-related movement disorders (SRMDs) are generally characterized as stereotyped movements disturbing to sleep or sleep onset associated with daytime functional complaints [33]. They include sleep-related leg cramps, sleep-related bruxism, and sleep-related rhythmic movement disorder, among others [33]. Key features that help distinguish SRMDs from other movements in sleep include the absence of neurological comorbidity, normal neurological examination, and normal EEG findings. Taking into account these features, it is expected that SRMDs would be of relatively similar prevalence in TBI samples compared to non-TBI samples. A previous study reported a 17% incidence of periodic limb movement disorder in TBI patients compared to population-based estimates ranging between 4% and 11% in adults [85], and meta-analyses highlighted pooled prevalence rates between 4% and 8% in TBI cases regardless of injury severity [36]. Although the physiological mechanisms for SRMDs remain unknown, it is believed to involve the spinal cord serving as an underlying generator of movement or inability of the CNS descending pathways to sufficiently inhibit the underlying movement generated from the spinal cord [33]. The significance of these disorders in TBI is related to frequent arousals, an increased number of sleep-stage transitions, and frequent overlap with other sleep disorders and medical comorbidities.

32.4 Sleep Disorders and Psychiatric Disorders in TBI

The most prevalent psychiatric illness in the general community, *anxiety disorders*, frequently occurs after TBI [86, 87]. All anxiety disorders are accompanied by increased noradrenergic discharge in the locus coeruleus, which, under normal physiological conditions, is incompatible with the state of sleep [88]. Recent data suggest that even moderate activity in the locus coeruleus system contributes to certain forms of insomnia or other conditions associated with elevated arousal levels, including stress-related disorders, such as PTSD [88]. The association between anxiety disorders and sleep disorders is persistent in TBI research, with all studies highlighting a moderate to strong association between the two [89–91]. Although, in the general population, it is possible that one disorder (anxiety) causes the other (sleep disorder), in TBI, it is reasonable to conclude that the conditions reflect night and day clinical aspects of the same underlying brain pathology, where the TBI mechanism and severity shape the trajectory of a particular genotype of an injured person toward comorbid sleep and psychiatric disorders [91]. A systematic review and meta-analysis on the topic of PTSD, one of the disorders within the anxiety disorders category, highlighted a shorter posttraumatic amnesia (PTA) duration and memory of the traumatic event as significant predictors of PTSD in TBI samples of various severities [92]. Although this research did not discuss sleep as a risk factor for PTSD development, the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* criteria for PTSD [93], a clinical syndrome characterized by re-experience, avoidance, and hyperaroused reactions that persist for more than 1 month after

exposure to a traumatic event, lists nightmares within the "re-experiencing" criterion (Criterion B) and difficulty sleeping within the "trauma-related arousal or reactivity" criterion (Criterion E), supporting the notion that the tightly regulated homeostatic process of sleep (NREM and REM sleep) may be disrupted as a result of trauma. Attention to sleep, therefore, is vital to proper differential diagnosis (causality or night and day clinical aspects) and intervention [94].

Mood disorders, which are characterized by a disturbance in the regulation of mood, behavior, and affect [33], have historically been shown to occur at elevated rates in persons with TBI relative to the general population, representing a major source of disability [31]. These disorders in TBI patients are poorly characterized [95] and have different treatment responsiveness, suggesting they may arise from variable causes [96]. A recent review of the epidemiology and progression of psychiatric morbidity before and after TBI highlighted elevated rates of depressive and anxiety disorders emerging in the first year post-injury in comparison to the general population. The most frequently observed disorders were major depressive disorder (MDD) and PTSD; delayed onset of these disorders was observed in most severe brain injury cases [86]. An earlier cited systematic review and meta-analysis of predictors of MMD in TBI patients highlighted that higher admission Glasgow Coma Scale scores, female gender, preinjury depression, and being unemployed after sustaining TBI led to higher odds of developing MDD [92]. A recent study of persons with mTBI/concussion in the chronic stage post-injury found that mood disorders as per *DSM-IV-TR*, present in 42% of the sample, and depression severity as measured by PHQ-9 were strongly associated with insomnia severity [34]; and this relationship was not unexpected. The structure of sleep is regulated in large part by monoamines, acetylcholine, and gamma-aminobutyric acid signaling, which are also implicated in the pathophysiology of mood disorders, in particular major depressive disorder [97, 98]. The structure of sleep was shown to be disturbed in mTBI patients compared to age- and sex-specific normative data, showing more nocturnal wakefulness and less consolidated sleep stage N2 and REM [64]. These alterations in sleep structure may underlie the reports of insomnia by depressed patients with mTBI. However, the heritability of mood disorders is reported to be approximately one-third [99], and the inheritance of specific alleles may produce vulnerability (or resilience) to the development of MDD (and other mental/psychiatric disorders that share genetic risks with mood disorders, including anxiety disorders, personality disorder, etc.) after exposure to TBI. Therefore, longitudinal research is needed to better understand the risk and prognosis of sleep and mood disorders after TBI.

32.4.1 Sleep Disorders and Psychotic Disorders After TBI

The etiology of schizophrenia, the most frequently studied psychotic disorder in TBI, is poorly understood [100], but meta-analysis supports an increased risk toward its development following TBI, with a larger effect in those with a genetic predisposition [101]. Postmortem studies and those in living persons with schizophrenia

show loss of gray matter, frontal and temporal volume, and overall brain size [102, 103]; neuroimaging findings of chronic TBI patients highlight a similar pathology [104, 105]. Sleep dysfunction is increasingly recognized as a major problem for patients with psychotic disorders with strong evidence that sleep dysfunction (nightmares, insomnia, circadian-rhythm sleep disturbance, etc.) predicts subsequent psychotic experiences, the transition to psychosis, and also relapse [106, 107]. Psychosis interrupts sleep continuity [108], and behaviorally, a patient may attempt to use sleep as an escape from voices during the day, disturbing their circadian and homeostatic sleep drives. Prolonged sleep deprivation has been shown to provoke psychosis, and improvement in sleep quality in patients with psychosis has been shown to lessen psychotic experiences [109]. Consequently, although increased risk of psychotic disorders in TBI patients may be related to injury-related myelin dysfunction and subsequent abnormality of neuronal connectivity [110], sleep disorders and sleep deprivation emerging after the injury or pre-existing may be important cofactors influencing psychosis development in persons with TBI. Future studies should determine which parameters or domains of sleep are most strongly associated with increased psychosis in a TBI patient to develop targeted interventions.

32.4.2 Sleep and Adjustment Disorders

According to the *DSM-5*, a diagnosis of adjustment disorder is appropriate when the following criteria are met: (1) Distress that is out of proportion with expected reactions to the stressor, (2) distress and impairment are related to the stressor and are not an escalation of existing mental health disorders, and the reaction is not part of normal bereavement, (3) once the stressor is removed or the person has begun to adjust and cope, the symptoms must subside within 6 months, and (4) symptoms must be clinically significant and cause marked distress and impairment in functioning [111]. This definition is relevant to the discussion of survival of TBI patients in competitive environments; these persons frequently face significant physical and cognitive limitations and may be unable to meet requirements of occupational, social, and familial functioning, and they magnify emotional and/or behavioral distress. Anxiety and fear are common responses to stressors associated with post-injury life. Low mood, irritability, anger, and aggressions are other responses to stressors [113], each highly prevalent in TBI patients and associated with sleep pathology. Research and clinical focus in this direction may allow for the detection of persons at risk for not only stress-related disorders (i.e., insomnia, anxiety, adjustment disorder, etc.) associated with TBI but also substance use disorders, anhedonia, or somatization as ways to cope with changes in post-injury life [91].

32.4.3 Sleep Disorders and Substance Use Disorders after TBI

Substance abuse and dependence before and after TBI are common [114]. Preinjury lifetime frequencies are reported in the range of 27.5% for alcohol dependence or abuse to 34.3% for any substance use disorder [115]. Alcohol is estimated to be a contributing factor in 30–50% of all mTBIs; among TBI patients with positive blood alcohol levels in the emergency department, 33% were legally intoxicated [116]. Rates of alcohol-related disorder during the first year following mild to severe TBI vary, ranging from 5.9% to 19.2%, with approximately 11% meeting criteria for a substance use disorder in the first year after TBI [117, 118]. Despite recent reports that acute ethanol administration results in a protective cytokine and neuroinflammatory profile in TBI, and that none of the alcohol use variables were related to 1-year post-injury outcomes [119, 120], ethyl alcohol is a CNS depressant and the injured brain is particularly sensitive to its effects at the highest centers (i.e., speech, thought, and cognition) and lower brain functions (i.e., spinal cord reflexes and respiration), with the magnitude of effects changing with increasing dosage [121]. In sleep, alcohol exacerbates obstructive sleep apnea, precipitates SRBDs in persons at risk, and increases the risk of nocturnal legs cramps in older people [122–125]. During drinking binges, persons report a polyphasic sleep pattern with short sleep periods distributed across the 24-h day, a pattern frequently observed in living organisms without a circadian pacemaker (i.e., lesioned suprachiasmatic nucleus) [126]. Abnormal sleep patterns (e.g., shortened and fragmented sleep and elevated REM sleep pressure) can persist during recovery and abstinence [127]. Likewise, nearly all drugs with a known abuse liability (e.g., prescribed and over-the-counter, recreational drugs, tobacco, caffeine, and steroids) have profound effects on sleep [121], and future research should consider such effects in TBI cases, as their potential to cross the blood-brain barrier and contribute to vulnerability not just to sleep disturbance or psychopathology, but to problems more generally (e.g., maladaptive behaviors, poor socialization, impulsivity, and aggression) is real. Likewise, long-term effects of alcohol are important to consider: A meta-analysis of TBI patients with a history of alcohol and/or substance abuse, comparing the outcomes of people with and without a history of abuse, found poorer neuroradiological outcomes, including reduced hippocampal and gray matter volumes, as well as enlarged cerebral ventricles, in TBI patients with a history of alcohol and/or substance [128]. These are also features of schizophrenia.

32.4.4 Sleep in TBI Persons and Somatoform Disorders

Somatoform disorders are a heterogeneous group of psychiatric syndromes characterized by common symptoms, which may mimic a physical condition but are not explained by a medical condition [129]. The neuroanatomical findings characterizing somatoform disorders include gray matter volume reductions in specific cortico-limbic regions associated with two overlapping circuits, the neuromatrix of pain, and the emotion regulation system [130]. In a study of

94 patients with mTBI/concussion under litigation, the presence of somatoform disorder as per *DSM-IV-TR* (present in 29%) and malingering (present in 14%) was not found to be associated with insomnia severity [34] or pain severity [131] in either bivariate or multivariate models; associations were observed, however, in reference to poorer community integration, consisting of family, social, and work integration [132]. To understand the meaning of these observations, implementation of psychosomatic approaches into TBI research, focusing on the effect of long-term litigation on sleep, pain, and somatization using neuroimaging techniques, is needed.

32.5 Assessment of Sleep in TBI Patients

To detect a disorder in a population, trained personnel and facilities for diagnosis and follow-up assessment are necessary. In developed countries, clinicians analyze sleep through clinical assessment and reviewing possible diagnoses with similar symptom manifestations. Available measuring tools, including standardized questionnaires completed by patients, neuropsychological testing, neuroimaging techniques, polysomnography, actigraphy, multiple sleep latency test (MSLT), and the maintenance of wakefulness test (MWT), among others, are of great support [31]. Standardized questionnaires completed by patients are currently accepted as a suitable first step for screening, because of their cost-effectiveness and ready application, though they may not in fact be completely reliable, especially in a situation where self-insight (e.g., ability to recognize aspects of one's condition) may be affected, which is a principal issue in the TBI population [133]. Various standardized questionnaires have been developed in sleep medicine and subsequently used in TBI clinical practice and research; 16 of these measures were comprehensively reviewed for their construct validity and measurement properties in TBI populations [133]. Two measures, the Pittsburgh Sleep Quality Index (PSQI; e.g., assessment of the quality of nocturnal sleep and daytime consequences) [134] and the Epworth Sleepiness Scale (ESS; e.g., assessment of daytime sleepiness) [135], have their properties described in TBI samples of various severities. The PSQI is a brief clinical measure covering multiple domains of sleep (e.g., sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction); the instrument is also one of the few measures incorporating questions regarding daytime sleepiness. The systematic review and meta-analysis of measurement properties of the PSQI as it concerns screening purposes in clinical and nonclinical samples highlighted its strong reliability and validity and moderate structural validity in a variety of samples [134]. In nonclinical and clinical samples with known differences in sleep quality, the PSQI global scores and all subscale scores, with the exception of sleep disturbance, differed significantly, supporting the notion it can be used as a screening tool for sleep dysfunction. When researchers utilized the PSQI in a subacute TBI sample of 50 consecutive patients [136], distinguished with respect to insomnia according to the *DSM-IV* criteria, the overall agreement rate of the PSQI with the *DSM-IV* diagnosis was 94%, with a sensitivity of 100% and a specificity of 96%

[136]. When the PSQI-derived calculations of sleep onset latency, sleep duration, and sleep efficiency were compared using sleep diaries, the mean paired differences were small and the Pearson correlation coefficient range was 0.633–0.796 ($P < 0.05$). The proposed global PSQI cut-off score of 8 was found to be appropriate for discriminating 96% of insomnia cases correctly, and a cut-off score of 9 accurately established the sleep dysfunction in 98% of cases in TBI samples [136]. A recent study examined the factor structure of the PSQI in a sample of 243 persons with TBI and tested the 1, 2, and 3 factor models derived from previous studies in other populations. Researchers proposed a two-factor model as more clinically relevant due to the grouping of time-related variables that could provide important information with regard to circadian rhythm disorders in TBI patients [137]. The concurrent validity of the PSQI and the ESS was studied, and their relation to the mean MSLT scores in 71 TBI patients of various severity 3–27 years after injury [137]. The authors found no significant correlation between the scores and the mean MSLT sleep latency, questioning the instruments' ability to study daytime sleepiness in TBI samples accurately [137]. Figure 32.2 proposes an algorithm to differentiate sleep pathology in all individuals with TBI, first using clinical assessment or standardized questionnaires completed by the person with the help of a significant other, followed by more costly evaluation such as polysomnography, actigraphy, MSLT, and MWT of those suspected of having a sleep disorder based on initial clinical assessment or those whose self-report data are unreliable.

32.6 Treatment Considerations

Table 32.2 summarizes the most recent scientific evidence regarding approaches to the treatment of post-TBI sleep disorders, based on the understanding of their underlying mechanisms. As can be seen, seven types of interventions (e.g., continuous positive airway pressure, cognitive behavioral therapy, blue light therapy, acupuncture, warm footbath, hyperbaric oxygen, and medications) have been utilized to support patients with TBI in managing various sleep disorders. The primary outcomes of clinical trials were generally limited to measures of effectiveness in alleviating SRBDs or other sleep-related pathology (i.e., insomnia and excessive daytime sleepiness). In patients with TBI, researchers examined the effectiveness of CPAP intervention for patients with obstructive sleep apnea (a form of SRBD) [139]. A significant improvement in the apnea-hypopnea index score was observed, but no change in total sleep time (TST) or excessive daytime sleepiness, as determined by the MSLT and the ESS scores [139]. The attrition rate from baseline assessment to posttreatment evaluation (regardless of the etiology of the sleep disorder) was 35% [139].

One study assessed the efficacy of acupuncture in treating insomnia in patients with TBI [140]. Twelve patients with TBI underwent acupuncture delivered by a physician-acupuncturist. The acupuncture point selection was based on the classically described energetic qualities of the points. The TST, measured by actigraphy, increased from baseline to post-acupuncture assessment; sustained perception of

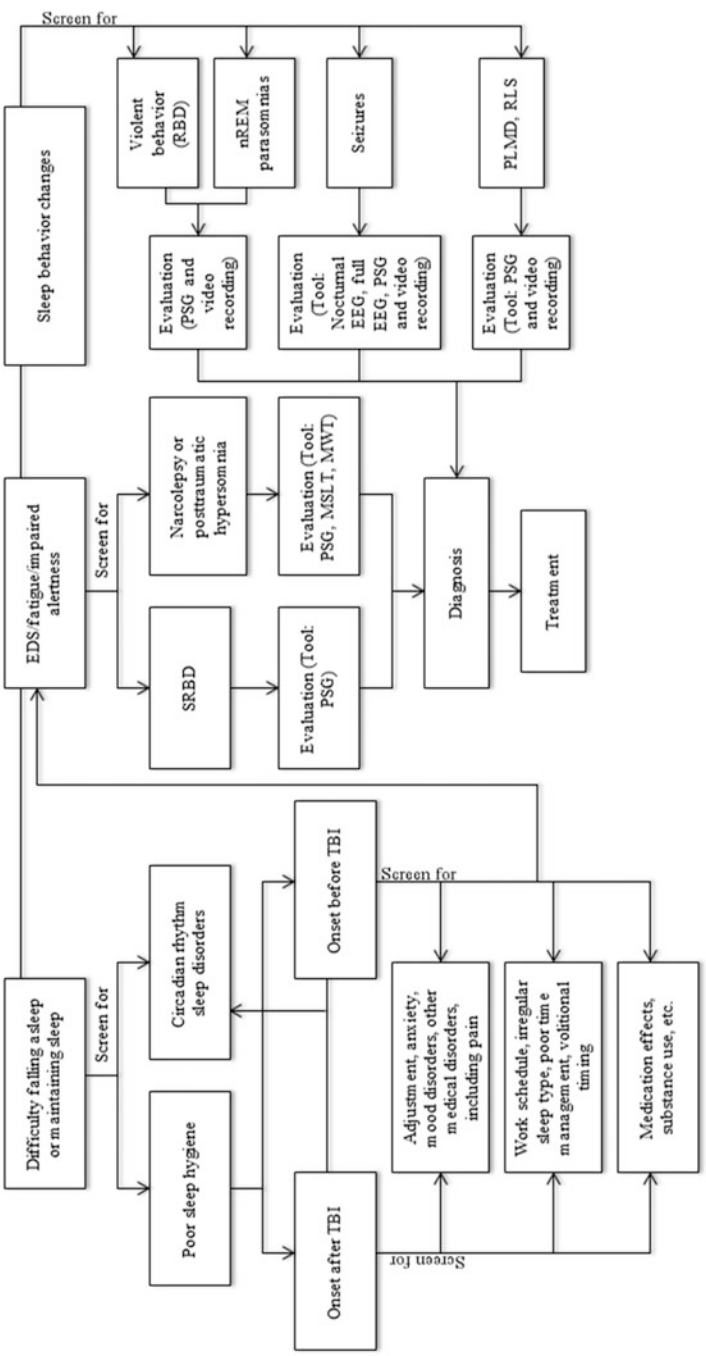

Fig. 32.2 Algorithm for differential diagnoses of symptoms in TBI. Reprinted from Mollayeva et al. [31]. Abbreviations: *EEG* electroencephalogram, *EDS* excessive daytime sleepiness, *MWT* maintenance of wakefulness test, *MSLT* multiple sleep latency test, *PLMD* periodic limb movement disorder, *PSG* polysomnography, *RBD* REM behavior disorder, *RLS* restless legs syndrome

Table 32.2 Selected randomized clinical trials and pre-post interventions

Author (year) Country, setting	Intervention	Study design inclusion/ exclusion criteria (IC/EC)	Sample size (N) withdrew age, sex (M/F)	Usage	Outcome measures	Results		Benefits	Notes adverse effects
						Pre	Post		
Sleep-related breathing disorders									
Castriotta et al. (2009), Veterans Medical center, USA [139]	CPAP	Prospective pre-post intervention IC: >18 y. a., ≥3 mos post-TBI, OSA EC: Circadian rhythm disorder, inability to give informed consent, use of sedating medications	$N = 13$ Withdrew = 0 Age: 38.56 ± 14.75 Sex: Not reported	Pts treated with nasal CPAP to eliminate apneas, hypoapneas, & snoring	ESS; AHI; amount of REM sleep	TST: 5.9 ± 1.5 SL: 50.9 ± 127 AHI: 31.4 ± 21.5 PLMI: 9.9 ± 17.1 MSLT: 10.3 ± 6.2 SOREM: 1.42 ± 3.1 ESS: 12.2 ± 6.2	TST: 6.1 ± 1.1 SL: 25.7 ± 37.1 AHI: 3.8 ± 3.7 PLMI: 19.8 ± 28.8 MSLT: 12.1 ± 5.1 SOREM: 0.8 ± 2.6 ESS: 13.0 ± 6.4	Primary: AHI decreased, amount of REM sleep increased Secondary: Significant decrease in PLMI	NR
Insomnias									
Lequerica et al. (2015), New Jersey medical school, USA [151]	Drug therapy Ramelteon vs. placebo	Double-blind placebo-controlled study with a crossover design IC: TBI (GCS < 15, LOC > 5 min, PTA > 30 min, abnormal neuroimaging) at least 1 mos earlier, PSQI>5, ≥18 y.a., free of hypnotics for ≥2 weeks EC: Abnormal liver enzymes, taking Luvox or fluvoxamine, other medications	$N = 8/6$ Withdrew = 0 Age: 42.5 ± 17.7 Sex: Not reported	Nightly dosage of Ramelteon (8 mg) over 3 weeks 5 visits/testing over 9 weeks	Sleep log Actigraphy (TST, SOL) Neuropsychological test battery BRUMS: Anger, confusion, fatigue, tension, vigor	PSQI: 12.0 ± 3.7 TST: 457.7 ± 97.4 SOL: 3.5 ± 1.9 CNS vital signs neurocognitive index: 74.8 ± 24.2	Main effect for treatment vs. placebo: TST: $F = 10.67$, $p = 0.007$ SOL: $F = 9.95$, $p = 0.008$ CNS vital signs neurocognitive index: $F = 7.92$, $p = 0.018$ Executive functioning score: $F = 13.43$, $p = 0.004$ Reaction time: $F = 4.47$, $p = 0.061$ Complex attention: $F = 2.41$, $p = 0.152$ BRUMS: Anger, confusion, fatigue, tension, vigor-NR	An increase in total sleep time and a small increase in sleep latency after 3 weeks drug vs. placebo; improved neuropsychological test scores (executive functioning)	NR

(continued)

Table 32.2 (continued)

Author (year) Country, setting	Intervention	Study design inclusion/ exclusion criteria (IC/EC)	Sample size (*N*) withdrew age, sex (M/F)	Usage	Outcome measures	Results		Benefits	Notes adverse effects
						Pre	Post		
		interfering with ramelteon							
Zollman et al. (2012), Outpt rehabilitation clinic, USA [140]	Acupuncture vs. sham	Randomized controlled study IC: TBI within 5 years of study entry, complaints of insomnia (≥15 ISI score), rancho cognitive scale level V or above, consent, ≥18 y.a. EC: Respiratory or neurological condition associated with sleep disorders (e.g., sleep apnea), pregnancy	*N* = 12 Withdrew = 0 Age: 44.50 ± 15.15 Sex: 7/5	5 weeks with biweekly sessions; each treatment 20 min; acupuncture points included: The kidney, heart, bladder, liver, large intestine, pericardium, governor vessel, & the ear points Tranquilizer & Shen men. 4 hertz electrical stimulation, using an electro-acupuncture device (IC1107)	ISI; Actigraphy (sleep time); RBANS; PASAT	Sleep time median (min): 384 ISI median: 20	Sleep time median (min): 379 ISI median: 20 F/u 1 mos: 11	Primary: ISI scores decreased after treatment Secondary: Improvement in PASAT & RBANS Total scale, depression improvement	1 pt. reported a headache after usage; effect did not last over trial period
Ouellet & Morin (2007), Outpt rehabilitation center, Canada [141]	CBT	Single-case design IC: Mild-severe TBI in ≤5 years, 18–50 y.a., insomnia syndrome EC: Medical/ psychiatric comorbidity, medication to produce insomnia,	*N* = 11 Withdrew = 0 Age: 27.3 (20–46y) Sex: 6/5	8 weekly sessions over 8–10 weeks; each session lasted an hour. Five components: (1) stimulus control instructions; (2) the sleep restriction procedure, (3) cognitive therapy of insomnia, (4) sleep-hygiene education,	Sleep diary, TST, sleep efficiency, diagnostic criteria	Total wake time: 128.46 ± 47.86 Sleep efficiency: 77.20 ± 8.76 Total sleep time: 425.68 ± 51.20 ISI score: 17.55 ± 4.03	Total wake time at Post-treatment/f/u 1 mos/ f/u 3 mos: 59.29 ± 39.54/ 71.49 ± 42.97/ 49.66 ± 27.96 Sleep efficiency Post-treatment/f/u 1 mos/ f/u 3 mos: 87.99 ± 7.99/ 86.26 ± 7.92/ 90.88 ± 5.29 Total sleep time at	Primary: Significant reduction in total wake time, in inter-night variability; all pts. increased their sleep efficiency, significant reduction in ISI scores No change in "mental" fatigue	Some pts. require more structure, encouragement from therapist, in order to ensure effects of the intervention last & they do not relapse (i.e., they need "booster" sessions)

		sleep problems before TBI, sleep Dz (e.g., sleep apnea), severe pain, inability to complete questionnaires due to visual, cognitive, language comprehension deficits		(5) the fatigue management skills training component			Post-treatment/f/u 1 mos/ f/u 3 mos: 444.43 ± 58.74/ 453.43 ± 59.48/ 496.72 ± 50.24 ISI score at Post-treatment/f/u 1 mos/ f/u 3 mos: 8.78 ± 3.38/ 11.33 ± 3.74/ 10.30 ± 5.38		
Nguyen et al. (2017), Monash University, Australia [142]	CBT vs. treatment as usual	Randomized controlled trial IC: TBI (all severities), complaints of insomnia (≥15 ISI score), rancho cognitive scale level V or above, Consent, ≥18 y.a.	$N = 24$ (13/11) Withdrew = 4 Age: 43.87 ± 12.95 Sex: 16/8	6 weekly sessions over 6-week period; each session 20–30 min. CBT arm: 6 components: (1) psychoeducation; (2) reorganize daily schedules, (3) graded activity/cognitive restructuring, (4) sleep interventions, (5) strategies for fatigue; (6) review/ relapse prevention	Primary: PSQI scores Secondary: ISI score FSS score ESS score HADS scores	PSQI: 10.96 ± 3.74 ISI: 17 ± 6.21 FSS: 5.28 ± 1.06 ESS: 6.17 ± 4.37 HADS-A: 7.17 ± ` 3.67 HADS-D:7.67 ± `3.35	Estimates of change from BS to last f/u (coef. (SE), p) in treatment arm: PSQI: −1.59 (0.43), $p < 0.001$ ISI: −3.06 (0.58), $p < 0.001$ FSS: −0.16 (0.09), $p = 0.73$ ESS: −0.96(0.33), $p = 0.04$ HADS-A: −1.09(0.40), $p = 0.007$ HADS-D:-1.23(0.35), $p < 0.001$	Sign differences between groups favoring CBI in all outcomes but fatigue (FSS)	Limited compliance in both groups to exercise recommendations
Theadom et al. (2018), Auckland university of technology Australia [143]	Online CBT (RESTORE) & education interventions vs. education	Two parallel-group, randomized controlled pilot study IC: TBI mild to moderate within 3 mos- 3 years after injury, complaints of	$N = 24$ (12/12) Withdrew = 4 Age: 35.9 ± 11.8 Sex: 9/15	6 weekly sessions over 6-week period; each session 20–30 min. CBT arm: 6 components: (1) psychoeducation; (2) relaxation training, (3) sleep restriction, (4) cognitive therapy,	Primary: PSQI scores Actigraphy measures Secondary: Symptom load, neuropsychological assessment, quality of life	CBT/education arm PSQI score: 13.00 ± 3.44/ 11.67 ± 4.38 SOL:34.43 ± 25.56/ 24.26 ± 8.39 SE: 82.08 ± 4.11/ 83.41 ± 6.03 Time awake:	CBT/education arm PSQI score: 8.75 ± 4.65/ 8.75 ± 4.86 (SMD:1.17) SOL: 27.40 ± 17.45/ 23.78 ± 812.19 (SMD:0.73) SE: 81.11 ± 8.01/ 84.12 ± 6.52 (SMD:0.43)	Similar improvement in both groups in all parameters, but PSQI (better in CBT online arm compared to education; test difference 52.00, $p = 0.04$)	2 pts. unable to complete due to visual disturbances due to cognitive overload

(continued)

Table 32.2 (continued)

Author (year) Country, setting	Intervention	Study design inclusion/ exclusion criteria (IC/EC)	Sample size (*N*) withdrew age, sex (M/F)	Usage	Outcome measures	Results		Benefits	Notes adverse effects
						Pre	Post		
		insomnia for <3 mos, PSQI score ≥ 5, ≥18–60 y.a., have access to high-speed internet EC: Severe TBI, unable to consent, unable to read English, presented with symptoms of sleep disorder, alcohol abuse, shift work, medically unstable, receives care from sleep specialist		(5) environment &sleep; (6) mindfulness meditation Education arm: 6 components: (1) about brain injury; (2) sleep & fatigue; (3) establishing a routine; (4) exercise & sleep; (5) environment & sleep; (6) diet & substance use		40.96 ± 6.3/ 47.08 ± 15.64 # of awakenings: 33.66 ± 6.96/ 38.80 ± 7.57 Neurocognitive index: 84.29 ± 10.56/ 81.50 ± 16.24 Symptoms (cognitive): 9.67 ± 2.67/8.81 ± 2.48 Symptoms (somatic): 21.67 ± 8.49/ 21.27 ± 5.68 Symptoms (emotional):11.17 ± 8.8/ 10.00 ± 2.97 QOL: 41.34 ± 14.44/ 50.96 ± 9.88	Time awake: 40.65 ± 18.99/ 48.44 ± 16.11 (SMD:0.05) # of awakenings: 34.90 ± 13.51/ 42.14 ± 10.60 (SMD:0.33) Neurocognitive index: 89.67 ± 12.40/ 90.50 ± 18.63 (SMD:0.82) Symptoms (cognitive): 9.00 ± 3.37/6.14 ± 3.85 (SMD:0.82) Symptoms (somatic): 19.86 ± 9.41/ 14.14 ± 9.03 (SMD:0.82) Symptoms (emotional):12.14 ± 5.61/ 7.29 ± 4.86 (SMD:0.47) QOL: 60.56 ± 23.74/ 53.72 ± 15.71 (SMD:0.97)		
Chiu et al. (2017), Chang Gung University memorial	Warm footbath before bedtime vs. usual care	Randomized controlled crossover study IC: First TBI, > 1 years post-injury,	*N* = 24 Withdrew = 1 Age: 35.9 ± 12.5 Sex: 9/15	3-day intervention or the usual-care arm; a washout period 3 days, opposite intervention for 3 days	Sleep efficiency, sleep onset latency, Total sleep time, wake after sleep	SE usual care arm: 86.13 ± 3.99 SOL: 20.50 ± 4.44 TST:452.49 ± 34.25 WASO: 15.70 ± 6.40	SE treatment arm: 87.15 ± 4.03 SOL: 15.39 ± 4.41 TST:458.49 ± 34.24 WASO: 13.40 ± 6.38	Effectiveness in reduction of SOL & WASO No difference in total	NR

hospital, Taiwan [144]		complaints of insomnia (>10 ISI score), 20–65 years of age EC: Psychiatric Dz, sleep disorder, substance use, uncontrolled CVD, peripheral neuropathy		Thermostatic footbath 44 × 41.5 × 36.5 cm, 41 °C 30 min, 20 cm above the ankle	latency (by actigraphy)		Sign differences in SOL & WASO (effect size −5.11 ± 3.10; −2.57 ± 4.03, respectively; $p < 0.05$)	sleep time & sleep efficiency	
Walker, et al. (2018), Div of hyperbaric medicine University of Utah, USA [147]	Hyperbaric oxygen (HBO_2) vs. sham	Double-blind longitudinal sham-controlled trial IC: Mild TBI (military), >26 mos after injury, 96% poor sleepers, 18–65 years of age EC: Moderate-severe TBI, penetrating injury, PTSD, intrusive recollection, unstable medically, daily prescription drugs	$N = 71$ (36/35) Withdrew = 7/5 Age:32.8 ± 7.3 Sex:70/1	40 chamber sessions 60 min each (>99% oxygen, 1.2 atm absolute) over 12 weeks	PSQI SD, WASO, SOL (actigraphy (A), sleep diary (D))	PSQI: 13.5 ± 3.8 SD (A): 400 ± 64.1; (D):301.7 ± 115.0 WASO (A):42.9 ± 17.7; (D):52.5 ± 55.2 SOL (D):58.9 ± 53.9	Longitudinal difference in change score (95% CI); p HBO_2 vs. sham: PSQI: −2.0 (−3.5, −0.4); $p = 0.02$ Other outcome measures reported in a figure format	Improvement in PSQI scores trended towards HBO_2 over sham at 13 weeks and 6 mos; Actigraphy- and sleep diary recorded sleep-wake measures slightly favored HBO_2 at 13 weeks for WASO and SE, not statistically different	NR
Hypersomnolence/excessive daytime sleepiness									
Kaiser et al. (2010), University of Zurich, Switzerland [150]	Modafinil vs. placebo	Randomized placebo controlled double-blind pilot trial IC: Closed TBI mild to severe, 1–10 years prior, ESS ≥ 10 &/or	$N = 10/10$ Withdrew = 7/5 Age:37 ± 9/ 43 ± 19 Sex:8/9	100–200 mg/day 6 weeks	ESS FSS Beck D Beck A PSG:SE SL, AHI, PLMI MWT: SL PVT	Drug/placebo: ESS: 8.2 ± 3.7/10 ± 4.2 FSS: 5.0 ± 1.4/4.6 ± 0.8 Beck D: 11 ± 9/9 ± 6 Beck A: 10 ± 11/10 ± 9 PSG SE: 87 ± 5/88 ± 11 PSG SL: 20 ± 16/ 16 ± 18	Drug/placebo change from BS: ESS: 0.7 ± 31.8/ −2.3 ± 2.3 (SS) FSS: 0.0 ± 0.6/ −0.8 ± 1.0 (NS) Beck D: −0.4 ± 3.5/ 1.1 ± 3.2 (NS)	Compared to placebo, drug group's ESS, PSG SL and MWT SL improved; FSS scores & others did not differ	No side effects reported

(continued)

Table 32.2 (continued)

Author (year) Country, setting	Intervention	Study design inclusion/ exclusion criteria (IC/EC)	Sample size (*N*) withdrew age, sex (M/F)	Usage	Outcome measures	Results		Benefits	Notes adverse effects
						Pre	Post		
		FSS > 4 EC: Neurologic, psychiatric or other disorders and psychoactive medications				PSG AHI: 3.3 ± 3.8/ 2.1 ± 4.4 PSG PLMI 0.8 ± 0.9/ 0.8 ± 0.9 MWT SL: 18.7 ± 9.3/15.6 ± 11.4 PVT (vel): 3.7 ± 0 6/3.8 ± 0.5	Beck A: 0.5 ± 5.2/ −0.1 ± 1.8(NS) PSG SE: 0.8 ± 5.7/ 0.0 ± 5.1(NS) PSG SL: −13.6 ± 16.4/ 2.7 ± 14.7 (SS) MWT SL: 0.4 ± 6.2/8.4 ± 9.6 (SS) PVT (vel): 0.0 ± 2.9/ 1.3 ± 2.6 (NS)		
Menn et al. (2014), 40 US centers, USA [149]	Armodafinil vs. placebo	Randomized placebo-controlled double-blind trial IC: 18–65y.o., closed TBI mild to moderate 1–10 years prior, ESS ≥ 10 &/or MSLT <8 EC: Neurosurgery, AXIS I Dz or unstable AXIS II (DSM-IV-TR), on pain or anticonvulsants; sleep disorder	*N* = 117 (88/29) Withdrew = 24/ 69 Age:32.8 ± 7.3 Sex:70/1	50, 150, or 250 mg mg/ day or placebo for 12 weeks followed by optional 12-mos open-label extension	MSLT ESS Clinical global impression change (CGI-S) TBI-work instability scale (WIS) Tolerability	Drug: MSLT: Reported in figure format ESS: 14.8 ± 2.6 CGI-S: 4.4 ± 0.5 TBI-WIS: 9.6 ± 6.9	Drug (last f/u): MSLT: Reported in figure format ESS: 5.8 ± 4.1 CGI-S: 2.1 ± 1.1 TBI-WIS: 4.8 ± 7.1	Pts on 250 mg drug improved in SOL vs. placebo (7.2 min vs. 2.4 min, $p = 0.001$) Pts vs. placebo on 150 and 250 mg improved on CGI-C (50% vs. 38%) ESS, TBI-WIS- no difference btw groups; gradual improvements over 48 weeks Drug well tolerated	Drug (any dosage): Adverse event (headaches) = 8 Consent withdrawn = 5 Protocol violation = 6 Noncompliant = 3 Lost to f/u = 1 Other = 1 Placebo: Consent withdrawn = 3 Noncompliant = 2 Other = 1
Circadian rhythm sleep disorders									
Sinclair et al. (2013), Epworth	Blue light therapy (Philips goLITE M2 light therapy device)	Study design: Randomized, placebo-controlled design	*N* = 10/10 Withdrew = 0 Age:	Blue light therapy device for 45 min each morning at home, within 2 h of waking,	FSS; daytime sleepiness; ESS; PSQI; BDI-II; PVT; NAART; CVLT-II	ESS: 10.1 ± 4.5 (treatment group-blue light therapy), 9.6 ± 4.8 (yellow light therapy),	ESS (ref: No treatment control): 0.89 (treatment group-blue light therapy), 0.88 (yellow light therapy)	Primary: Significant reduction in fatigue with blue light therapy, Secondary:	1 pt. reported a headache after usage, but the

hospital, Australia		IC: 18–65 y.o., TBI $\leq$ 3 mos, FSS $\geq$ 4 &/or ESS $\geq$ 10 &/or PSQI $>$ 5 EC: Other Dz with fatigue (e.g., neurological disorders, preinjury sleep disorders, chronic fatigue syndrome), obesity, high risk of OSA on BQ, trans meridian travel, night shift work in <6 weeks, use of sleep medication	47.2 $\pm$ 13.7 Sex: 8/2	for 4 weeks Pts sat in front of light panel approximately 50 cm in front of the eyes & looked into light source for a few sec every few min		8.8 $\pm$ 3.4(no treatment control) FSS: 5.9 $\pm$ 0.8 (treatment group-blue light therapy), 5.6 $\pm$ 0.5 (yellow light therapy), 6.2 $\pm$ 0.4 (no treatment control)	FSS (Ref: No treatment control): -0.30 (treatment group-blue light therapy), -0.37 (yellow light therapy)	Significant reduction in daytime sleepiness	effects did not last long
Grima et al. (2018), Monash University, Australia [148]	Melatonin 2 mg/daily 2 h before bedtime (Circadin®, sigma pharmaceutical)	Study design: Randomized, placebo-controlled double-blind crossover phase III IC: 18–65 y.o., mild to severe TBI with LOC &PTA; GCS 3–14, & PSQI $\geq$ 8 EC: Preinjury sleep neurological disorders, chronic fatigue syndrome, pregnant, obesity, high risk of OSA on BQ, use of sleep medication or other	$N = 33/33$ Withdrew = 0 Age: 37 $\pm$ 1 Sex: 22/11	4-week melatonin or placebo before crossover Placebo matched for appearance, consisted mannitol, acacia, icing sugar 1 capsule orally 2 h prior sleep initiation Text messages daily	Primary: PSQI; sleep latency Secondary: Sleep efficiency; ESS; HADS-A; HADS-D; FSS; SF-36	PSQI: 11 $\pm$ 3 Sleep latency: 24 (14–52) Sleep efficiency: 81 (75–83) ESS score:8 $\pm$ 5 HADS-A: 8 $\pm$ 4 HADS-D:10 $\pm$ 6 FSS score: 49 (41–57) SF-36 (phys): 38 $\pm$ 15	Adjusted mean (95%CI) PSQI: 7.68 (6.34;9.02) Sleep latency: 1.37 (1.26; 1.48) Sleep efficiency: $-3.22(-3.61; -2.,87)$ ESS score: 2.36 (2.00;2.73) HADS-A: 7.84 (6.23–9.45) HADS-D: 8.53 (6.93; 10.13) FSS score: -4.18 (-4.74; -3.62) SF-36 (phys) 43.17 (39.15–47.2)	Primary: Effect size, Cohen d: PSQI global (0.46, $p < 0.001$) Sleep latency NS Secondary: Sleep efficiency (0.28. $p = 0.04$); HADS-A (0.27, $p = 0.006$), FSS (0.29, $p = 0.03$) SF-36; ESS, HADS-D-NS	No adverse effects reported

(continued)

Table 32.2 (continued)

Author (year) Country, setting	Intervention	Study design inclusion/ exclusion criteria (IC/EC)	Sample size (*N*) withdrew age, sex (M/F)	Usage	Outcome measures	Results		Benefits	Notes adverse effects
						Pre	Post		
		psychoactive drugs within 12 months							
Sleep efficiency									
Makley et al. (2019), Craig hospital, USA [151]	Sleep hygiene protocol+ standard of care vs. standard of care; acute brain injury rehab. unit	Study design: Prospective, 2-arm, unblinded intervention IC: Closed head injury; restricted of taking centrally acting medications EC: Previous moderate–severe injury, history of SRBD, other sleep disorder, or neurodegenerative condition	*N* = 9/9 Withdrew = 1/1 Age: 34 ± 9/ 26 ± 10 Sex: 7/2 (both groups) GCS: 9 ± 4/ 7 ± 4 DRS:12 ± 6/ 11 ± 4	4-week sleep hygiene protocol (SHP): 1. Improved night sleep environment. 2. Increased daytime activation. 3. Enhanced circadian stimuli. 4. Consistent wake time/bed time routines 5. Limit caffeine intake to before noon. Standard care: PT, OT, and SLT 3+ h/day Monday–Friday	Primary: TST, SE, WASO Secondary (rehab): Discharge DRS score & LOS (in days) Perceived change	Week 1 Median (min, max) TST: 469 (216, 551)/467 (322, 484) SE:78.3 (36, 92)/77.5 (54, 84) WASO: 55 (28,170)/ 70.5 (42,133) DRS:5 (2.9)/5(1, 7) LOS:48 (32, 70)/54 (29,176)	Week 3 Median (min, max) TST: 477 (390,526)/476 (390,526) SE:79.6 (67, 92)/79.3 (65, 88) WASO: 48.5 (25, 72)/53.3 (33, 94) DRS change: 5 (2, 18)/6 (4, 13)	Primary & secondary: Not significantly different between groups week 1 & week 3 88% pts. and 60% nurses indicated intervention helps sleep Actigraph sleep metrics improved in both groups; however, only in SHP, the change was significant	Of pts. who met IC/EC 19% declined to participate 1 pt. withdrawn after consenting (before assignment to a study arm) 1 pt. from each group was dropped from analysis (< 21 days of data collection due to early discharge)

Abbreviations: *AHI* apnea-hypopnea index, *BQ* Berlin questionnaire, *BS* baseline, *CBT* cognitive behavioral therapy, *CPAP* continuous positive airway pressure, *DRS* disability rating scale, *EDS* excessive daytime sleepiness, *ESS* Epworth sleepiness score, *f/u* follow up, *FSS* fatigue severity scale, *GCS* glasgow coma scale, *IQR* interquartile range, *ISI* Insomnia severity index, *LOC* level of consciousness, *LOS* length of stay, *mos* month, *MSLT* multiple sleep latency test, *NPSG* nocturnal polysomnography, *NR* not reported, *NS* not significant, *pt. (s)* participant(s), *PASAT* paced auditory serial addition test, *PLMI* periodic limb movement index, *PSQI* Pittsburgh sleep quality index, *PT* physical therapy, *QOL* quality of life, *RDI* respiratory disturbance index, *REM* rapid eye movement, *OSA* obstructive sleep apnea, *OT* occupational therapy, *SD* sleep duration, *SDB* sleep-disordered breathing, *SE* sleep efficiency, *SLT* speech language therapy, *SOL* sleep onset latency, *SOREM* number of sleep-onset REM periods on MSLT, *TBI* traumatic brain injury, *TST* total sleep time, *vs.* versus, *WASO* wake after sleep onset, *Wk* week, *y.a.* years of age

sleep quality (as measured by the Insomnia Severity Index) improved more in the acupuncture group than in the control group, and overall cognitive functioning and divided attention improved as well, as measured by neuropsychological tests [140]. Besides, participants were able to taper sleep medications during the first week of the acupuncture treatment. One patient reported headache after the procedure, which subsided within the trial period [140].

Three studies tested the efficacy of cognitive behavioral therapy (CBT; different versions) for dealing with insomnia and other sleep difficulties in patients with TBI [141–143]. An earlier CBT study reported on 11 of 20 (55%) participants who completed the initial assessment, met inclusion criteria, and underwent a CBT program for 8 weeks [141]. This intervention included stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education, and fatigue management applications. An average reduction of 53.9% in the total wake time was observed across participants from pre-CBT to post-CBT application, with significant improvement in sleep efficiency (from 77.2% to 87.99%), accompanied by a reduction in symptoms of general and physical fatigue. No adverse effects were reported. We refer the reader to Table 32.2 for the results of the most recent CBT studies [142, 143].

Researchers from Taiwan tested the effectiveness of a warm footbath (30 min each, 41 °C) in 24 patients with insomnia symptoms who sustained their first TBI more than a year prior [144]. Researchers reported that compared to usual care, a footbath was effective in reducing sleep onset latency and wake after sleep onset, but had no difference on total sleep time or sleep efficiency [144].

One study examined the efficacy of home-based blue-light therapy (goLITE, Phillips Consumer Lifestyle, American Fork, UT, USA) for 45 min per day for 4 weeks to alleviate fatigue (primary outcome) and EDS, as well as to enhance sleep quality and sustained attention in patients with TBI [145]. Compliance with the technology application was acceptable if the device was switched on at least 5 days per week for at least 3 of the 4 weeks. After a 4-week period of using the blue-light device, participants reported improvement in fatigue ($P < 0.001$) and reduction in EDS ($P < 0.01$) compared to the non-intervention group; however, no improvement was observed in sleep quality. Adverse effects included headaches and diarrhea (one patient, each); however, these were considered to be unrelated to the treatment [145]. Compliance was high, with the majority of participants using the light therapy as instructed in the morning, although outside of the 2-h window on just 8% of days during the testing period. In comparison, the adherence to the prescribed home-based exercise program reported to be much lower, approximately 33% [146].

One study examined the efficacy of hyperbaric oxygen (HBO_2) over 12 weeks in 71 patients with mTBI [147]. An improvement in PSQI scores from baseline assessment to follow-up was observed at 14 weeks and 6 months. Actigraphy and sleep diary records of sleep-wake measures slightly favored HBO_2 over sham at 13 weeks for wake after sleep onset and sleep efficiency; however, the results were not statistically significant [147].

For more information about medication effectiveness (modafinil, armodafinil, or melatonin) [148–150], refer to Table 32.2. At present, scientific evidence supports

the idea that many interventions affect sleep and functional outcomes in a positive direction and rehabilitation of sleep dysfunction can be started as earlier as in the acute rehabilitation setting [151, 152].

32.7 Conclusions

The World Health Organization published a consensus on the impact of sleep disorders on body functions (e.g., sleep, energy, and drive), body structures (e.g., brain and respiratory organs), activities and participation (e.g., focusing attention, driving, handling stress, and other psychological demands, following the daily routine), and environment (e.g., immediate family, health services, systems, policies, and health professionals) [153]. It is well known that TBI of any cause and severity is frequently associated with impairments in one or more wakefulness functions, including physical function (e.g., ambulation, vision, hearing, and balance), cognitive function (e.g., speech and language processing, memory, attention, concentration, and reasoning), and complex psychosocial function (e.g., anger management, impulsivity, social withdrawal, and poverty), which may compromise one's aptitude for seeking care [154]. Scientific literature on seeking care and treatment in general (and on sleep disorder treatment in particular) that takes into account these specific aspects relevant to patients with TBI is sparse. At the same time, research and clinical observations have produced solid evidence that sleep and neurocognitive and mental/psychiatric disorders in persons with TBI are tightly linked. Future developments aiming to bridge the gap between neuroendocrine, autonomic, homeostatic functions, sleep-wake cycles, and emotional behavior in research are timely. Improvements in differential diagnosis and in therapeutic interventions are challenges in TBI research that, if undertaken, are an exciting prospect for future TBI assessment and management.

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Sleep and Epilepsy

33

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Abstract

In people with epilepsy, sleep may be disrupted by nocturnal epileptic activity as well as by the use of antiseizure medications (ASM). Conversely sleep states and circadian rhythm can also influence the onset and course of seizures and can modulate interictal epileptiform discharges occurrence. Depending on the stage of sleep, epileptic discharges can either be activated or inhibited. Many types of epilepsy have sleep-activated seizures and interictal epileptiform discharges, with highest preponderance reported in NREM sleep (N1/N2 > N3) and smallest occurrence during REM sleep, based on brain region of seizure onset. In the microstructure of sleep, certain dynamic key points have been found to be associated with epileptic activation. These are identified as cyclic alternating pattern (CAP) consisting of alternating patterns of high-frequency and low-frequency EEG discharges. Arousals during sleep also tend to activate certain types of epilepsies, such as juvenile myoclonic epilepsy (JME), possibly pointing to the hypersynchronization during arousal as a cause for seizures. Moreover, occurrence of seizures also has circadian variation. Two principal mechanisms can mediate the circadian variation of epileptic excitability in both human and animal epilepsy: circadian variation in CLOCK protein and circadian variations of the mammalian target of rapamycin (mTOR) pathway. This chapter explores these mechanisms as well as discusses the effect of epilepsy and its management on various sleep disorders, such as insomnia, restless legs syndrome, and obstructive sleep apnea.

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Epilepsy · Sleep-related hypermotor epilepsy · Circadian rhythm · Insomnia · Antiseizure medications

33.1 Introduction

It is well known that there is a complex interaction between sleep and epilepsy [1]. Beyond the common denominator of a change in consciousness, there are various clinicopathological connections between sleep and epileptic phenomena. In people with epilepsy, sleep may be disrupted by nocturnal epileptic activity as well as by the use of antiseizure medications (ASM). Conversely sleep states and circadian rhythm can also influence the onset and course of seizures and can modulate interictal epileptiform discharges occurrence [2]. The knowledge of the interplay between the two can help in guiding management of disorders in both areas. Sometimes it can be difficult differentiating between nocturnal seizures from sleep disorders [1].

33.2 Historical Introduction

Going as far back to ancient times, a relationship between sleep and epilepsy was recognized by the Greeks. Aristotle believed that altered states of consciousness, such as sleep or seizures, involved dissociations of the soul from the body, allowing prophecy of the future [3]. In the late 1800s, Gowers [4] recognized that approximately 20% of those patients with epilepsy experience seizure solely in sleep. Further observations were that (i) sleep onset and awakening were periods of peculiar susceptibility for seizures (seizures may be more frequent during the states of transition between sleep and wake) and (ii) diurnal seizures were clustered in the early morning and late afternoon. In 1953, Janz [5] described "awakening epilepsy" as an idiopathic generalized epileptic (IGE) syndrome with generalized tonic-clonic seizures (GTCS). With the dawn of electroencephalography, Gibbs [6] recognized that epileptiform activity increased during sleep. It was observed that close to half of patients with GTCS had a nocturnal predominance [1]. Thus, it appears that sleep and epilepsy are intricately related. In this chapter, relationship between both will be reviewed.

33.3 Effects of Sleep on Epilepsy

Sleep is a dynamic process, during which the electrical rhythms of the brain orchestrate a complicated progression of changing frequencies, patterns, and connectivity [7]. Recording of overnight sleep improves the yield of interictal epileptiform discharges compared to routine daytime electroencephalograms (EEG) [8].

33.3.1 Effects of Sleep Stages on Epilepsy

Depending on the stage of sleep, epileptic discharges can either be activated or inhibited [1]. Many epilepsies have sleep-activated seizures and interictal epileptiform discharges, with highest preponderance reported in NREM sleep (N1/N2 > N3) and smallest occurrence during REM sleep, based on brain region of seizure onset [9–15]. In NREM sleep, particularly during the deeper stages of NREM sleep, interictal epileptiform discharges are activated (Fig. 33.1), as this is a state of relative hypersynchronization [1].

During sleep, progressive synchronization within the thalamocortical network takes place via a synchronous discharge of the thalamic reticular nucleus [16], which enables the generation of non-REM sleep (NREM) oscillations such as slow waves and sleep spindles [17]. Similar circuits are thought to be involved in the generation of spike-wave discharges (SWD) in patients with generalized epilepsy [18]. It has been seen that during NREM sleep generalized epileptiform discharges are more frequent [19].

It has been proposed that seizures are more common in NREM sleep because of the presence of slow-wave downstate, which elicits interictal epileptiform discharges and high-frequency oscillations through the engagement of inhibitory mechanisms which synchronize neural activity. Two lines of evidence were provided for this hypothesis: (1) interictal epileptiform discharges preferentially occur during the early slow-wave downstate where neuronal firing is normally silenced but synchronization is high; and (2) interictal epileptiform discharges occur more frequently during larger slow wave where synchronization is assumed to be greater [20]. Interictal epileptiform discharges functionally interact with diverse and remote cortical regions via induction of coupled spindles [21]. With deepening of NREM sleep, generalized interictal epileptiform discharges increase and can look irregular and focal [22]. The differing stages of sleep also have an effect on focal epilepsies [1]. NREM sleep has been shown to activate focal interictal epileptiform discharges in patients with focal epilepsy, with more spikes seen during slow-wave sleep (N3) [8]. While interictal epileptiform discharges are more prevalent in slow-wave sleep, seizures tend to occur out of earlier stages of sleep more commonly [1].

One of the main theories proposed to explain nocturnal seizures is the presence of circadian mechanisms. We report some examples:

- Seizures of primary generalized tonic-clonic epilepsy have two peaks during sleep: the first 2 h after sleep onset and then toward the end of sleep [4].
- Myoclonic and generalized tonic-clonic seizures in juvenile myoclonic epilepsy occur characteristically in the morning during the first 1–2 h after awakening [23].

NREM sleep is also associated with increased propagation of spikes, while rapid eye movement (REM) sleep is more frequently associated with restriction of those abnormalities [24]. Although they are less frequent, interictal epileptiform discharges occurring during REM can be more accurate for definitive localization, especially when patients are evaluated for epilepsy surgery [7]. When more than one

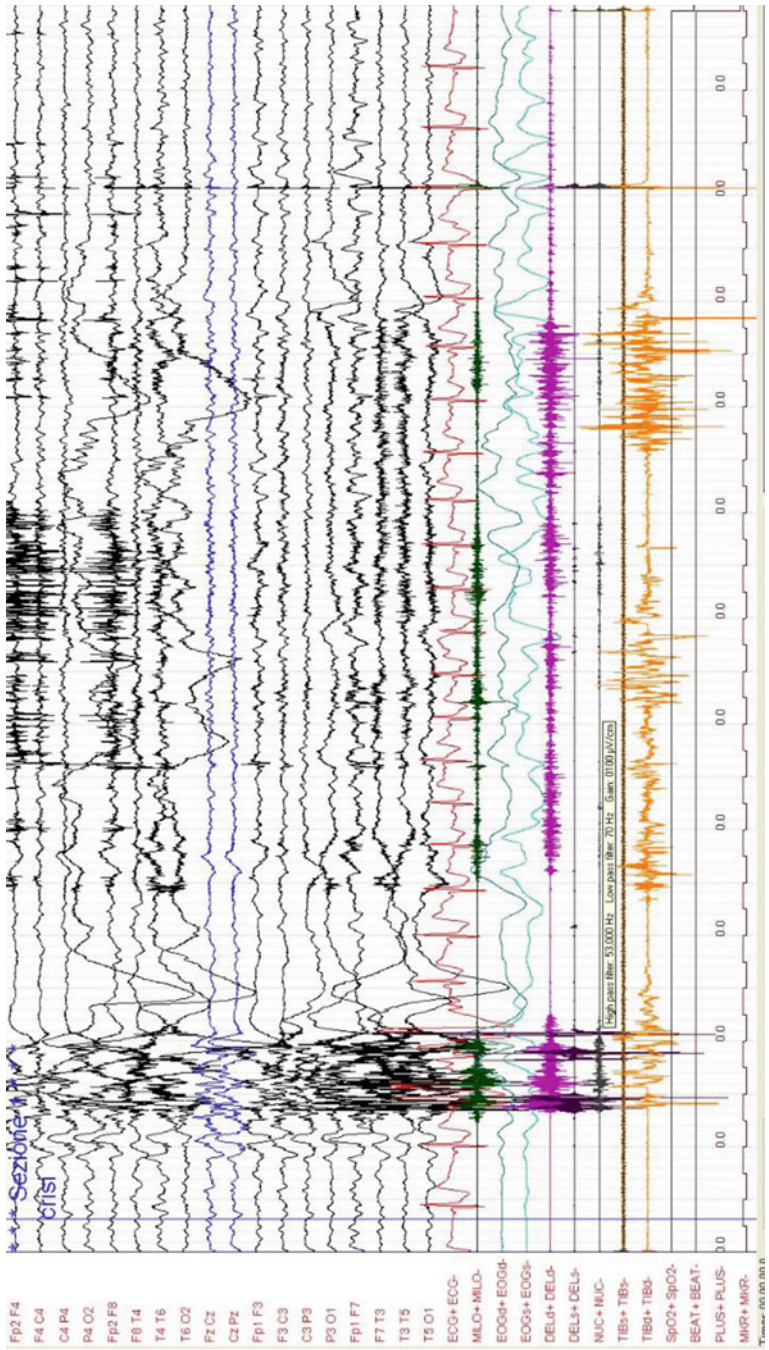

Fig. 33.1 Tonic seizure occurring in N2 sleep in an adult subject with Lennox-Gastaut Syndrome. EEG shows rhythmic generalized epileptiform discharges for 1 s, followed by diffuse slow activity for 1 min. The illustration is taken from an EEG performed in the Epilepsy Center of San Paolo Hospital in Milano (the patient's relatives gave informed consent instead of the patient suffering from intellectual disability)

epileptic focus is seen during wakefulness or non-REM sleep, discharges persisting during REM sleep are more likely the site of onset for the patient's seizures [25, 26]. Montplaisir and others [27, 28], on the basis of depth electrode studies, have proposed a restricted field with limited spread of interictal discharge to regions outside the epileptogenic region during REM sleep. The less frequent spiking in this stage may have a localization value.

33.3.2 Cyclical Alternating Pattern (CAP) and Epileptic Phenomena

In the microstructure of sleep, certain dynamic key points have been found to be associated with epileptic activation. These are identified as cyclic alternating pattern (CAP) consisting of alternating patterns of high-frequency and low-frequency EEG discharges. In the majority of epilepsies, seizures and interictal epileptiform discharges are gated by CAP and within CAP-A phase, which is characterized by a paroxysm of phasic activity representing a state of greater arousal with respect to CAP-B and non-CAP phases [29]. Bonakis suggests that increased seizure activity and poor seizure control in JME correlate with enhanced intrusion of SWD into CAP-B phase [30].

If the interictal epileptiform discharges that emerge at the very end of phase B/very beginning of the phase A (the "B to A" of view 1) were to be deemed as generators of the ensuing phase A of enhanced arousal, more than one-half of the total (those well inside B phase plus the "B to A") would be considered as lying within the B phase; from this viewpoint, the A phases that begin with an epileptic discharge would reflect the failure of the inhibitory mechanisms to maintain a lower state of arousal (phase B) as they yield to an increased "epileptic pressure"; this would be an obvious reason for the increased CAP rate in patients with JME compared to nonepileptic subjects. Such increased pressure is probably implied also by the large number of interictal epileptiform discharges in phase B that is significantly associated with poor seizure control. Increased epileptic pressure may cause disruption of the inhibitory mechanisms of phase B, increase CAP rate by contributing to more A phases, and beget more [30].

33.3.3 Effects of Sleep Fragmentation on Epilepsy

Arousals tend to activate certain types of epilepsies, such as juvenile myoclonic epilepsy (JME), possibly pointing to the hypersynchronization during arousal as a cause for seizures [1].

Sleep deprivation has been known to activate epileptic seizures and interictal epileptiform discharges independent of duration of sleep deprivation or NREM sleep stage after sleep deprivation [31–33]. High wake after sleep onset (WASO) rate is a marker of sleep disruption. This can result in relative sleep deprivation [2]. Sleep deprivation has been shown to lead to an increase in cortical excitability [34], which is even more pronounced in patients with genetic generalized epilepsy (GGE) [35].

After sleep deprivation in patients with focal or generalized epilepsy, the cortical excitability increases with time awake and appears to vary according to the epilepsy syndrome [35]. Cortical excitability is also modulated by the circadian phase, it is more reduced in the evening hours than during the day [33]. Clinically, patients report an increase in seizure probability the morning after sleep deprivation [33]. Seizures that occur exclusively during sleep are less associated with patient injury. Overall, seizures that happen exclusively during sleep carry a better prognosis (Park et al. 1998), although this may be less for focal epilepsies [36].

33.4 Circadian Rhythm and Epilepsy

Epileptic phenomena tend to occur in patterns that follow the time of the day [10]. Cortical excitability is modulated by circadian phase, such that cortical excitability is lesser in the evening hours than during the day [37]. Circadian mechanisms play a part in activating interictal epileptiform discharges [38]. The circadian timing system affects brain function relevant to epilepsy in two ways:

1. The system contributes to the regulation of the timing of wakefulness and sleep and its phases.
2. The system modulates brain function during sleep and wakefulness [39].

Different focal epilepsies can have different circadian peaks (Table 33.1).

Clearly sleep, a physiologic process strongly regulated by the circadian system, plays a role in these patterns. However, there is a greater appreciation of the role of the circadian pathways in epilepsy and the mechanisms underlying this pattern are still being defined [10]. Possible mechanisms underlying this pattern can be:

– A link between melatonin and epilepsy.
– A link between genes and circadian rhythm.

Although some evidence indicates that epilepsy types are related to chronotype, data are conflicting [37]. Studies founded that subjects with epilepsy were more morning oriented, having earlier mid-sleep time, and longer sleep duration on free days than healthy controls. However, there is no difference between patients with generalized and focal seizures in this regard [33, 45]. Other researches have suggested that patients with genetic generalized epilepsy might have a late chronotype compared with patients with focal epilepsy [33, 46]. A study found that Morningness-Eveningness Questionnaire (MEQ) scores were lower (indicating evening preference) in patients with genetic generalized epilepsy than in those with focal epilepsy, but were not lower than in healthy controls [47]. Dim-light melatonin onset in patients with genetic generalized epilepsy occurred around 40–50 min later than in healthy controls and patients with focal epilepsy [47]. These data support an endogenous late circadian phase for patients with genetic generalized epilepsy [47].

Table 33.1 Circadian variation in various types of seizures

Seizures' type	Circadian peaks
Mesial temporal lobe seizures	Two diurnal peaks: 1. Morning 2. Late afternoon They are more likely to generalize during sleep [10]
Frontal lobe seizures	Occur mostly during sleep with an early morning peak [10]
Occipital lobe seizures	Peak in the early evening and rarely occur during sleep [10]
Parietal lobe seizures	Have mixed reports, some reporting an early morning peak occurrence and others with rare sleep-related frequency [11, 12, 40–44]

Corticospinal excitability was reported to depend on chronotype and to undergo a time-of-day influence, which appeared independent of sleep [33].

The literature indicates there might be a relationship between circadian rhythmicity and epilepsy. Circadian rhythms in several physiological functions have been shown to be changed in epileptics. Also several human studies have shown diurnal rhythmicity in seizure occurrence. Unfortunately, none of these studies has taken circadian rhythmicity into account [45].

The discrepancies between studies about epilepsy type and chronotype are not easily explained. Some possible explanations can be differences of age in samples and small dimension of the samples.

A link between melatonin and epilepsy has been established over time [10]. Phase shifts of melatonin secretion have been demonstrated in patients with epilepsy [48] and overall decreases in melatonin levels have been described in patients with epilepsy as well [47, 49].

As reviewed by Jain and Besag [50], evidence for the role that melatonin may play in clinical practice is mixed and may be due to the aforementioned difference between the interaction of circadian rhythm with distinct seizure types. Melatonin has been shown to reduce seizure frequency and severity even in patients with intractable epilepsy [51].

Several studies have considered the possibility of using melatonin to improve seizure control; however, results have been conflicting [37]. A Cochrane review did not draw any conclusion about the role of melatonin in reducing seizure frequency [52].

Chronotherapy might also entail application of bright-light therapy in the treatment of epilepsy. A randomized controlled trial of 77 adults with medically intractable focal epilepsy not only showed some improvement in selected patients with hippocampal pathology but also cautioned that light stimulation can provoke seizures in other patients. Initial findings of Baxendale's study suggest that caution should be exercised in using bright light therapy in people with extratemporal focal epilepsy as it may result in an increase in seizures for some [53].

Another aspect of the circadian rhythm occurs at the cellular/molecular level, where certain genes are believed to be integral to keeping this clock attuned (e.g., CLOCK, PER1, and PER2) [54].

In animal epilepsy models, expression of many neurotransmitter receptors (e.g., benzodiazepine and GABA) and ion channels (e.g., the voltage-dependent potassium channels) is under circadian regulation [55, 56].

Two principal mechanisms can mediate the circadian variation of epileptic excitability in both human and animal epilepsy [37].

A histopathological study reported that the CLOCK protein is substantially reduced in excitatory and inhibitory neurons in epileptic tissue of patients with focal cortical dysplasia and tuberous sclerosis complex [57, 58]. Clock genes (e.g., CLOCK and BMAL1) and circadian transcription factors have been shown to influence excitability and seizure threshold.

Another mechanism contributing to circadian variation in epileptic activity is mediated by the circadian variations in the mammalian target of rapamycin (mTOR) pathway that is a master regulatory system of cell functions [59–63].

33.5 Epilepsies Associated with Sleep

Some epilepsy syndromes are known to have close relationships with sleep state [7] (Table 33.2). Many of the sleep-related epilepsies tend to start in childhood. In the pediatric population, one of the more common epilepsies is self-limited epilepsy of childhood with centrotemporal spikes [1, 64].

Self-limited epilepsy with centrotemporal spikes has a characteristic clinical picture [7]. Seizures occur predominantly or exclusively during sleep and consist of hemifacial twitching lasting less than 2 min rarely leading to bilateral tonic clonic seizures [7]. Characteristic centrotemporal spikes always increase with sleep, typically dramatically [65, 66]. CEOP or Panayiotopoulos syndrome consists of seizures with predominantly visual hallucinations, rarely evolving in bilateral tonic clonic seizures and commonly with coexisting migraine symptoms [67]. Landau-Kleffner syndrome is a condition of acquired aphasia, with a markedly epileptiform EEG, particularly in sleep and frequently (but not always) with epileptic seizures and with documented hypometabolism on SPECT [68]. This epilepsy presents in childhood with language regression. EEG is characterized by continuous spike-wave discharges during sleep, associated with cognitive and psychological deficits [1].

In electrical status epilepticus in sleep (ESES), epileptic discharges are nearly continuous throughout NREM sleep (Fig. 33.2) but resolve with wakefulness [7]. If

Table 33.2 Epilepsies associated with sleep

- Benign epilepsy of childhood with centrotemporal spikes (BECTS)
- Childhood epilepsy with occipital paroxysms (CEOP or Panayiotopoulos syndrome)
- Landau-Kleffner syndrome
- Electrical status epilepticus in sleep (ESES)
- Lennox-Gastaut syndrome (LGS)
- Genetic generalized epilepsies
- Sleep-related hypermotor epilepsy (SHE)

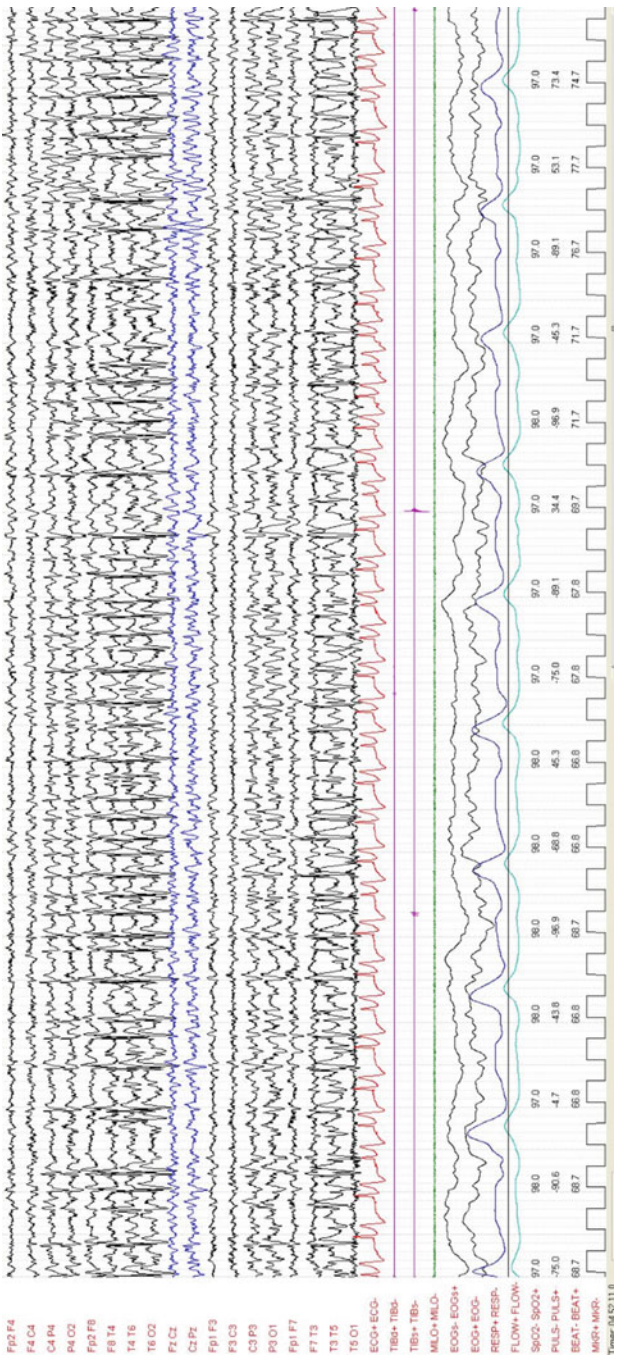

Fig. 33.2 ESES. The illustration is taken from a video-EEG performed in the Epilepsy Center of San Paolo Hospital in Milano. The patient's relatives gave informed consent instead of the patient suffering from intellectual disability

seizures occur they resolve in adolescence; neurocognitive status also improves around this time; however, some patients have residual deficits [69].

Lennox-Gastaut syndrome is a severe epileptic encephalopathy with childhood onset that usually continues through adolescence and into adulthood. In the long term, patients still have intractable seizures, intellectual disability, behavioral problems, and physical comorbidities. In adult LGS patients, tonic seizures during sleep remain the major seizure type; moreover, a standard waking EEG may be normal [70]. Thus, ideo-polisomnography represents the most important means of investigation also in adult Lennox-Gastaut syndrome patients [70].

Another common sleep-related epilepsy of adolescence is JME, but all the GGE are strongly modulated by sleep-wake rhythm (Fig. 33.3) [1].

GGE is a group of epileptic syndromes particularly modulated by the sleep-wake transition process, with a pronounced susceptibility to sleep deprivation, both in terms of the occurrence of seizures and of interictal epileptiform discharges [71]. Spike-wave discharges with a frequency of 3 Hz is the EEG marker in GGE. In all GGE, GTCS tend to occur after awakening and are particularly likely to happen when the person is aroused after sleep deprivation followed by brief sleep [72, 73]. JME is the most common GGE and the prototypical awakening epilepsy commonly precipitated by lack of sleep [71]. Janz observed that the patients with awakening epilepsies were often late sleepers and late risers, predisposing them to chronic sleep deprivation [74]. JME classically presents with myoclonic jerks or GTCS within 1–2 h of awakening.

In GGE with GTCS only, seizures occur exclusively in the morning hours [7]. A second peak of seizure occurrence, sometimes representing the principal one, is frequently observed in the evening hours or late afternoon or on relaxation. In adults, focal onset seizures are the most common types of epilepsies occurring out of sleep [1]. Of those, frontal and temporal lobe seizures are the most common types, with frontal lobe classically being the most common epilepsy to occur out of sleep [1].

Frontal lobe epilepsy is frequently a diagnostic challenge for several reasons [7]. Awareness during violent movements can suggest nonepileptic events [7]. Prominent choking and abnormal motor activity can lead to a misdiagnosis of sleep apnea [75] or other sleep disturbance [76].

In a review of 100 consecutive cases of nocturnal frontal lobe epilepsy (NFLE), 28% occurred in stage 3 sleep and only 3% during REM [77].

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is characterized by enuresis, sudden awakenings with dystonic or dyskinetic movements, and complex and violent behavior in sleep [75]. Most patients showed ictal or rhythmic activity over the frontal region [7].

Classically nocturnal frontal lobe seizures are characterized by paroxysmal arousals with hypermotor movements with complex motor movements, lasting a brief amount of time [1]. About half of the time the EEG is normal interictally and can even be normal during the seizures [1].

NFLE is recognized worldwide and has been studied in a wide range of clinical and scientific settings [78]. To improve the definition of the disorder and establish diagnostic criteria with levels of certainty, a consensus conference using formal

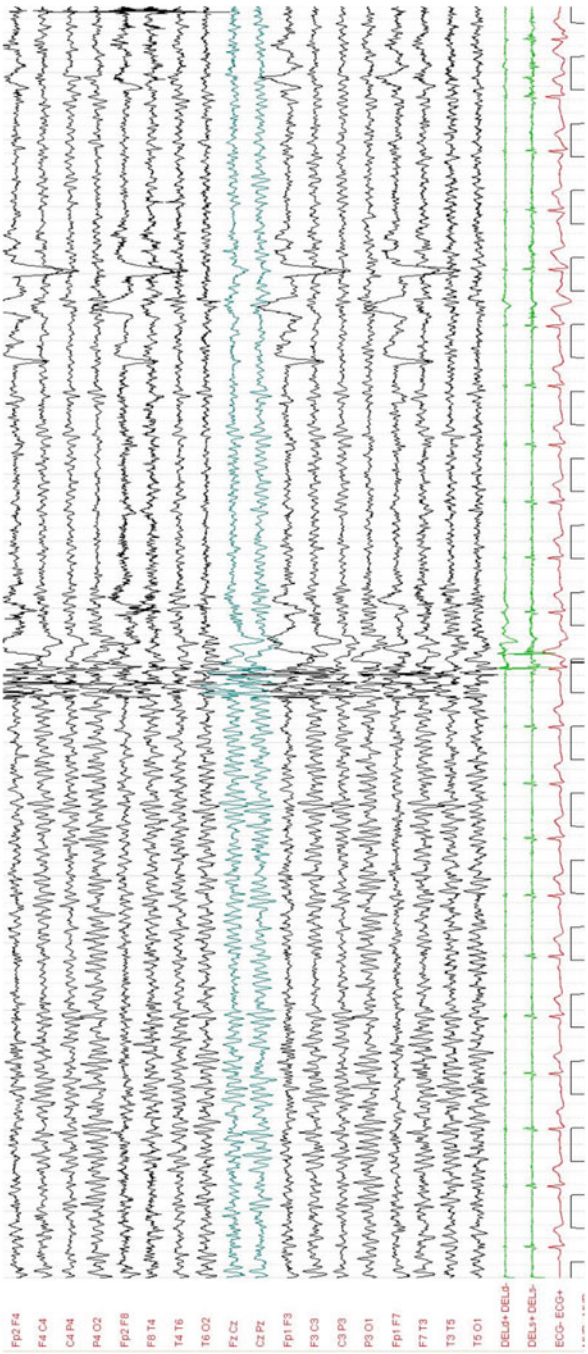

Fig. 33.3 Myoclonic seizures after awakening in a patient with EMG. The illustration is taken from a video-EEG performed in the Epilepsy Center of San Paolo Hospital in Milano. The patient gave informed consent

recommended methodology was held in Bologna in September 2014 [78]. It was recommended that the name be changed to sleep-related hypermotor epilepsy (SHE), reflecting evidence that the attacks are associated with sleep rather than time of day, the seizures may arise from extrafrontal sites, and the motor aspects of the seizures are characteristic [78]. The etiology may be genetic or due to structural pathology, but in most cases remains unknown [78].

Sleep-related temporal lobe seizures are also quite frequent, representing one-third of overall temporal lobe seizures in epilepsy monitoring units [1].

Many of these patients awaken from sleep with an aura and then progress to their typical focal seizure and have amnesia of the event [42].

Sleep not only affects seizure onset but also influences seizure propagation [7]. Temporal seizures, but not frontal seizures, are more likely to become diffuse when beginning during sleep compared to wakefulness, suggesting differential seizure spread in sleep depending on site of onset [9].

33.6 Comorbid Sleep Disorders in Epilepsy

Patients with epilepsy can have comorbid sleep disorders epilepsy [1].

33.6.1 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is a common complaint among epilepsy patients. Vaughn et al. [79] reported complaints of EDS in 61% of 154 epilepsy patients given the ES. One study found little effect of the number of antiepileptic medications, seizure frequency, epilepsy syndrome, or nocturnal seizures on the complaint of excessive daytime sleepiness [80]. This finding can result from a major effect of sleep disorders on subjective sleepiness. The study of Malow et al. [80] found that symptoms of treatable sleep disorders are strong predictors of subjective sleepiness than the number or type of antiepileptic medications or the frequency of seizures. Before attributing sleepiness in epilepsy patients to antiepileptic medications, clinicians should consider the possibility of an underlying sleep disorder.

It is well known that the evaluation of this symptom in patients with epilepsy is highly likely to be biased by factors such as antiepileptic multidrug treatment, seizure recurrence, or associated intellectual disability [81].

33.6.2 Obstructive Sleep Apnea (OSA)

In 2003, a systematic, clinical, and PSG investigation of unselected adult subjects with epilepsy found an OSA prevalence of 10.2% (15.4% in men and 5.4% in women) [81], while the prevalence of coexistent OSA and epilepsy in children was reported to be 20% [82]. Obstructive sleep apnea is associated with seizure

exacerbation in older adults with epilepsy and its treatment may represent an important avenue for improving seizure control in this population [83]. Approximately one-thirds of patients undergoing epilepsy presurgical evaluation have been found to have sleep disordered breathing with the most common one being obstructive sleep apnea [84].

Several retrospective studies have shown improved seizure control in patients with refractory epilepsy with continuous positive airway pressure treatment, with one study showing a comparable effect in some patients with adjunctive antiepileptic drug treatment; with 50–60% of patients experiencing a 50% or greater seizure reduction [85].

In cases when sleep deprivation (or sleep inefficiency) is due to OSA, respective treatment might lead to a reduction in seizure frequency [2]. The study of Popkirov et al. does not support the claim that OSA is a particularly common cause of sleep disruption in epilepsy patients, which can lead to a worsening of seizures' control [2]. If a patient with epilepsy reports sleep disturbances, other factors such as medication effects, psychiatric comorbidities, and nocturnal epileptic activity must be considered [2].

33.6.3 Insomnia

Insomnia can also affect patients with epilepsy [1]. Arousals can be due to multiple factors, including epilepsy itself or medication effects [1]. Patients can also have fears associated with sleep, such as having a seizure out of sleep [1]. Frequent arousals have been shown to be a trigger and manifestation of seizures themselves [66]. Patients with epilepsy have higher incidences of anxiety and depression compared to the general population, with these disorders frequently being associated with insomnia [1].

Even when restricted to sleep, seizures can affect quality of life through sleep disruption, possibly contributing to the memory problems that many patients report [7]. Many aspects of memory are known to require restoring sleep [86, 87], particularly REM and slow-wave sleep [88, 89]; therefore, this should be a consideration not only in counseling patients about sleep but also in choice of ASMs. Newer research suggests that the slow oscillations seen during sleep may influence the consolidation of memories from the hippocampus, which could be particularly important in patients with uncontrolled hippocampal onset seizures [90].

33.6.4 Parasomnias

Seizures occurring out of sleep can be difficult to distinguish from NREM and REM parasomnias [1]. Video-polysomnography (VPSG) with extended EEG montage may be necessary for a definitive diagnosis [1].

NREM sleep parasomnias, disorders of arousal, including sleep walking, sleep terrors, and confusional arousals, occur in the first half or first third of the night. They

are associated with minimal or partial memory of the event and typically occur in childhood or adolescence [91].

REM sleep behavior disorder is a REM sleep parasomnia characterized by patient's acting out their dreams due to loss of atonia during REM sleep; it is more common during the latter half of the night [91]. Undiagnosed or misdiagnosed RBD can coexist with epilepsy in the elderly. The neurobiological meaning of the coexistence of seizures and RBD is still unclear. The two conditions could co-occur by chance or they may both be underlain by neurodegenerative processes [92].

To differentiate seizures from parasomnias, it can be helpful to consider that epileptic seizures are characterized by their stereotypy, brief duration, amnesia of the event, and postictal state with the caveat that consciousness may be intact and postictal state may be very brief with some frontal lobe onset seizures [1].

Epileptic seizures must also be differentiated from psychogenic nonepileptic seizures (PNES). PNES may occur during what appears to be behavioral sleep (pseudosleep) while EEG is consistent with wakefulness; eyes are typically closed during PNES, whereas eyes are open during epileptic seizures [1].

33.6.5 Effects of Epilepsy on Sleep Quality

People with epilepsy have poorer sleep quality and impaired micro- and macrostructure of sleep, while the manifestations of epilepsy, including timing and severity of seizures, appear to be influenced by endogenous circadian pathways. Understanding of these interactions has led to new strategies in evaluating patients for epilepsy [10].

The effect of epilepsy on sleep can be related to the same pathophysiological mechanism causing epilepsy, can be the effect of seizures, ASMs therapy, or a combination of these factors [1, 7].

Increased sleep onset latency, wake time after sleep onset, instability of sleep stages, stages N1 and N2 NREM sleep (light sleep), CAP rate, decreased sleep spindle density, and REM sleep have all been reported in patients with epilepsy [1].

A seizure occurring out of sleep may be associated with decrease in REM sleep and sleep efficiency and increase in light sleep [1]. REM sleep and sleep efficiency may be further reduced if a seizure occurs before the first REM cycle [93].

Patients with temporal lobe epilepsy showed increased wakefulness after sleep onset compared with patients with frontal lobe epilepsy and, therefore, decreased sleep efficiency [7]. When patients with temporal lobe epilepsy were compared under baseline conditions (seizure free) and following daytime complex partial or secondary generalized seizures, there was a significant decrease in REM the following night without significant changes in other sleep stages or in sleep efficiency. When seizures occurred at night, this decrease in REM was more pronounced and there were increases in stage 1 and decreases in sleep efficiency [94]. A report of sleep following focal status showed severe inhibition of REM sleep for several days [95].

Many patients note postictal hypersomnolence following seizure which may last for more than a day at times. This report is frequent in temporal lobe and in convulsive seizures [1] [9]. Seizures can cause sleep disruption by decreasing sleep efficiency, increasing sleep stage shifts, and increasing periods of wakefulness [93]. Increased sleep fragmentation and instability can happen on seizure-free nights as well [1].

33.7 Effects of ASMs on Sleep

Antiseizure medications (ASMs) can cause sedation or may promote alertness and may have direct effect on sleep architecture [1]. Moreover, ASMs are known to be involved both in the genesis and the treatment of sleep disorders such as OSA or RLS. Studies looking at the effect of anticonvulsivant medications on sleep must be interpreted with caution [7] [96]. A review of studies describing the effects of ASMs is shown in Table 33.3. For details, please refer to Chap. 35.

Studies on Brivaracetam have not been published previously.

It is interesting that agents with very different mechanisms have similar effects on sleep structure [7]. Probably like many drugs, anticonvulsants affect sleep through multiple potential mechanisms. ASMs with very different mechanisms can also affect sleep disorders [7].

The effect of ASMs on sleep may vary from patient to patient. Patients should be closely monitored and questioned about changes in sleep patterns upon initiation or change in ASMs therapy. Knowledge of the effects of ASMs on sleep can help in medication selection based on the patient's sleep history. Patients with insomnia may benefit from being on ASMs with higher sedating potential or a higher dose of it in the evening. On the other hand, patients with hypersomnia or daytime sleepiness may benefit from being on an ASMs with less potential to cause sedation or one that promotes alertness in the morning [1].

33.8 Effect of Vagus Nerve Stimulation on Sleep

Vagus nerve stimulation (VNS) is a Food and Drug Administration–approved therapy for refractory epilepsy [112]. VNS is believed to modulate vagal input to the nucleus of the solitary tract, although its antiepileptic mechanisms are largely unknown [113].

Increased sleep latency on the MSLT indicating reduced daytime sleepiness was noted in patient on VNS therapy [114].

Higher VNS stimulus intensities (> 1,5 mA) are associated with disturbed sleep due to increased arousals, NREM stage 1 sleep, increased wake after sleep onset, reduced percentage of REM sleep [115], and increased mean sleep latency on MSLT test [116].

Patients with VNS therapy at relatively low stimulus intensities were found to have a significant improvement in sleep latency as observed on MSLT in a study

Table 33.3 Effect of antiepileptics on sleep

Effect on sleep architecture or on nocturnal/diurnal symptoms	Related drugs
Decrease in sleep onset latency (SOL)	• Phenytoin • Phenobarbital • Gabapentin [97] • Benzodiazepine (clonazepam and clobazam) [7]
Increase of SOL	• Felbamate [7]
Increase in arousals from sleep	• Valproate [98]
Increase in slow-wave sleep (SWS and N3 NREM sleep)	• Pregabalin [99] • Gabapentin as monotherapy [100] and add-on• Therapy [101]
Increased sleep efficiency	• Carbamazepine • Tiagabine [102]
Decrease in SWS	• Levetiracetam • Ethosuximide • Benzodiazepine [7, 97] • Lamotrigine (in one study as add-on therapy) [103, 104]
Increase in NREM Increase in N1	• Benzodiazepine • Valproic acid [100]
Increase in REM duration	• Ethosuximide • Gabapentin • Lamotrigine (in one study as add-on therapy) [101]
No significant effect on sleep architecture	• Topiramate • Zonisamide [104, 105] • Lacosamide did not have any subjective or objective effect on sleep in healthy individuals [107] • Lacosamide • Lamotrigine (in one study as monotherapy) [100] • Levetiracetam did not reveal significant effect on sleep [108]
Daytime sleepiness, tested by MSLT or MWT	• Phenobarbital • Valproic acid • Levetiracetam • Carbamazepine • Phenitoin (the study could not distinguish between the drugs) [109]
No sleepiness, tested by MSLT or MWT	• Topiramate [106] • Lamotrigine • Zonisamide • Vigabatrin [7]
Improvement of sleep quality	• Gabapentin [110]
Worsening of sleep apnea	• Benzodiazepines • Phenobarbital • Pregabalin • Valproate
Improvement of sleep apnea	• Topiramate • Zonisamide [7]
Worsening of restless legs syndrome	• Lamotrigine

(continued)

Table 33.3 (continued)

Effect on sleep architecture or on nocturnal/diurnal symptoms	Related drugs
Improvement of restless legs syndrome	• Carbamazepine • Gabapentin • Pregabalin [7] • Perampanel [111]

[116] and in daytime sleepiness (decreased ESS scores) [114] or decreased naps on sleep diaries [115], even without improved seizure frequency from preimplantation baseline [114–116].

Increased slow-wave sleep and stage NREM sleep in patients on VNS therapy have also been reported [117].

Lower current intensity may increase sleep-onset REM periods compared to baseline, though it does not appear to change percentage of sleep stages or other sleep parameters on overnight polysomnography [114, 115]; however, increased N3 sleep has been observed in children [117].

VNS has been associated with SBD in some cases possibly due to the reduction in the laryngeal space related to VNS stimulation [114, 118].

Higher VNS stimulus intensities and rapid cycling on and off have been associated with development of nocturnal stridor, snoring, and development and/or worsening of obstructive and central sleep apnea [10].

Lowering the frequency and increasing the cycle time may be helpful to prevent worsening of sleep apnea during VNS therapy [119].

Thus, it is important to screen for sleep apnea before and after VNS implantation and to keep in mind that decreasing VNS stimulus intensity may improve VNS-induced sleep apnea [10].

33.9 Sudden Unexpected Death in Epilepsy and Sleep

Sudden unexpected death in epilepsy (SUDEP) is defined as a "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus in which postmortem examination does not reveal a toxicologic or anatomic cause for death" [120].

The incidence may be as high as 6, 0–9, or 3 per 1000 patient-years among patients evaluated for or treated with epilepsy surgery or those who continue to have seizures after epilepsy surgery [120].

The mechanism responsible for SUDEP remains unclear but the role of sleep has been suspected [1].

Several different mechanisms probably exist and most research has focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction. Changes in autonomic function during sleep increasing

vulnerability to cardiorespiratory decompensation during seizure may be a possible reason for increased occurrence of SUDEP during sleep [1].

Convulsive seizures are the most important risk factor for SUDEP, as they have been observed in a vast majority of witnessed and monitored SUDEP cases [121, 122].

Although the risks of SUDEP associated with sleep are unknown and likely multifactorial, the prone position might be an important contributory factor [123].

Most researches have focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction [120].

Changes in autonomic function during sleep increasing vulnerability to cardiorespiratory decompensation during seizure may be a possible reason for increased occurrence of SUDEP during sleep [1].

33.10 Conclusions

Sleep and epilepsy are closely related, with certain stages of sleep providing a hypersynchronous state, allowing more frequent IED, along with more frequent seizures. Certain epilepsies are associated with sleep, especially in childhood, with epilepsies in adults activated by both sleep and sleep deprivation.

Comorbid sleep disorders are common in patients with epilepsy and can affect epilepsy management. Treatment of sleep disorders may improve seizure control [1].

Some parasomnias may mimic seizures. Polysomnography with extended EEG montage may be necessary for characterization.

Seizures can adversely affect quality and quantity of sleep, whereas antiepileptic therapy (ASMs, VNS, or surgery) can have negative or positive effect on sleep [1].

Inquiring about quality as well as screening evaluation and treatment for sleep disorders should be a part of care in patients with epilepsy [1].

The complex interplay among sleep, sleep disorders, and epilepsy is important for the care of epilepsy patients on many levels [7]. Diagnostically, the usefulness of sleep and sleep-deprived EEG/PSG recordings in the complete characterization of patients is well demonstrated [7].

Relationship of seizures to sleep and wakefulness can help in classifying epilepsy syndrome and in prognosis definition [7].

While exclusively or predominantly nocturnal seizures may be less disruptive to patients on certain levels, their elimination should still be a primary goal [7].

The choice of antiepileptic treatment can affect sleep and this is an important consideration in the total management of the patient with epilepsy [7].

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Sleep Disorders in Multiple Sclerosis

34

Govind Madhaw and Niraj Kumar

Abstract

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system. Along with a variety of motor features, MS patients may develop several non-motor features including fatigue, sleep disturbances and pain. Multiple factors such as pain, nocturia, depression, muscle weakness, effect of multiple drugs and disease severity all contribute to sleep disruption in cases of MS. Lack of sound sleep in MS patients often leads to increased fatigue, excessive daytime somnolence, metabolic disturbances such as diabetes and obesity as well as increased risk of cardiovascular disorders. Roughly 2–21% of MS patients suffer from obstructive sleep apnoea (OSA) and 40% from insomnia, resulting in increased fatigue, impaired cognition, poor sleep quality, excessive daytime sleepiness and overall poor quality of life. This chapter focuses on the prevalence, pathogenesis and management of sleep disorders in patients with MS.

Keywords

Multiple sclerosis · Demyelination · Insomnia · Sleep · Obstructive sleep apnoea · Fatigue · Daytime sleepiness

34.1 Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system. It commonly affects young adults, with female-to-male ratio being 3:1 [1]. Both genetic and environmental risk factors

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influence the occurrence of MS [2]. Among the several genetic risk factors being currently explored in the causation of MS, presence of HLADRB1*1501 haplotype carries a great significance [1]. Geographical latitude (increased risk in temperate regions), vitamin D deficiency, smoking and infection caused by *Epstein-Barr* virus are few of the environmental factors which may contribute to the development of MS [1].

Depending on the geographical latitude, the prevalence of MS varies with the highest prevalence in North America (140/100000) and lowest in East Asia and Africa (2.1–2.2/100000). The prevalence of MS is gradually increasing with the mean global prevalence reported in 2013 being 33/100000 population [3]. Although rapidly changing lifestyle and global environmental disarray are commonly linked to the increased disease prevalence, the role of better diagnostic facilities leading to early disease detection cannot be overlooked. Introduction of several disease-modifying drugs over the past couple of decades has revolutionized the treatment of MS. Most of the new drugs are powerful immunomodulatory agents with the ability to reduce inflammatory relapses and the long-term disability.

The clinical features of MS depend on the primary site of demyelination. Optic nerve, brainstem and spinal cord are the common sites affected in MS [2]. Along with a variety of motor features, MS patients may develop several non-motor features including fatigue, sleep disturbances and pain [4]. Sleep-related issues are often ignored when clinicians are dealing with any chronic illness. Moreover, at times, sleep-related issues are considered just a part of long-term illness or a symptom of depression or an adjustment problem. Among such patients, sleep disturbances increase the disease impact and are associated with poorer mental health and reduce work productivity overburdening the healthcare system. MS is one such chronic condition with a wide spectrum of symptoms requiring long-term treatment, where sleep-related disorders are prevalent as well as ignored. Sleep problems are quite commonly seen in MS with 25–54% patients being affected with it [5–8].

Multiple factors such as pain, nocturia, depression, muscle weakness, effect of multiple drugs and disease severity all contribute to sleep disruption in cases of MS. Lack of sound sleep in MS patients often leads to increased fatigue, excessive daytime somnolence, metabolic disturbances such as diabetes and obesity as well as increased risk of cardiovascular disorders. Increasing awareness among the medical community will contribute to early detection and treatment of these sleep abnormalities. The spectrum of sleep disorders seen in MS is included in Table 34.1 [9].

34.2 Fatigue in MS

Fatigue is the most frequent symptom in MS, affecting nearly 90% of cases and is often difficult to treat. It is the major reason for reduced functionality resulting in early retirement, reduced employment, and impaired quality of life, regardless of depression or disability [10]. Fatigue can appear at any stage of disease, even years before onset of classical motor symptoms. Fatigue is often confused with the term

Table 34.1 Spectrum of sleep disorders seen in multiple sclerosis (MS)

1.	Fatigue
2.	Excessive sleepiness
3.	Insomnia
4.	Sleep related Breathing disorders (SRBD): Apnoea, Hypopnoea
5.	Nocturnal urinary symptoms and sleep
6.	Narcolepsy
7.	REM sleep behavioural disorders/RBD
8.	Circadian rhythm in MS
9.	Nocturnal movement disorders: Restless legs Syndrome (RLS), Periodic Limb Movement during Sleep (PLMS)

sleepiness (Please refer to Chap. 6 in this book). While fatigue is a subjective feeling of lack of energy even early in the morning that increases during the day, sleepiness is characterized by difficulties to stay awake and alert during the day. If a patient with MS is asked whether he would like to sit and relax in a sofa this afternoon, patient with fatigue will affirm but those with sleepiness will be afraid of dozing. Fatigue is often difficult to assess quantitatively, although specific scales have been developed. The Modified Fatigue Impact Scale (MFIS) is an extended questionnaire developed from the Fatigue Severity Scale (FSS) which may have utility in monitoring MS-related fatigue [11]. Severity of fatigue exacerbates with increasing temperature, age, expanded disability status scale (EDSS) score, concomitant infections or physical and mental exertion.

Pathogenesis of fatigue in MS is multifactorial as already explained, with major contributors being pro-inflammatory cytokines such as TNF-alpha, altered hormonal profile including cortisol and dehydroepiandrosterone and loss of axons. In addition, various other sleep disorders are discussed in next section, comorbid depression and drugs used in the management of MS such as steroids or other disease-modifying therapies (DMTs), which contribute to fatigue [12] (Fig. 34.1).

In a study done by Čarnická Z et al. [13], poor sleep was present in 38%, excessive daytime sleepiness in 18% and fatigue in 38% of MS patients. The focus of this study was to assess the relationship between these subjective complaints using self-reported scales and nocturnal polysomnography (PSG) findings and clinical characteristics of the population. It was found that poor sleep, daytime sleepiness and fatigue were significantly influenced by the presence of restless legs syndrome (RLS).

Management: The first step includes identification and treatment of other co-morbid conditions such as diabetes mellitus, congestive heart failure, obesity, sleep apnoea, other sleep disorders, depression and anxiety. Lifestyle modifications such as quitting smoking, healthy eating and weight reduction are extremely useful. Various non-pharmacological therapies including yoga, acupuncture, muscle relaxation techniques, cooling therapy, Tai-chi and other stretching exercises often reduce fatigue in MS patients. Specially designed rehabilitation programmes including endurance and resistance exercises may be helpful [14]. Pharmacological

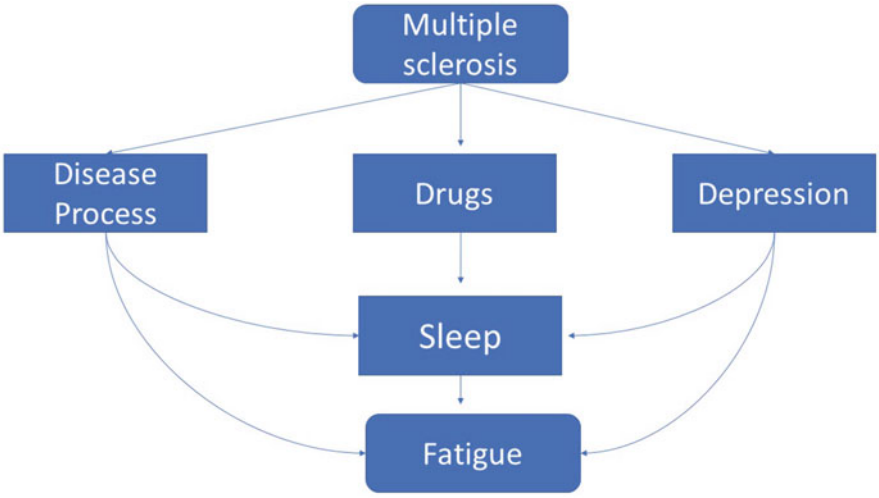

Fig. 34.1 Possible mechanism of fatigue in multiple sclerosis

interventions including amantadine, pemoline, modafinil and carnitine have been tried with encouraging results. Aminopyridines and coenzyme Q10 have been found to ameliorate fatigue by improving nerve conduction. Non-invasive brain stimulation (NIBS) techniques are also being used with some success [15].

34.3 Hypersomnia/Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) or hypersomnia in patients with MS may be due to thalamic lesions, concomitant psychiatric illness, mainly depression, sleep deprivation or effect of drugs such as muscle relaxants (baclofen) and antidepressants (tricyclic antidepressants). A score of 10 or more on Epworth Sleepiness Scale (ESS), a screening tool for daytime somnolence, indicates excessive daytime sleepiness (EDS) and warrants need of polysomnographic (PSG) assessment [16]. All fatigued patients must be screened for EDS as these two often mimic each other. Neuroimaging, that is, MRI, may reveal demyelinating plaque in brainstem or thalamus in patients of MS with hypersomnia.

Management: Identification and discontinuation of culprit drugs are helpful. Management of acute episode of MS with corticosteroids will be helpful if EDS is part of the episode.

34.4 Insomnia in MS

Insomnia is the most common sleep disorder affecting 10% of the adult population, though insomnia complaints are more frequent [17]. Patients of MS are at a greater risk for insomnia with a prevalence rate of more than 40% [8]. They often complain of difficulty falling asleep, maintaining sleep or getting up earlier than desired. Pain associated with muscle spasms, periodic limb movements, RLS, nocturia, effect of drugs such as steroids, selective serotonin reuptake inhibitors (SSRIs) and psychiatric illnesses such as depression are some of the common factors contributing to insomnia in MS patients. Insomnia Severity Index (ISI), a questionnaire designed to assess the nature, severity and impact of insomnia, is a useful tool to monitor the effects of insomnia interventions [18]. Chronic insomnia increases risk for major depression as well as frequent exacerbations and increasing severity of MS.

Management: Identification and discontinuation of medications interfering with sleep is the first step for correcting insomnia. SSRIs that are frequently used for comorbid depression; stimulants and wake-promoting agents commonly used for fatigue and antihistamines used as sedative by up to 25% of patients with MS may worsen RLS, resulting in sleep-onset insomnia. On the other hand, treatment of other co-morbid conditions including neuropathic pain with tricyclic antidepressants or pregabalin; spasticity using baclofen or tizanidine and urinary urgency with anticholinergics may significantly improve the insomnia [19]. Cognitive behavioural therapy could reduce anxiety and depression and consequently reduce the symptoms of insomnia. If the above measures fail, medications including benzodiazepines, benzodiazepine agonists, melatonin receptor agonists and orexin receptor antagonists may be used to improve insomnia and sleep quality [19]. Long-term treatment of insomnia is best directed towards addressing the underlying cause.

34.5 Sleep-Related Breathing Disorders

Reduction of airflow in the upper airway resulting in either hypopnoea or apnoea is called sleep-related breathing disorders (SRBDs). SRBDs are common in MS and may produce fatigue and reduced concentration ability. They may influence mood and memory as well and result in autonomic symptoms as disabling as erectile dysfunction.

Patency of the upper airway is maintained by tone of pharyngeal and laryngeal muscles innervated by vagal and hypoglossal nerves. Baroreceptors in airways, chemoreceptors in carotid bulb and various respiratory nuclei of brainstem, particularly those situated in medulla, regulate the firing rate of IX^{th} and X^{th} cranial nerves (Fig. 34.2). Any derangement in this pathway will impair nocturnal breathing. When the apnoea is due to lack of respiratory effort, brainstem pathology is suspected, and the situation is called central apnoea, whereas collapse of pharynx resulting in increased airway resistance despite good respiratory effort results in obstructive sleep apnoea 9Fig. 34.3). These two are easily distinguished by nocturnal PSG [20].

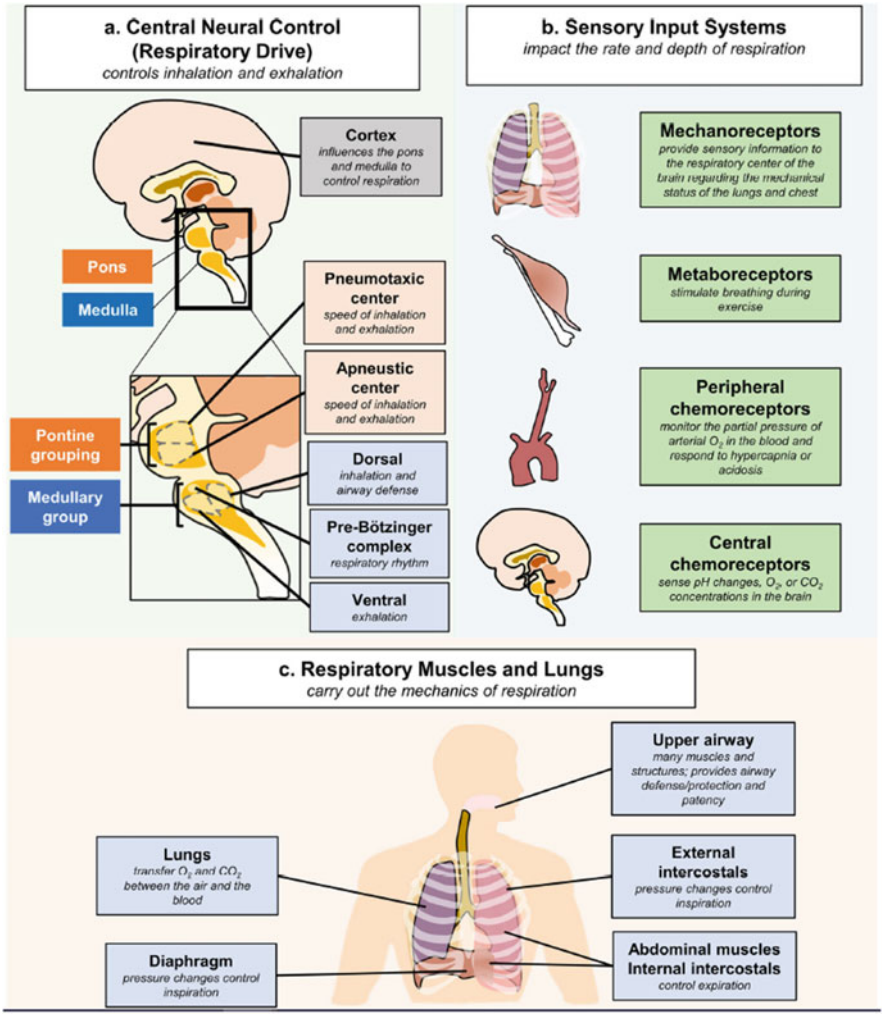

Fig. 34.2 Control of respiration. (**a**) The respiratory centre in the brain controls various components of respiratory drive, including inhalation, airway defence, exhalation and breathing patterns. (**b**) The sensory input systems are composed of mechanoreceptors, metaboreceptors and peripheral and central chemoreceptors that sense chemical changes and influence various components of respiration, such as breathing, lung space and irritation triggers. (**c**) Neuronal processes and sensory input systems are communicated to the respiratory muscles and lungs to control the mechanical aspects of respiration. (*Courtesy: Webster, L.R., Karan, S. The Physiology and Maintenance of Respiration: A Narrative Review. Pain Ther 9, 467–486 (2020).* https://doi.org/10.1007/s40122-020-00203-2*) Springer*

Obstructive sleep apnoea: Roughly 2–21% of MS patients suffer from obstructive sleep apnoea (OSA) resulting in increased fatigue, impaired cognition, poor sleep quality, excessive daytime sleepiness and overall poor quality of life [21].

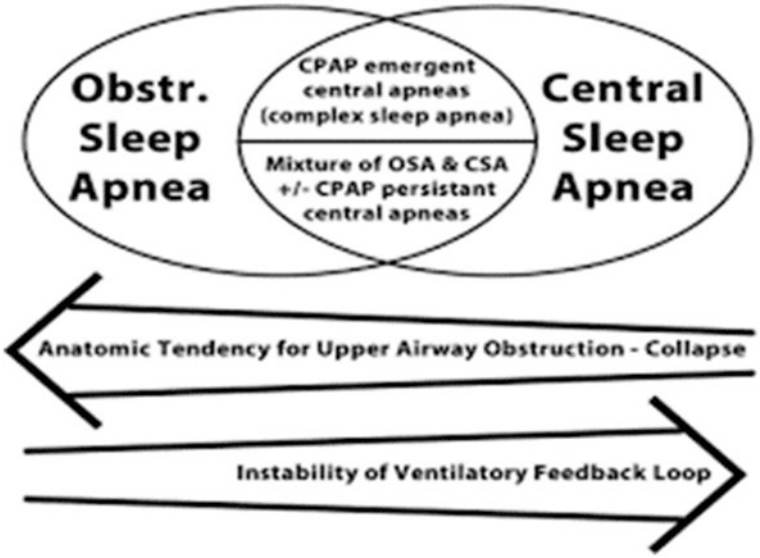

Fig. 34.3 Basic characteristics of central and obstructive sleep apnoea. (*Courtesy: Patz D. Complex Sleep Apnea (CPAP Emergent Central Apneas), and Apnea Related to Narcotics and to Altitude. In Primary Care Sleep Medicine 2014 (pp. 141–151). Springer, New York, NY*)

Management: The primary management includes identifying the co-morbidities, primary apnoea subtype and severity using nocturnal PSG. Drugs including central nervous system depressants such as opiates, antispasmodics and sedatives should be discontinued. Positive airway pressure (PAP) therapy such as bi-level PAP with or without supplemental oxygen alleviates the symptoms. Even disease-modifying therapies (DMTs) help in reducing apnoea symptoms, thus, supporting the potential role of inflammation in SRBDs [18].

Central sleep apnoea: Although the prevalence of central sleep apnoea (CSA) is much less as compared to OSA even in general population, patients with central nervous system disorders, particularly those affecting brainstem such as MS, are more vulnerable for this condition as well; the infamous Ondine's curse resulting in sudden nocturnal death (Box 34.1). In fact, MS can have whole spectrum of central nervous system-related respiratory disturbances such as central sleep apnoea, paroxysmal hyperventilation, hypoventilation, respiratory muscle weakness and respiratory arrest.

Box 34.1: Mythical story of Ondine's curse

In the ancient mythical story, a young nymph named Ondine falls in love and marries. Upon discovering that her husband been unfaithful to her, she uses her supernatural powers to set a curse on him. Ondine's curse is an unusual

(continued)

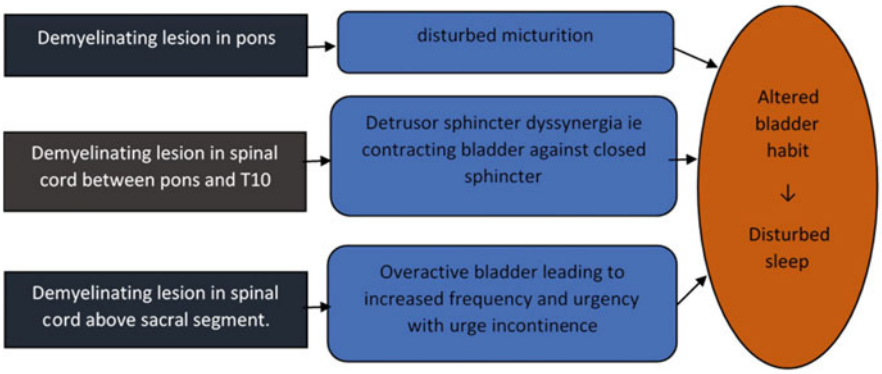

Fig. 34.4 Effect of spinal cord lesions on bladder function and sleep

Box 34.1 (continued)
spell that sneakily robs her disloyal husband of rest. He is doomed to a life in which he retains the ability to breath but only when he is awake and conscious. Once afflicted by Ondine's curse, the victim cannot breathe if he falls asleep—and therefore, must choose between sleeping and remaining alive. The dramatic fictional tale has a real-life counterpart in a rare disorder, central hypoventilation syndrome, often called Ondine's curse. Patients who are afflicted with central hypoventilation syndrome do not have the ability to maintain regular respiration during sleep or may stop breathing during sleep (Fig. 34.2).

Management: Almost 20% of central sleep apnoea cases resolve spontaneously. In case of symptomatic central sleep apnoea, various therapies can be helpful including PAP, carbon dioxide inhalation to increase respiratory drive, device to add dead space and rebreathing mask [18].

34.6 Nocturnal Urinary Symptoms in MS

Increased nocturnal urinary frequency is one of the common symptoms in MS and it can disturb the quality of sleep. Involvement of bladder pathway in spinal cord in patients of MS can result in various types of neurogenic bladder syndromes such as upper motor neuron type, that is, spastic bladder and detrusor sphincter dyssynergia (DSD). Involvement of pontine micturition centre can result in incontinence, hence, disturbing the sleep quality by frequent bed wetting. Increased frequency and urgency with or without incontinence can be there due to overactive bladder syndrome leading to nocturia. Bladder outlet obstruction or chronic pelvic pain syndrome is frequently seen in MS, thereby resulting in nocturia and, hence, poor sleep quality (Fig. 34.4). Concomitant comorbidities including urinary tract

infection, obesity, diabetes mellitus and cardiac disorders can also produce nocturia and sleep disturbances [22].

Management: Treating the co-morbid conditions such as diabetes mellitus, urinary tract infection, congestive heart failure or sleep apnoea is of utmost importance. Lifestyle modifications such as decreasing fluid intake after evening and emptying the bladder before sleep are helpful. Non-pharmacological measures such as cognitive behavioural therapy is specifically designed for nocturia. Anticholinergics (solifenacin) can be tried for overactive bladder. Other pharmacological measures include alpha-blockers, 5-alpha reductase inhibitors, oral phosphodiesterase-5 inhibitors, desmopressin and appropriately timed diuretics [23].

34.7 Narcolepsy in MS

Narcolepsy is a rapid eye movement (REM) phase of sleep disorder characterized by daytime sleep attacks, impaired nocturnal sleep, hypnogogic/hypnopompic hallucinations, cataplexy and sleep paralysis. Mean sleep latency of less than 8 min with two or more sleep-onset REM periods is the characteristic PSG finding. OSA, insufficient sleep, shift work or other disorders of circadian rhythm must be excluded before making the diagnosis of narcolepsy. Prevalence of narcolepsy in general population is estimated to be 0.02–0.05%. Although exact prevalence of narcolepsy among persons with MS is unknown, there are literatures describing narcolepsy like symptoms in MS resolving with steroid [18].

Subtypes of narcolepsy:

- *Primary narcolepsy Type 1*: reduced hypocretin level (<110 pg/ml) of CSF due to immune-mediated loss of secretory cells in lateral hypothalamus.
- *Primary narcolepsy Type 2*: normal hypocretin level.
- *Secondary Narcolepsy:* associated with other medical conditions such as Infection, inflammation, degeneration due to inherited defect, infiltration or injury to CNS, particularly brainstem. MS is fourth most common cause (12%) of secondary narcolepsy after inherited disorders, tumours and head trauma [24]. Both MS and narcolepsy are more common in person with human leucocyte antigen haplotype (HLA) DQB1*0602 and HLA-DR2, suggesting that similar autoimmune mechanism may be working in the development of each disorder [25].

Management: While CNS stimulants are helpful to increase wakefulness, antidepressants may be used for cataplexy and sleep paralysis. In case of secondary narcolepsy due to hypothalamic lesions, high dose of steroid is indicated [24].

34.8 REM Sleep Behaviour Disorder in MS

REM sleep is characterized by rapid movement of eyeballs with brainstem-mediated hypotonia of limbs and vivid dreaming. REM sleep behaviour disorder (RBD) is characterized by loss of hypotonia due to any reason leading to dream-enacting and

sleep talking episodes. Although RBD is rare in MS, it can be an initial sign of MS lesion where steroid or ACTH therapy may be helpful like narcolepsy caused by an MS lesion [26, 27].

Management: Every patient of RBD must be evaluated in sleep laboratory. Drugs such as alcohol or sedative-hypnotic withdrawal, tricyclic antidepressant (such as imipramine), serotonin reuptake inhibitor use (such as fluoxetine, sertraline, or paroxetine) or other types of antidepressants (mirtazapine) may result in RBD and must be meticulously looked for and discontinued [28]. If associated with a causative MS lesion, treatment of the acute episode with steroids is helpful.

34.9 Circadian Rhythm in MS

Suprachiasmatic nuclei situated in hypothalamus are supposed to work as pacemaker of circadian rhythm. Melatonin, a hormone produced by pineal gland, regulates circadian and seasonal rhythms. Sorensen et al. [29] found loss of diurnal variation in cerebrospinal fluid somatostatin during MS relapses, which is suggestive of disturbed circadian rhythms. Alteration in circadian rhythm in patients with MS can be due to hypothalamic demyelinating lesions, optic neuritis affecting the functioning of suprachiasmatic nuclei, disturbed melatonin production, effect of various drugs such as benzodiazepine, steroid, non-steroid anti-inflammatory drugs (NSAIDs) or concomitant depression. Loss of circadian rhythm alters expression and regulation of various genes and, thus, creates a pro-inflammatory state [30]. Circadian rhythm along with melatonin is key regulator of immune system. Blood-brain barrier is also disrupted by prolonged sleep deprivation. All these collectively can further exacerbate the disease activity of MS [31].

Management: The primary management includes improving sleep hygiene. Melatonin can help to treat insomnia. Corticosteroids for hypothalamic lesions resulting in circadian rhythm disturbances in MS.

34.10 Sleep-Related Movement Disorders in MS

Restless leg syndrome (RLS) is a common neurological disorder characterized by abnormal sensations that occur primarily at rest or during sleep, which are alleviated by movement of the affected limb. The diagnosis of RLS is solely clinical, and International RLS Study Group (IRLSSG) has revised the diagnostic criteria in 2012 as given below:

1. Urge to move the limbs due to unpleasant sensations.
2. Worsen during periods of rest.
3. Relieved by getting up or movement of limbs.
4. Worse in the evening or night.
5. Secondary causes must be excluded (e.g. myalgia, venous stasis, leg oedema, arthritis, cramps, positional discomfort, neuropathy or drug-induced akathisia).

Theory of dopaminergic dysfunction in spinal cord is thought to be the most convincing mechanism of pathogenesis. Various ascending and descending tracts may be involved in the spinal cord giving rise to the sensory motor symptoms of RLS [32]. RLS symptoms are common in patients of MS, the reason is not clearly understood. One likely explanation commonly sought is cord involvement in MS mimicking RLS. To avoid false-positive diagnosis, detailed assessment of the five essential diagnostic criteria for RLS is necessary. It is also required because treatment strategy for frank RLS and RLS-like symptoms secondary to cord involvement is completely different [33].

Approximately 80% of patients with RLS experience periodic leg movements during sleep (PLMS) or while awake [34]. PLMS is characterized by brief (0.5–5.0 s) lower extremity movements during sleep, which typically occur at 20 to 40 sec intervals, most commonly during the first 3 h of sleep. The affected individual is usually not aware of such movements or of brief arousals. To define PLM, there must be a minimum of four leg movements (LM), each lasting for more than 0.5 s. The period length between LMs (defined as the time between onsets of consecutive LM) to include them as part of a PLMS series is 5 to 90 s. Leg movement in two different legs separated by less than 5 s between movement onsets is counted as a single LM. The period length to the next LM following this group of LMs is measured from the onset of the first LM to the onset of the next [35]. In the study of patients with MS by Ferini-Strambi et al., prevalence of PLMS was 36% compared to healthy controls (8%). RLS is a clinical diagnosis but PLMS requires polysomnography for confirmation [36].

Management: It is important for a clinician to distinguish true RLS from RLS symptoms as both are prevalent in MS. Secondary causes of RLS such as iron deficiency, renal dysfunction and neuropathy must be sought and treated accordingly. Medications that can worsen RLS or PLMS such as dopamine antagonists, SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), antihistamines, tricyclic antidepressants, alcohol, tobacco and caffeine should be discontinued. Iron should be supplemented for ferritin level of less than 50 ng/ml [18]. Pharmacological therapies for alleviation of RLS symptoms include dopamine agonists such as pramipexole and ropinirole, and gabapentin and pregabalin.

34.11 Conclusion

Sleep disorders are common among patients with MS and are often underrated, and treating physicians must assess the quality of sleep regularly. By impairing the quality of sleep, above disorders result in reduced functionality of patients suffering from MS. Each of the above-mentioned conditions need special attention and independent diagnosis to give appropriate specific treatment (Table 34.2). Evaluation of MS patients in sleep laboratory often helps clearly identify the type of sleep disorders thereby providing an appropriate therapy to these patients.

Table 34.2 Sleep-related issues in multiple sclerosis and pharmacological therapies to treat them

	Sleep-related issues in MS	Clinical scales or investigations for diagnosis	Drugs used for treatment
1.	Fatigue	Modified fatigue impact scale (MFIS)	Amantadine (p.o. 100–400 mg/day) Pemoline (p.o. 37.5–112.5 mg/day) Modafinil (p.o. 200–400 mg/day) Carnitine (p.o. 250–3000 mg/day) 4-Aminopyridine (p.o. 10 mg BD) Coenzyme Q10 (p.o. 50–200 mg/day)
2.	Excessive daytime sleepiness	Epworth sleepiness scale (ESS)	Corticosteroids
3.	Insomnia	Insomnia severity index (ISI)	Tricyclic antidepressants: Amitriptyline (p.o. 10–200 mg HS) Pregabalin (p.o. 50–300 mg/day) Baclofen (p.o. 5–30 mg TDS) Benzodiazepine: Diazepam (p.o. 2–10 mg HS) Melatonin receptor agonist: Ramelton (p.o. 8 mg HS) Orexin receptor antagonists: Suvorexant (p.o. 10–80 mg HS)
4.	Obstructive sleep apnoea	Polysomnography Airway assessment	Positive airway pressure Disease-modifying therapies (DMT) Oxygen inhalation
5.	Central sleep apnoea	Polysomnography MRI brain	Positive airway pressure Disease-modifying therapies (DMT) Carbon dioxide inhalation
6.	Nocturnal urinary symptoms	USG abdomen Uroflowmetry MRI spine	Anticholinergics: Tolterodine (p.o. 2–4 mg/day) Alpha-blockers: Tamsulosin (p.o. 0.4 mg/day) 5-alpha reductase inhibitors: Dutasteride p.o. 0.5 mg/day Desmopressin (10–40 mcg in two divided dose) Diuretics Phosphodiasterase-5 inhibitors: Sildenafil (p.o. 5–100 mg/day)
7.	Narcolepsy	Polysomnography MRI brain	Modafinil (p.o. 200–400 mg/day) Antidepressants Corticosteroid
8.	REM sleep behavioural disorders	Polysomnography MRI brain	Corticosteroid
9.	Altered circadian rhythm	MRI brain	Melatonin (p.o. 3–5 mg HS) Corticosteroid

(continued)

Table 34.2 (continued)

	Sleep-related issues in MS	Clinical scales or investigations for diagnosis	Drugs used for treatment
10.	Restless legs syndrome	International RLS study GROUP (IRLSSG) criteria	Pramipexole (p.o. 0.125–2 mg/day) Ropinirole (p.o. 0.25–4 mg/day) Gabapentin (p.o. 300–2400 mg/day) Pregabalin (p.o. 50–300 mg/day) Iron

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Sleep Disorders in Myopathies

35

Ishita Desai and Niraj Kumar

Abstract

The myopathies are inherited or acquired neuromuscular disorders characterized primarily by muscle weakness due to dysfunction of muscle fiber. Sleep disturbances are frequent in patients with myopathy but are often ignored or missed. Timely identification and treatment of these disorders can improve the quality of life of such patients. Therefore, patients with myopathy should routinely be assessed for features of sleep disturbances because of their treatable nature in an otherwise progressive disease process. This chapter covers various sleep disorders in myopathies, their clinical presentations, role of various investigations, and available treatment options. Before discussing that, it is important to have a clear concept of the functional anatomy and physiology of sleep and breathing. The first section contains an overview of the anatomy and physiology of sleep, clinical presentations of various myopathies, and control of breathing during sleep. The second section focuses on myopathy-associated sleep abnormalities and their management.

Keywords

Myopathy · Sleep apnea · Sleep-related breathing disorders · Parasomnias · Circadian rhythm sleep-wake disorders · Sleep-related movement disorders

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35.1 Introduction

Sleep and breathing are controlled by anatomic structures situated in both central as well as peripheral nervous system. Thus, neurologic illnesses can adversely affect sleep and breathing and vice versa [1, 2]. The effect of acute and chronic muscle disorders on sleep and the resulting interactions with breathing has not received wider attention yet. This understanding may prove essential for deciding the treatment as well as prognosis in various muscle disorders. Varied presentations of sleep disturbances in myopathies include the following:

1. *Breathing abnormalities*: Sleep-related breathing disorders (SBD), resulting in hypopnea, apnea, alveolar hypoventilation.
2. *Duration abnormalities*: Insomnia, hyposomnia, or hypersomnia.
3. *Behavior abnormalities*: Parasomnias (sleep terrors, sleep talking, somnambulism, nightmares).
4. *Tone abnormality*: Sleep-related movement disorders (rapid eye movement [REM] sleep behavior disorders), periodic limb movements of sleep (PLMS), restless leg syndrome (RLS).
5. *Rhythm disorders*: Circadian rhythm sleep-wake disorders.
6. *Excessive day time sleepiness.*

35.2 Functional Anatomy of Sleep and Awake State

The neuroanatomic structures involved in maintenance of wakefulness, rapid eye movement (REM) sleep, and non-rapid eye movement (NREM) sleep are located in different parts of the central nervous system (CNS) [3, 4]. There are no separate sleep and wake-promoting centers in brain; rather, these states are generated by changes in the balance between the interconnecting neuronal circuits modulated by neurotransmitters and neuromodulators. The parts of CNS and concerned neurotransmitters involved in sleep physiology are illustrated in Fig. 35.1.

35.3 Myopathies

They are inherited or acquired disorders, characterized by muscle weakness, muscle cramps, stiffness, and spasm and can be grouped into multiple types (Table 35.1) [12].

Most of the muscle diseases share common features of diaphragmatic weakness, reduced strength of upper airway dilators, as well as cardiomyopathy, leading to sleep disorders including sleep-disordered breathing (SDB).

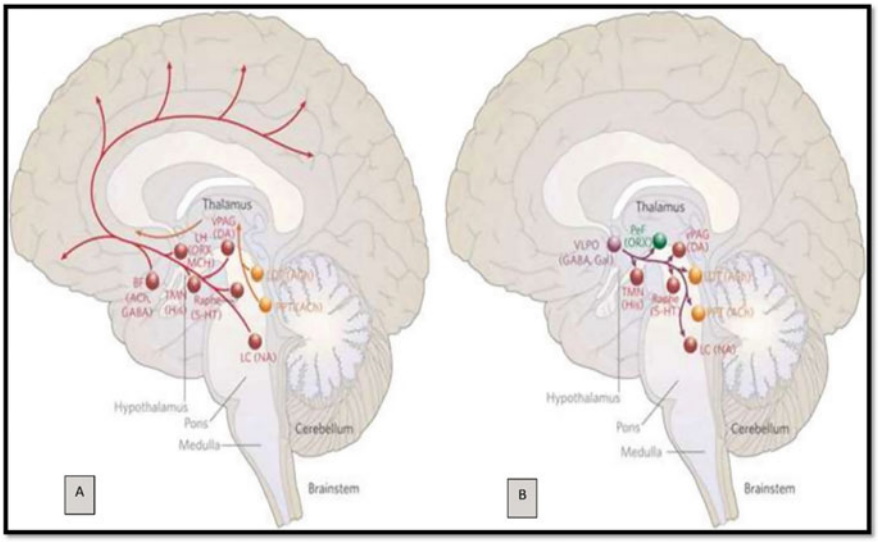


Fig. 35.1 The neurobiology & physiology of sleep and wakefulness. (**a**) Ascending reticular activating system (ARAS): Two major pathways are shown in figure **a**. One (in yellow) depicting upper brain stem input to be delivered to the thalamic-relay nuclei as well as reticular nucleus of the thalamus. This input is coming from acetylcholine (ACh)-producing neuronal groups, which are located in the Pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei of brainstem. The second major group of neurons (in red) are located in noradrenergic (NA)- locus coeruleus (LC), serotoninergic (5-HT)- dorsal and median raphe nuclei, dopaminergic (DA)- periaqueductal gray matter (vPAG), and histaminergic (His)- tuberomamillary neurons (TMN). Additional cortical input also originates from the GABA or Ach neurotransmitter containing basal forebrain (BF) neurons as well as from lateral hypothalamic (LH) peptidergic neurons that contain melanin-concentrating hormone (MCH) or orexin (hypocretin) (ORX). (**b**) Projections from the ventrolateral preoptic nucleus (VLPO) to the components of the ascending wakefulness system. *PPT* pedunculopontine tegmental area, *LDT* laterodorsal tegmental area, *NA* noradrenergic, *LC* locus coeruleus, *5HT* serotoninergic, *DA* dopaminergic, *vPAG* periaqueductal gray matter, *His* histaminergic, *TMN* tuberomamillary neurons, *BF* basal forebrain, *LH* lateral hypothalamus, *MCH* melanin-concentrating hormone, *ORX* orexin, *VLPO* ventrolateral preoptic nucleus. *Reproduced from van Someren E., Cluydts R. (2015) Sleep Regulation and Insomnia. In: Pfaff D., Volkow N. (eds) Neuroscience in the twenty-first Century. Springer, New York, NY* [5]

35.4 Pathophysiology of Sleep Disorders in Myopathies

During sleep, arterial partial pressure of carbon dioxide (PaCO2) usually increases by 2–4 mmHg due to reduction of alveolar ventilation (because of a fall in central respiratory drive), blunted arousal thresholds, and reduced respiratory muscle activity. Disproportionate loss of upper airway muscle tone and diaphragm weakness may contribute additional loads, particularly during rapid eye movement (REM) sleep, the time of maximal muscle hypotonia. GABA- and glycine-mediated muscle atonia in REM sleep reduces the contribution of intercostal muscles toward tidal volume by

Table 35.1 Different types of muscle disorders with their characteristic features

Sr. no.	Group disorders of muscle disorders	Examples	Characteristic features
1.	Congenital myopathies [6]	– Nemaline myopathy (rods) – Central core disease (cores) – Centronuclear/ myotubular myopathy (central nuclei) – Congenital fiber-type disproportion (hypotrophy of type 1 fibers)	Present at birth or in early infancy as hypotonia and skeletal muscle weakness with static or slowly progressive clinical course
2.	Muscular dystrophies [7]	– Duchene and Becker muscular dystrophy – Limb-girdle muscular dystrophy – Congenital muscular dystrophies – Myotonic dystrophy	A group of inherited disorders characterized by progressive muscle wasting and weakness
3.	Mitochondrial myopathies [8]	– Kearns-Sayre syndrome – MELAS – MERRF – Chronic progressive external ophthalmoplegia (CPEO)	Primarily caused by genetic impairment in oxidative phosphorylation of mitochondria. Besides myopathy, other systemic features such as cardiomyopathy, epilepsy, or stroke-like episodes may occur
4.	Glycogen storage disorders involving muscle [9, 10] and myoglobinuria	– Von Gierke disease – Pompe's disease – Andersen's disease – Cori's diseases – McArdle's disease – Tay Sachs disease	They result from mutations in genes encoding enzymes involved in glycogen and glucose metabolism; manifests in infancy or childhood as myopathy, hypoglycemia, marked hepatomegaly, and retarded growth
5.	Inflammatory myopathies [11]	– Polymyositis – Dermatomyositis – Inclusion body myositis – Necrotizing myopathy (NM)	Characterized by acute, subacute, or chronic onset with proximal and symmetrical myopathy (except IBM). EMG shows irritative muscle disease, and muscle biopsy reveals inflammatory exudates
6.	Familial periodic paralysis	Channelopathy (hypokalemic and hyperkalemic periodic paralysis)	Characterized by episodic weakness of arms and legs

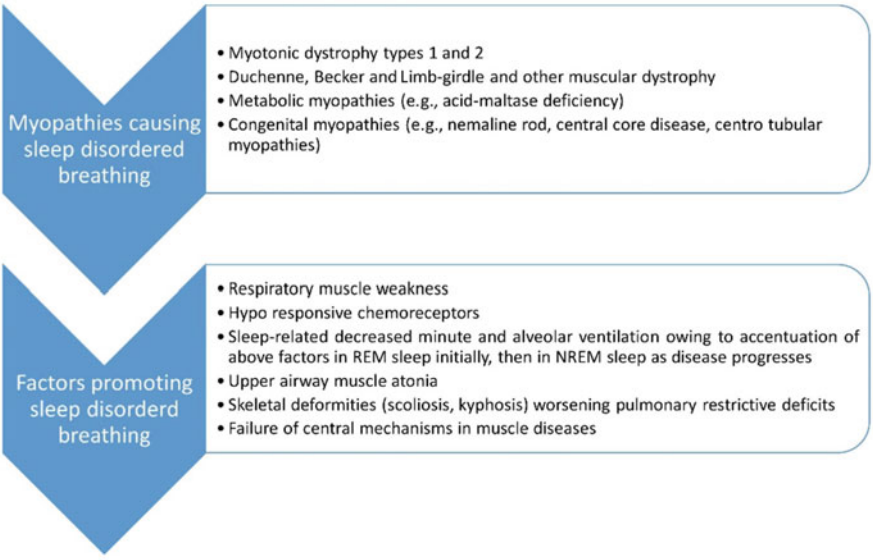


Fig. 35.2 Common myopathies and their Factors promoting sleep-disordered breathing [18]

up to 19% as compared to 40% occurring in awake state as well as during early sleep [13–16]. In normal state, an intact activity of diaphragm and accessory respiratory muscles compensate for these type of sleep alterations [17]. But these sleep changes may precipitate respiratory dysfunction in muscle disorders. Imbalance between respiratory load, drive, and muscular capacity predisposes to SDB with desaturations, hyperpnea, obstructive and central apneas, and hypercapnic hypoventilation which occur preferentially during REM sleep. Various myopathies and their factors leading to breathing disorders during sleep are shown in Fig. 35.2, while pathophysiological process is depicted in Fig. 35.3.

35.5 Patterns of Sleep Disorders in Myopathies

In the early stage, SDB may manifest as REM-related alveolar hypoventilation. Later as the disease progresses, there will be gradual worsening of respiration in NREM sleep followed by disordered breathing in the awake state. In addition, weakness of upper airway dilator muscles may cause superimposed OSA. Diaphragmatic weakness usually develops late in the course of disease. In myopathies not affecting diaphragmatic function sufficiently enough to cause alveolar hypoventilation, REM-related respiratory abnormalities such as hypopneas, apneas, and paradoxical breathing may occur.

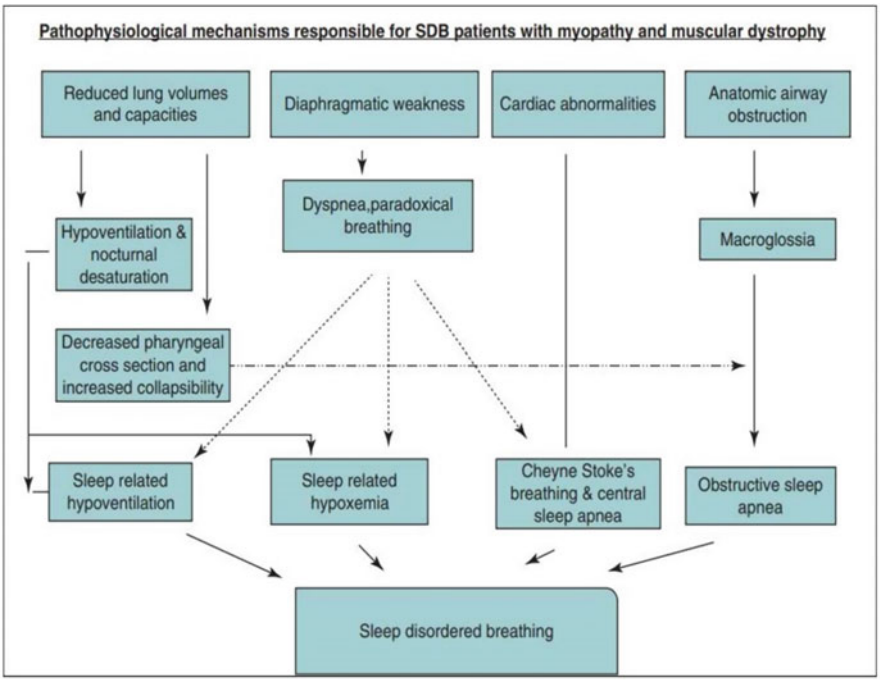


Fig. 35.3 Pathophysiological mechanisms responsible for sleep disordered breathing in patients with myopathy and muscular dystrophy [19].

35.6 Various Sleep Disorders in Specific Myopathies Are as Follows

1. *Duchene muscular dystrophy (DMD)*, an X-linked recessive disease characterized by aggressive progression of skeletal muscle weakness along with development of pseudohypertrophy of the calves and skeletal deformities (scoliosis). Alveolar hypoventilation (caused by respiratory muscle weakness with scoliosis) results in severe nocturnal sleep hypoxemia and hypercapnia. Obstructive apnea and hypopnea are also common (resulting from upper airway muscle weakness). The utility of noninvasive positive pressure ventilation (NIPPV) in DMD is debated and its use for preventive purposes should be avoided in patients with FVC between 20% and 50% of predicted values [20].
2. *Congenital myopathies* can also present with sleep abnormalities, respiratory insufficiency, and SDB. Reduced total sleep time along with decreased REM sleep duration and presence of signs of upper airway resistance has also been reported [21, 22].
3. *Myotonic dystrophy type 1 (DM1),* an autosomal dominant multisystem disorder characterized by muscle weakness and extra-skeletal features. More than 50%

patients suffer excessive daytime somnolence and show presence of sleep-onset REM periods during the multiple sleep latency test (MSLT), while up to two-thirds manifest fatigue. A combination of OSA, central apneas, periodic breathing, and nocturnal hypoventilation commonly predispose these patients to SDB, which may not be detected by daytime pulmonary function test. Developmental orofacial structural abnormalities due to poor muscle tone may further predispose them to OSA [23]. Such patients often report longer sleep periods, less restorative sleep, more difficulty falling asleep, being less alert in the morning, and having more trouble staying awake after meals. The excessive daytime sleepiness is often out of proportion to their degree of SDB and persists despite adequate treatment of SDB. They have short sleep latencies on multiple sleep latency test (MSLT) as well as short sleep-onset REM periods (SOREMPs), suggesting a narcoleptic phenotype. However, no correlation has been reported between the CSF hypocretin level and the degree of hypersomnolence. Nevertheless, this along with the occurrence of periodic breathing suggests a central mechanism, responsible for sleep dysfunction in DM1, and a correlation has been found between the degree of corpus callosum atrophy and severity of hypersomnolence detected on MSLT [24].

4. *Myotonic dystrophy type 2* (DM2 or proximal myotonic myopathy, PROMM) is clinically and genetically distinct from DM1. Such patients seem to be less hypersomnolent, but more fatigued than patients with DM1. PSG-based analysis suggested increased arousals, decreased sleep efficiency, alpha-delta sleep, obstructive apneas, paradoxical breathing in REM sleep, excessive daytime sleepiness, snoring, or insomnia. An abnormality of central control of breathing and sleep-wakefulness related to a common generalized membrane abnormality of the brainstem may be responsible for sleep-wake and respiratory dysfunction [25].
5. *Mitochondrial myopathies:* They are a heterogeneous group of disorders caused by heritable or spontaneous mutations in nuclear or mitochondrial DNA and share the common feature of mitochondrial abnormalities in muscle fibers on histochemical (ragged-red fibers on modified Gomori's trichrome stain) and electron-microscopic examination. Both nuclear and mitochondrial DNA mutations can lead to cellular energy failure, resulting in both central as well as peripheral neuromuscular alteration. All these can cause abnormal sleep patterns, commonly manifesting as central sleep apnea and poor ventilatory response to hypercapnia, which predispose them to develop sleep-related respiratory disorders. This activates a vicious cycle of progressive daytime fatigue, hypotonia, and exercise intolerance, leading to poor quality of life [26].
6. *Acid maltase deficiency:* Acid maltase deficiency, also called Pompe's disease is a glycogen storage disease primarily involving cardiac and skeletal muscle. The clinical features depend on residual acid maltase enzyme activity. The disease may have either a childhood or an adulthood presentation. SDB and respiratory failure are reported in this disorder. Respiratory muscle weakness resulting in respiratory failure is the most common cause of early mortality. Sleep disturbances resulting from diaphragmatic weakness and obstructive sleep

apnea are common factors predisposing to sleep disturbances [27]. Diaphragmatic weakness in the early stage of the disease may result in hypoventilation. It is initially seen during REM sleep but may cause daytime respiratory failure as the disease progresses. Macroglossia and weakness involving tongue muscles may result in upper airway dysfunction causing OSA [28].

35.7 Clinical Manifestations

The clinical features can be grouped into specific and general features. Specific manifestations depend on the nature of the neurologic deficit. General features include excessive daytime sleepiness, fatigue, early morning headache, unexplained pedal edema, disturbed nocturnal sleep, intellectual deterioration, personality changes, and in men, impotence, plus nocturnal restlessness, frequent unexplained awakenings, and loud snoring [21]. Difficulty waking in the morning with prolonged sleep inertia may interfere with morning activities. During the day, patients may manifest with somnolence, fatigue, and inappropriate napping that underlie failure to thrive in the very young and declining school grades or poor work performance at later ages. More ominously, some patients develop nocturnal cyanosis, severe insomnia, morning lethargy, headaches, vomiting, and leg edema that indicate the insidious but relentless occurrence of acute respiratory failure and cor pulmonale.

35.8 General Approach and Suggested Management

1. *History and examination:* To make a clinical diagnosis of sleep disorders, a careful history from the patient and their caregivers along with a detailed physical examination is essential (Fig. 35.4). Diaphragm weakness is the most important determinant of sleep-related respiratory insufficiency. Chest wall weakness and restrictive lung diseases resulting from chest wall deformities and kyphoscoliosis also contribute to hypoventilation in REM and NREM sleep. Weakness of the pharyngeal wall muscles, compounded with obesity of sedentary origin and craniofacial maldevelopment, may facilitate the appearance of obstructive sleep apneas. Some patients exhibit nocturnal hypoventilation in excess of muscle weakness or diaphragmatic failure, suggesting an alteration of central respiratory drive.
2. *Polysomnographic evaluation*: It is a gold standard test used to distinguish different causes of sleep disturbance and to assess the severity of the disorder (Fig. 35.4). A sleep apnea protocol is recommended. The study may show obstructive, central, and mixed sleep apneas, hypoventilation with oxygen saturations under 89%, or profound REM sleep-related desaturation of oxygen events indicating diaphragmatic failure. The sleep architecture may reveal fragmentation of sleep with many arousals and awakenings, many of them associated with episodes of respiratory interruption. Various polysomnographic patterns of myopathy are shown in Fig. 35.5. Since PSG may be expensive and may not be

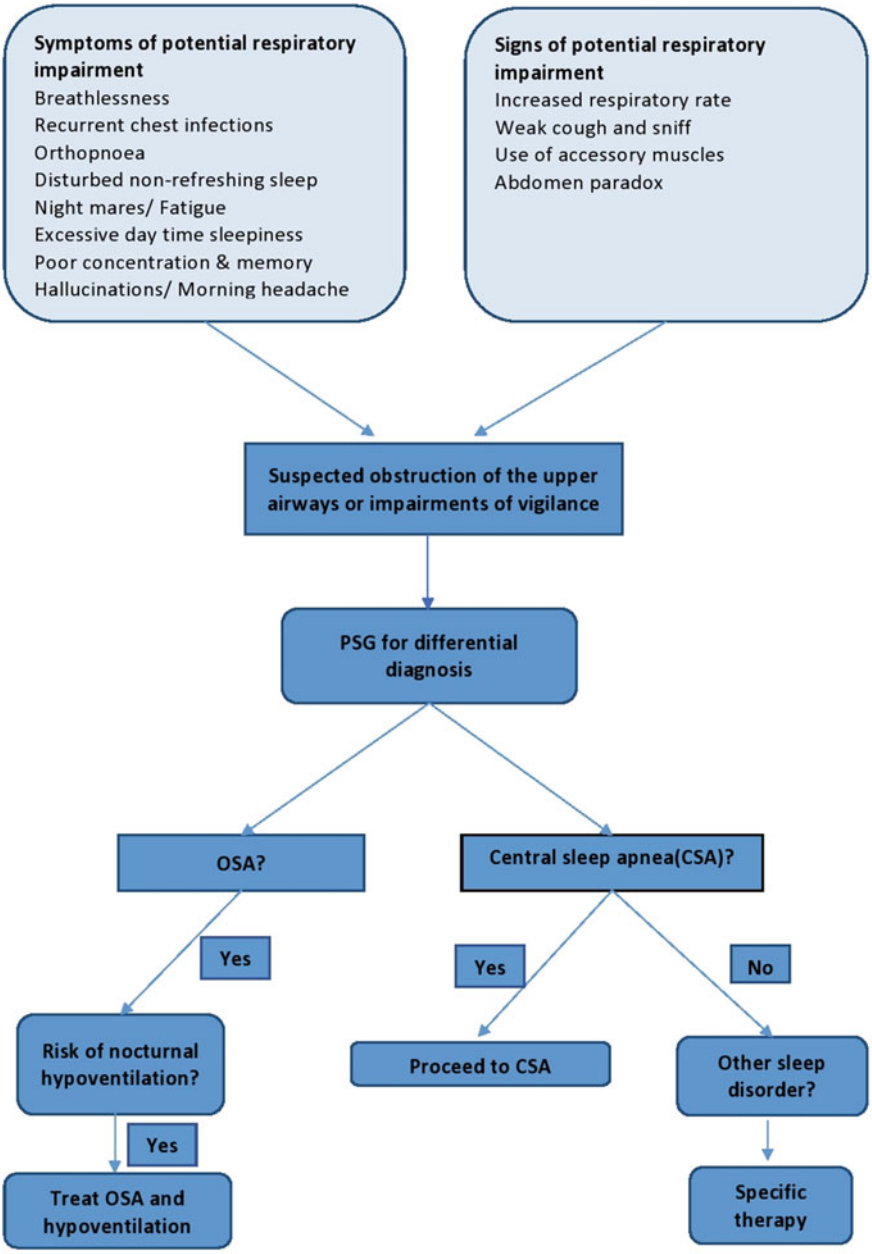
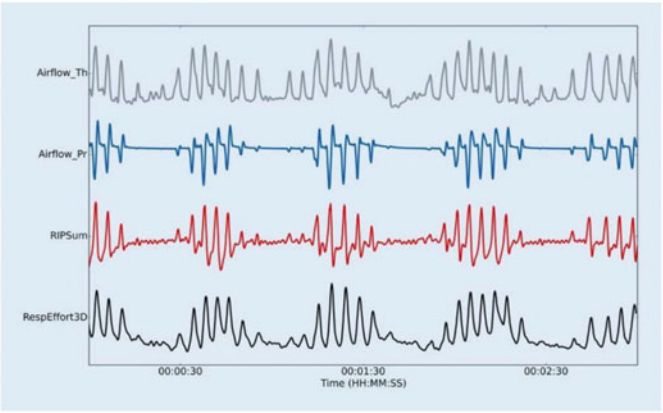
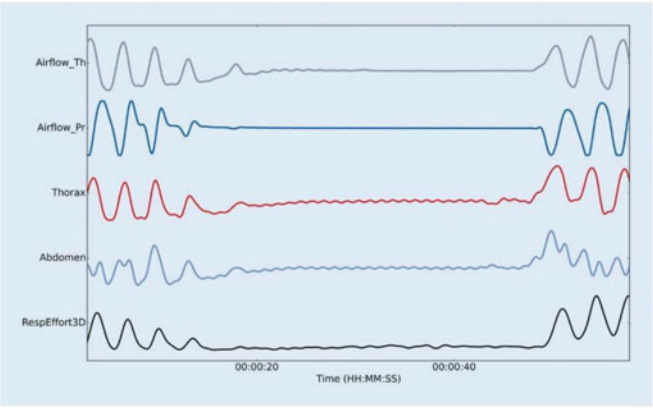


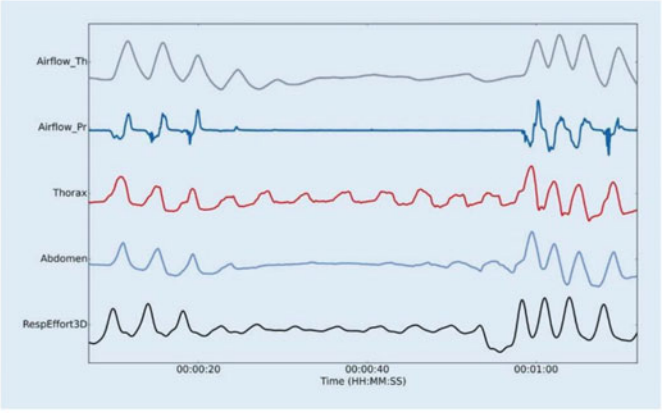
Fig. 35.4 Algorithm for management of sleep disorders in myopathies [29]



A. Normal respiratory efforts



B. Central sleep apnea



C. Obstructive sleep apnea

Fig. 35.5 Polysomnographic patterns in normal respiratory effort and sleep apnea. **Airflow_Th:** signal from the nasal thermistor, **Airflow_Pr:** signal from the nasal pressure cannula,

available at all centers; the simplest way to assess SDB is overnight oximetry monitoring.

3. *Hematological investigations:* Analysis of arterial blood gases as well as PaO_2 and $PaCO_2$ (partial pressure of oxygen and carbon dioxide) to look for presence of hypoxia (Pa o $_2$ < 60 mm Hg) and hypercapnia (Pa co $_2$ > 45 mm Hg) [21].
4. *Pulmonary function test (PFT):* It is used to diagnose and classify ventilatory disorders, whether they are of intrinsic pulmonary, neurologic, or musculoskeletal etiology. Various tests including lung volumes, forced vital capacity (FVC) in sitting and supine positions, forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio, maximal peak inspiratory force (PImax or negative inspiratory force, NIF), maximal peak expiratory force (PEmax) should be done to check for presence of any restrictive lung disease related to myopathy and its impact on sleep architecture.
5. *Other tests*: Maximal sniff maneuvers, esophageal, transdiaphragmatic, nasal pressures (Pnsn), overnight pulse oximetry, and capnography to check for presence of dynamic obstructions of upper airways due to upper airway muscle.

In short, no single diurnal test has been found to be uniformly predictive of nocturnal hypoventilation, and overnight oximetry plus capnography have their own limitations. A combination of maximal inspiratory pressure and nasal sniff pressure testing may be the most sensitive test in this regard, but in-laboratory polysomnography is the recommended gold standard diagnostic tool for SDB in patients with myopathies.

35.9 Consequences of Sleep Disorders

Persistent nocturnal hypoxemia resulting from SDB from any cause results in cardiovascular and pulmonary morbidity as well as mortality from various causes such as lethal cardiac arrhythmias, pulmonary hypertension, right heart failure (cor pulmonale), and propensity to develop myocardial infarction as well as stroke. In addition, SDB causes fragmentation of sleep and excessive daytime sleepiness and fatigue, decreasing the quality of life and affecting mood and cognition.

Fig. 35.5 (continued) RespEffort3D: **Respiratory effort signal derived from the depth signal of the 3D camera,** RIP Sum thorax/abdomen **respiratory inductance plethysmography belts' sign.** ***Coronel, C., Wiesmeyr, C., Garn, H.* et al.** ***Somnologie; 2019; 23: 86, Springer Medizin***

35.10 General Principles in the Treatment of Sleep Dysfunction in Myopathies

Most myopathies have no specific treatment, and management is largely supportive. In addition to optimization of treatment and alleviation of discomfort from symptoms attributable to the neurologic disease itself, the early diagnosis and treatment of SDB associated with myopathies is crucial. The goal of treatment of SDB is to support the weakened ventilatory muscles, thereby improving alveolar ventilation and gas exchange. In the case of syndromes related to increased nocturnal upper airway resistance or decreased drive to breathe (OSA and central sleep apnea, respectively), treatment is aimed at overcoming these issues, primarily through the use of devices meant to supply upper airway pressurization. In turn, this leads to improved sleep quality.

35.11 Treatment Options

Assisted mechanical ventilation at night improves the symptoms and protects patient from fatal apnea during disease. Furthermore, such treatment may prevent the development of serious complications resulting from episodic or prolonged hypoxemia, hypercapnia, and respiratory acidosis in sleep. Various treatment modalities available for sleep dysfunction in muscle disorders include the following:

- Upper airway pressurization.
- Continuous positive airway pressure (CPAP).
- NIPPV (noninvasive positive pressure ventilation) [30].
- Supplemental oxygen therapy.
- Surgical treatment like cricoidotomy.
- Tracheostomy.
- Diaphragmatic pacing.
- Pharmacotherapy like melatonin, non-benzodiazepine sedatives.
- For excessive daytime sleepiness.
  - Wakefulness-promoting agents (modafinil, armodafinil).
  - Stimulants (methylphenidate and amphetamines).
- For restless legs syndrome: Dopamine agonists such as pramipexole, ropinirole, and rotigotine; gabapentin and pregabalin; serum ferritin in case of iron deficiency state.

Specific therapeutic options for the management of sleep disorders in myopathy are summarized in Table 35.2.

Table 35.2 Sleep-related disorders in myopathy and therapeutic options for their management

Sr. no.	Sleep disorders in myopathy	Clinical scales or investigations for diagnosis	Therapeutic options
1.	Insomnia [31]	Insomnia severity Index (ISI)	Benzodiazepine: • Diazepam (p.o. 2-10 mg HS), Flurazepam (p.o. 15–30 mg H5) Non-benzodiazepines: • Zolpidem (p.o. 5–10 mg HS) Melatonin receptor agonist: • Ramelteon (p.o. 8 mg HS) Orexin receptor antagonists: •Suvorexant (p.o. 10-8Omg H5) Tricyclic antidepressants: • Amitriptyline (p.o. 10- 200 mg HS) • Doxepin (p.o. 3–6 mg HS)
2.	Obstructive sleep apnea	– Polysomnography – Airway assessment – Overnight pulse oximetry – Capnography	• Upper airway pressurization • Positive airway pressure • Disease-modifying therapies (DMTs) • Oxygen inhalation • Mandibular advancement devices • Surgical interventions (cricoidotomy)
3.	Central sleep apnea	– Polysomnography – MRI brain – Overnight pulse oximetry – Capnography	• Positive airway pressure • Disease-modifying therapies (DMTs) • Carbon dioxide inhalation
4.	Excessive daytime sleepiness—narcolepsy	– Polysomnography – MRI brain	• Modafinil (p.o. 200-4O0mg/day) • Methylphenidate (p.o. 20–60 mg/day in 2–3 divided doses) • Amphetamines (p.o. 5–60 mg per day in divided dose) Tricyclic antidepressants: • Amitriptyline (p.o. 10-200 mg HS) • Corticosteroid
5.	REM sleep behavioral disorders	– Polysomnography – MRI brain	• Corticosteroid
6.	Altered circadian rhythm	– MRI brain	• Melatonin receptor agonist (Ramelteon p.o. 8 mg HS) • Corticosteroid

35.12 Summary

Sleep dysfunction, particularly SDB, is common in many neuromuscular diseases, including myopathies. A high index of suspicion is crucial because patients are often unaware of the specific symptoms of SDB, attributing them to the underlying neurologic illness. A variety of diurnal and nocturnal tests, including blood gas analysis, pulmonary and sniff function testing, oximetry, and capnography are available to aid in making the diagnosis. However, there is still lack of consensus available about the optimal daytime indicator in neuromuscular patients with suspected nocturnal hypoventilation. In laboratory, PSG and upper airway titration studies remain the gold standard for diagnosis and treatment. NIPPV is the mainstay of treatment of nocturnal respiratory failure in neuromuscular diseases, although the precise timing and indications for this therapy, as well as the long-term outcomes, especially on symptoms related to sleep dysfunction, remain to be elucidated with further research.

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Sleep in Critically Ill Patient

36

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Abstract

Sleep is an essential physiological need that allows body and mind to recharge, alert, and restore health which is regulated by circadian rhythm. Critically ill patients often suffer with disrupted and fragmented sleep, which is manifested as increased percentage of light sleep (NREM: 40–60%) and decrease in deeper sleep (REM: 10%). Sleep disruption in critically ill patient is a multifactorial phenomenon which is contributed by patients' medical illness, psychological stress, and intensive care unit (ICU) environment factors (noise, artificial light, uncomfortable bedding, frequent investigation, and medication) because these factors create abnormality in circadian rhythm and sleep disturbance. Although sleep deprivation and sleep hygiene have been extensively studied, sleep disturbance, its management, and role of nurses in the prevention of sleep deprivation in critically ill patients still need a precise understanding. Therefore, this chapter comprehensively highlights the major contributing factors of sleep disruption and its prevention and management including nursing care among critically ill patients.

Keywords

Critically ill · Sleep deprivation · Nursing care · Environmental factors · Pharmacological interventions · Non-pharmacological interventions

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36.1 Background

Nightingale (1912) [1] identified that two essential factors for promoting and restoring patient's health are light and rhythm of day and night. Sleep and wakefulness are regulated by circadian rhythms and come under basic human needs (Henderson 1966) [2] promoting healing and host defense and regulating energy balance. Sleep is a physiological condition which occurs on a cyclical basis and is characterized by relative reduction of cerebral activity, limited movements, involuntariness, autonomic, and absence of defined purpose [3, 4]. In spite of its importance, critically ill patients in medical, cardiac, and surgical intensive care units (ICUs) invariantly suffer from disturbed sleep characterized by poor-quality prolonged sleep latency, sleep fragmentation, and reduced sleep efficiency which may contribute to morbidity. More than half to two-thirds of patients admitted in ICUs suffer from disturbed sleep [5]. It has been reported that 71% of acutely ill patients at ICU complain of poor sleep quality [6]. Data revealed that more than 50% of critically ill patients suffer from sleep disturbances [7].

Most of the critically ill patients in ICU have altered sleep architecture characterized by increased percentage of light sleep, i.e., stage 1 (40–60%), and decrement of deeper sleep, i.e., stages 2 (20–40%), 3/4 (10%), and REM sleep (10%) [8]. The total sleep time (TST) over day and nighttime may be normal (7–9 h); however, nearly 50% of the daytime is spent in short bouts of sleep which makes it more difficult for REM and delta sleep to occur [9]. This less restorative sleep results in daytime napping and 38% even suffer from difficulty in falling asleep [10]. Culpepper (1988) reports that critically ill patients remain awake 40–50% of their total sleep time and rest 3–4% experience REM sleep [11].

According to Richards-Campbell Sleep Questionnaire (RCSQ), critically ill patients have sleeping problem which is manifested as shallow depth of sleep (94%), poor sleep quality (88%), increased number of awakenings (76%), difficulty returning to sleep after awakenings (74%), and falling asleep (61%) [10, 12] (Ref). About 38.55% of patients who survived from critical illness (after almost 48 h spent on mechanical ventilation) are not able to sleep, around 40% wake up and remain awake in the middle of the night, and 30% suffer from insomnia during their ICU admission time [10, 12]. Critically ill patients may be mechanically ventilated (60–80%) or non-ventilated (20–55%), experience sleep disturbances already mentioned above and nightmares, and show impaired circadian rhythm which is frequently associated with delirium [10, 13]. Prevalence rate of pathological wakefulness is 38% and that of atypical sleep is 46% among mechanically ventilated critically ill patients but odds ratio product or polysomnographic findings proved that it is not associated with spontaneous breathing trail [14]. Patients in ICU who were sedated or ventilated show sleep disturbances even after discharge; for example, 9.3% of them have reported nightmares and 6.6% suffer from hallucination; data have revealed that 52.7% had disturbed quality of sleep during their ICU stay [14–16].

Admission data of critically ill patients in respiratory ICU revealed that 71% of patients had poor sleep quality during their stay. These patients who were admitted

in respiratory ICU had medical conditions like COPD (70%), intestinal lung diseases (13%), bronchial asthma (11%), and pulmonary embolism (6%) [14]. Another study revealed that patients who were critically ill due to hematological disorder had insomnia (14%). Patients undergone liver transplant complained of sleep disorder who were on treatment with tacrolimus (29.2%) and cyclosporine (20.2%) [17, 18]. About 4% of critically ill patients suffer from sleep problem when they are under treatment with antipsychotic medication [19].

Clinical staff members identified that factors associated with sleep disturbances among critically ill patients are noise (100%); routine procedures (38%) like investigation, medication administration, physical examination, and assessment of weight; time-sensitive activities (38%) like admission, discharge, assessment, positioning, or any emergency; psychological factor (57%); and illness or physical discomfort (50%), i.e., pain [20]. Polysomnography is considered as the most useful tool for sleep assessment among critically ill patients in ICU settings [21].

To deal with sleep disturbances 83% of staff suggested to cluster the care and 96% to reschedule the care; otherwise they suggested different sleep-promoting activities like 58% agreed on reduction of noise, 38% asked to avoid daytime napping, 29% said to promote comfort measure, 21% believed on sleep-promoting medication, and 4% recognized awareness among medical team through proper educational curriculum [20].

36.2 Prevalence of Sleep Deprivation in Critically Ill Patients

Prevalence of delirium among critically ill patient is estimated to be 31.8% . . . .by a recent meta-analysis, which shows link between ICU patient and sleep disturbance [22, 23]. During critical illness 61% of ICU patients report sleep deprivation [24, 25]. Polysomnographic studies show that critically ill patients spend 40–50% of total sleep time as daytime naps [26]. According to standard EEG pattern criteria it has been observed that 30–50% sleep disturbances coexist with critical illness [21, 27]. A systematic review concluded that all patients admitted in medical ICU demonstrate sleep–wake cycle abnormalities, out of which about 20–30% had arousal attributed to noise and 7% was due to self-care activities [28]. Another study revealed that nearly 60% patients report sleep disturbances till 6 months after discharge from ICU [13]. A study on "Sleep Quality as Perceived by Critically Ill Patients" revealed that 84% of patients had sleep disturbances during ICU stay, out of which more than two-thirds (67%) had moderate sleep disturbance [28].

Box 36.1: Source of Noise in ICU Setting

Alarms/equipment sounds (intravenous pump, cardiac monitors, pulse oximeters, ventilators, suction apparatus, pagers, overhead paging, fans) [29].

Talking considered as cause of frequent awakening and even footsteps (providers, visitors, and patients) [30].

(continued)

Box 36.1 (continued)

Noise from other rooms or nursing workstation (including television, telephone, computer, mobile phones).

Floor cleaners/moving equipment [30].

During nursing interventions (oxygenation, nebulization, analytical testing, administration of medication) [29].

36.3 Factors Affecting Sleep in Critically Ill Patients

Sleep deprivation among critically ill patients can be attributed to a number of factors. For example, critically ill patients are more vulnerable to environment factors (i.e., noise, light), sleep disruption due to the fixed schedule of patient care activities, applied treatment modalities (i.e., mechanical ventilation, drug therapy), patient demographics like population ages 65 & above and acute nature of disease condition like respiratory, cardiac, renal, endocrine, and neurological diseases [31].

In 2017, one study focused on staff perception about the factors associated with sleep disturbances in ICU and found that 100% agreed that noise was the factor, 62% for routine procedure and 38% for time-sensitive procedure; 57% attributed to psychological and cognitive factor; and 50% reported the association with their clinical illness and related discomfort [17]. In spite of all these well-known factors there could be some unknown factors which contribute to sleep disturbance in this population [32].

36.3.1 Environmental Factors

36.3.1.1 Noise

In ICU settings, critically ill patients live in a noisy environment which contributes to sleep disturbances [33]. Sources of noise in intensive care units are listed in Box 36.1. The World Health Organization recommended that in patient care zones noise level should be less than 35 dB and during nighttime maximum level can be 40 dB [34]. However, studies showed that result does not match with the proposal of the Environmental Protection Agency and the World Health Organization and it remains around 45–85 dB (average 44–59 dB) during daytime, 57–61 dB in evening time, and 53–60 dB in nighttime with a mean noise level of 55–65 dB (over 24-h cycle) [35, 36]. This level is comparable to a factory (80 dB), busy office (70 dB), and noisy bedroom (40 dB) [37]. One study identified that 35 dB can arouse a person from sleep and another study observed that 70 dB can force a patient towards lighter stage of sleep [29].

This loudly environment resulted in less REM activity and shorter REM-period duration [38].

Noise provokes physiological changes similar to generalized stress reaction (i.e., vasoconstriction, elevated diastolic blood pressure, dilated pupils, and muscle tension) and stimulates sympathetic nervous system to release adrenaline which prevents the patient from falling asleep and relaxing [36]. Because of age-related changes and neurodegeneration, elderly persons already do not experience deep stage of sleep, so noise affects them more than others [39].

36.3.1.2 Light

In ICU, patients are exposed to constant artificial light which disturbs their normal sleeping patterns owing to perturbation of circadian rhythms [40]. Exposure to artificial light is reported to alter secretion of melatonin which controls circadian rhythms and elevate cortisol production (hormone of alertness) which indirectly affects sleep [31, 32].

Standard nocturnal light levels of 100–500 lux can negatively affect melatonin secretion, 300–500 lux triggers circadian pacemakers [41], nighttime level is 2.4–145 lux, and daytime level is 55.3–165 lux with mean maximum level ranging from 5 to 1400 lux [3, 7, 42]. Minimal presence of daylight and profound exposure of artificial light may impair diurnal variation to induce circadian disruption [43]. Moreover, artificial light of insufficient intensity cannot act as a zeitgeber which is also responsible for variation in circadian clock [3, 7, 42, 44].

36.3.1.3 ICU Structure

Box 36.2: Common Time-Sensitive Routine Patient Care Activities

Dealing emergency patient [30].
Patient admission or discharge [30].
Vital signs or timed nursing assessment (e.g., RASS, GCS) [45].
Support-device adjustment [30].
Pain management [30].
Wound care [27].
Patient turning and skin check [46].
Urine and stool monitoring for intake output.
Personal hygiene (such as bathing, eye care, oral hygiene, changing of bed linen, catheter care which are mostly performed in midnight and 5:00 a.m.)
Medication administration [30].
Respiratory care/treatment [31].
Laboratory work, radiography, computed tomography scan, magnetic resonance imaging [38].
Phlebotomy [25, 45].
Physicians rounds [30].

Intensive care units are designed with different electronic equipment, monitor, and tubing. The space between the beds is very less, and also the practice of privacy is a

concern. Most of the time there is no window from where daylight can come and the sound of opening and closing the doors is also disturbing [45].

36.3.1.4 Discomfort

General discomfort due to uncomfortable hospital beds, attachment of different monitoring equipment, presence of intravenous central lines, and continuous presence of nasal cannula for oxygen administration can disrupt the initiation as well as continuity of sleep [47]. Too hot or too cold room temperature can hamper REM sleep [48]. Presence of strange or bad odors can be a precipitating factor for poor sleep [26, 49].

36.3.1.5 Treatment Modalities

Frequent Monitoring and Patient Care Activities

Continuous monitoring and patient care activities can result in disruptive sleep [50–52]. Data revealed that sleep is disrupted approximately 60 times each night due to these issues [53]. Common time-sensitive routine patient care activities, which may affect sleep in critically ill patients, are listed in Box 36.2.

36.3.2 Medication

Medications used in ICU settings have both direct and indirect effects on sleep owing to their direct effects on brain [32, 45]. A comprehensive detail may be perused from Table 36.1. Commonly used medications which may affect sleep in critically ill patients have been described below:

36.3.2.1 Sedatives

Use of benzodiazepine increases total sleep time but chronic use decreases deep sleep, REM sleep, and withdrawal effect associated with insomnia [45]. Propofol can be used for deep sleep but reduces REM sleep and may cause delirium [45, 53, 54].

36.3.2.2 Analgesics

Opioids which are mainly used for pain may have negative effects like reduction of REM even causing sleep fragmentation, central sleep apnea, and delirium [53, 54]. Use of nonsteroidal anti-inflammatory drugs causes frequent arousal in nighttime which decreases sleep efficiency [54].

36.3.2.3 Antipsychotics

Most frequently a typical antipsychotic haloperidol is prescribed for the treatment of agitation or delirium in ICU settings. Haloperidol induces N2 sleep and some amount of slow-wave sleep . Olanzapine or risperidone increases total sleep time and deep stages of sleep, i.e., stages 3 and 4 [55].

Table 36.1 Effect of medications used in the intensive care unit on sleep [47]

Medication	Total sleep time	Wakefulness after sleep onset	Stage 2%	SWS %	REM%	Sleep-onset latency
Sedative/hypnotics						
Benzodiazepines	+	−	+	−	−	−
Zolpidem	+	−	±	+	±	−
Chloral hydrate	+	NA	NA	NA	NA	−
Dexmedetomidine	NA	NA	NA	+	−	−
Propofol	+	−	NA	NA	No effect	−
Eszopiclone	+	−	+	±	±	−
Ramelteon	+	±	±	±	±	−
Analgesics						
Opiates	−	+	NA	−	−	NA
Antipsychotics						
Haloperidol	+	−	NA	+	−	−
Atypical antipsychotics, i.e., risperidone	+	−	NA	+	−	−
Stimulants						
Methylphenidate	−	+	−	NA	−	NA
Antidepressants						
Trazodone	NA	−	NA	+	−	−
SSRI	−	+	NA	NA	−	+
Tricyclics	NA	NA	NA	NA	−	NA
Cardiovascular drugs						
β-Blockers	NA	+	NA	NA	Variable	+
Epinephrine/ norepinep hrine	NA	NA	NA	−	−	NA
Dopamine	NA	NA	NA	−	−	NA
Respiratory drugs						
Xanthines, i.e., theophylline	−	+	NA	−	−	+
Corticosteroids	NA	+	+	−	−	NA

+ refers to an increased effect, − decreased effect, ± no significant effect, *NA* information not available, *SWS* slow-wave sleep, *REM* rapid eye movement sleep, *SSRI* selective serotonin reuptake inhibitors

36.3.2.4 Antidepressants

Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) have negative effects on REM sleep. While TCA increase total sleep time due to their antihistaminic actions, SSRIs are associated with reduction of total sleep time, may cause insomnia, and produce daytime somnolence [45, 56].

36.3.2.5 Cardiovascular (CVS) Drugs

Commonly used CVS medication beta-blocker can cross the blood-brain barrier increasing the chances for nightmares, insomnia, and reduced REM sleep. Amiodarone in 20–40% of cases is related with insomnia and nightmares [54]. Antihypertensive medications do not have prominent effects on sleep. Norepinephrine, epinephrine, and dopamine have identified effects on deep stages of sleep and on REM sleep too [45].

36.3.2.6 Respiratory System Medication

Beta-agonist drugs have the potential for CNS stimulation to produce insomnia and sleep fragmentation [47, 53, 54].

36.3.2.7 Other Medications

Use of corticosteroids may result in insomnia, reduction of REM sleep, and frequent nighttime arousals [47, 56].

36.3.3 Mechanical Ventilation

Forty percent of ICU-admitted critically ill patients are subjected to mechanical ventilation [57]. It has been observed that sleep disruption is common among these patients which manifests as 20–63 arousals per hour from sleep [8, 58]. Ventilated patients have dyssynchrony most frequently during periods of NREM sleep, increased sleep fragmentation, reduced sleep efficiency, reduced rapid eye movement (REM) sleep, and reduced percentage of slow-wave sleep (SWS) [8, 59, 60].

Multiple factors are associated with mechanical ventilation and sleep fragmentation; some of these are the following:

1. Prevalence of acute illness among ventilated patients is more [61].
2. Mechanical ventilation may be associated with alarms, masks, tracheal tubes, suctioning, mouth guards, nasogastric tubes, and physical restraints which may contribute to sleep fragmentation [40, 53].
3. Sedatives and analgesics are frequently used during mechanical ventilation and are identified as factors [32].
4. Stress related to increased difficulty while communicating.
5. *Mode of mechanical ventilation:* Sleep architecture and circadian rhythms get altered according to the mode of mechanical (i.e., high or low levels of pressure) ventilation. High-level pressure is responsible for ventilator dyssynchrony, increased ventilatory effort, alterations in gas exchange, and air trapping whereas low-level pressure causes sleep disruption specially with heart failure patients [31, 40, 53]. Study findings revealed that sleep disruption is more with pressure-support than assist-control ventilation mode and neutrally adjusted support mode creates more problem than pressure-support mode [61].
6. Serum melatonin and urine 6-sulfatoxymelatonin (6-SMT) levels are significant because it is accepted as a biological marker for circadian rhythm. If low it will affect sleep [62].

All these factors directly or indirectly affect sleep. Data suggest that patients on mechanical ventilation experience increased levels of daytime sleepiness.

Noninvasive ventilation also creates impairment in circadian rhythm and REM sleep. Those who spend more than 24 h in noninvasive ventilation are vulnerable for sleep disruption [31].

36.3.4 Nutritional Support

One of the important zeitgebers of mammalian circadian clock is feeding time and cycle that consists of alternating periods of food intake and fasting [63, 64]. Here food acts as a triggering factor for circadian clock which controls rest cycle and in turn metabolism [65]. Food intake is associated with hormonal rhythms related to adrenal glucocorticoids, pineal melatonin, adipocyte-derived leptin, pancreatic insulin, and ghrelin, which convey temporary signals for the entrainment of circadian clock [66]. Critically ill patients mostly have nasogastric tube or parental feeding which alters this rhythmicity. This impaired rhythmicity can cost systemic inflammatory response to multiple-organ dysfunction syndrome [65, 67].

36.3.5 Patient Factors

36.3.5.1 Patient Demographics

It has been observed that critically ill patients admitted in ICU are mostly more than 65 years old and age is considered as an identified risk factor for increased sleep latency, less total sleep time, decreased sleep efficiency, as well as changes in sleep architecture [40, 67]. Female genders are also prone to sleep fragmentation [13].

36.3.5.2 Patient's Conditions

Presence of preexisting diseases (i.e., respiratory, cardiac, renal, endocrine, and neurologic) can impair normal circadian homeostasis [54].

For example:

1. Patients with pulmonary disorder will have problem in REM sleep due to oxygen desaturation. COPD patients have prolonged sleep latency, decreased total sleep time, frequent arousals, and decreased REM sleep due to hypoxia and hypoventilation [53].
2. Diabetic patients might have fragmented sleep due to unbearable neuropathic pain and polyuria [53].
3. Patients with renal disease usually have complaints of uremia, itching, pain, or nausea which may cause sleep apnea, fragmented sleep, and restless legs syndrome [53].
4. Multisystem complications like sepsis cause increase in NREM sleep, decrease in REM sleep, and poor sleep quality due to alteration in melatonin secretion as well as inflammation [54, 68].

5. Heart failure patient complains of disruptions in sleep due to altered breathing patterns usually manifested as Cheyne-Stokes breathing [54].
6. Psychiatric disorders (i.e., anxiety, depression, and personality disorder) or cognitive dysfunction increases the problem in falling asleep and lighter stages of NREM 1 and 2 [40].
7. Acute or chronic inflammation can lead to desynchronization of circadian cues which may in turn increase chances for organ failure and even death [69].
8. Pain either due to medical/surgical illness or from any invasive procedure causes sleep disruption [70].
9. Patients on dialysis and intra-aortic balloon counterpulsation (IABP) also suffer from severe sleep disturbances [26].

36.3.5.3 Sleep Knowledge Deficit among Healthcare Professionals

Since the last three decades a number of articles regarding sleep deprivation among critically ill patients have been published. But still medical as well as nursing personnel do not pay much attention during diagnosis or while writing a plan of care [40, 71]. This knowledge deficit can be a factor which indirectly prolongs ICU stays. This topic must be included in medical and nursing school curriculum [47].

36.4 Effects of Sleep Deprivation on Physiological Processes of Critically Ill Patients

Deprivation of sleep among critically ill patients followed by several negative consequences in different systems affects quality of life, impairs recovery, enhances mortality, and also increases risk of delirium [40, 72, 73].

36.4.1 Changes in Temperature Regulation

Sleep deprivation disrupts the normal circadian pattern of thermoregulation, i.e., alteration of temperature sensitivity during NREM stage, alteration of the ability to shiver or sweat during REM sleep, and alteration of changes of core body temperature irrespective of particular time [31, 53, 54].

36.4.2 Changes in Respiratory Function

Sleep deprivation worsens the condition of critically ill patients with respiratory problem who are in mechanical ventilation, responsiveness to hypercapnia, or weaned from mechanical ventilation [27, 59]. It results in respiratory muscle fatigue, decreased inspiratory muscle endurance, loss of respiratory drives, increased oxygen consumption, and increased CO_2 production. [31, 32, 58]. It has been observed that sleepless night of COPD patients results in poorer FEV1 and FVC [74].

36.4.3 Changes in Cardiovascular Function

Sleep deprivation stimulates sympathetic tone, enhances the chance of acute myocardial infarction by endothelial disruption, elevates catecholamine level leading to hypertension, and increases the risk of ischemic cardiac events [31, 75].

36.4.4 Changes in Gastrointestinal Function

Sleep deprivation changes esophageal mobility, swallowing, saliva production, and gastric acid secretion levels [31].

36.4.5 Changes in Endocrine Function

Sleep deprivation disrupts normal neuroendocrine system [76]. It predominantly elevates the T3, T4, thyroid-stimulating hormone, cortisol, norepinephrine, and prolactin level and decreases growth hormone (GH) level [31]. Prolonged cortisol secretion affects normal healing process and lessens the ability of fighting against infection. Prolactin level needed for cell differentiation and proliferation helps in tissue healing and restoration. Thus impaired level may lead to muscle wasting and hampers immunity [31]. Among ICU patients, impaired glucose metabolism problem can lead to morbidity and mortality. Elevated catecholamine and corticosteroid levels create stress-like symptom in critically ill patients [77].

Hormonal and metabolic responses during critical illness after sleep deprivation [45]. Hormonal and metabolic responses in critically ill patients due to sleep deprivation have been listed in Table 36.2.

Table 36.2 Hormonal and metabolic responses after sleep deprivation in critically ill patients

Type of hormone	Sleep deprivation	Critical illness
Thyroid hormone	Increased	Decreased
Norepinephrine	Increased	Increased
Growth hormone	Decreased	Acute illness: Increased Prolonged illness: Decreased
Cortisol	Increased	Increased
Insulin resistance	Present	Present
Hyperglycemia	Absent	Present
VO2	No change	Increased
VCO2	No change	Increased
Nitrogen balance	Negative	Negative

36.4.6 Changes in Hematologic/Immunologic Function

Sleep deprivation decreases T-helper cell and phagocytosis activity. So, critically ill patients due to sleep deprivation may become prone to opportunistic infection and it increases inflammatory cytokines (such as IL-1, IL-6, and TNF) which may leads to endothelial dysfunction, alteration in insulin resistance and risk for sepsis [32, 78].

36.4.7 Changes in Psychological/Neurocognitive Function

ICU psychosis and delirium are major impacts of sleep loss. 60–80% of mechanically ventilated patients and 20–50% of non mechanically ventilated patients are sufferers of delirium [79, 80]. Helton et al. stated that significant correlation exists between intensive care syndrome (confusion, agitation, psychosis) and sleep deprivation [53]. Other patients may have complaints of decreased attention and concentration span, prolonged reaction time, slurred speech, incoordination, increased stress, depression, anxiety, psychological aberrancies, cognitive impairment, mood instability, perceptual distortions (delusions, hallucinations), memory loss, and altered consciousness as a manifestation of delirium [79, 81]. Sleep deprivation adversely effects Amygdala and mesolimbic system's reactivity which precipitate greater lability of emotional reaction [82, 83]. This may lead to post-traumatic stress disorder after getting discharged from ICU [81].

Others effects [31, 84]:

- Obesity.
- Decreased quality of life.
- Excessive daytime sleepiness, decreased energy.
- Reproductive changes.
- Animal data shows that sleep deprivation may lead to death but not in case of humans.

36.5 Management of Sleep Problems of Critically Ill Patients

It is really tough to continue vigorous 24-h needed care for critically ill patients after resuming proper sleep-promoting strategies [45]. But an integrative and multidimensional approach with summation of pharmacological and non-pharmacological strategies can strengthen normal circadian clock and improve sleep and indirectly early recovery [31, 45].

In 2017 in one study on staff perception about the factors associated with sleep disturbances in ICU, those staff suggested some interventions, like 83% asked for clustering of care and for sleep-promoting intervention, 58% talked about reducing the noise level, 38% recommended for avoiding daytime snaps, 29% asked for promoting comfort, 17% suggested reducing light and noise intervention, and 42% considered that education is much needed [20].

36.5.1 Non-pharmacologic Strategies

Non-pharmacological interventions play a vital role in the management of sleep deprivation problem in critically ill patients. These interventions are discussed below:

36.5.1.1 Control of Noise

Control of noise can act as a healing environment for sleep. It has been observed that 60% of noise comes from staff activity, 32% from staff speech, and 6% from equipment alarms.

36.5.1.2 Measures to Control Unnecessary Noise in Critical Care Unit

1. Control use of televisions, pagers, and telephones and minimize the volume as low as 40 dB [31, 33].
2. Try to close the patients' doors by 11:00 PM [33].
3. Always check if staff's and visitors' volume of conversations is high and completely avoid the bedside team discussion after 11 PM [33]
4. Set all volume of monitor alarm calls to 50 dB by 11:00 PM [33].
5. Be quick to respond to an alarm within 1 min [33].
6. Reduce the noise coming from fan and patient care activities.

36.5.1.3 Other Strategies

- Ask to use earplugs which can increase REM sleep, reduce REM latency, lead to fewer arousals, elevate melatonin levels, increase sleep efficiency, and even decrease the incidence of delirium [77].
- Can use headphones also [33].
- Can practice the use of white noise [85].

36.5.1.4 Minimizing Lights

Proposed Interventions for Minimizing the Light During Night in the ICU

- Introduce a cycled lighting system in ICU setting, which stimulates natural light by 14 different light scenes controlled by software for 24 h and is normally switched on during daytime. These light sources are usually located at floor level, on walls (147 lux daytime), a light fitment (color of light in two tubes 2700 K and 6500 K) 45 cm down from ceiling (shining upward to avoid unnecessary stimulation). And reported value of lighting in ceiling and walls is 810 lux [3]. This system helps in vitamin D absorption, improves regulation of melatonin, and makes patient comfortable [30, 86].
- Do nocturnal modification like in nighttime use dim light (40 lux) for stimulating melatonin secretion and indirectly inducing sleep [33, 53]
- Can make ICU environment more healing by using lighting system as per individualized disease condition demand [3].
- For reducing postoperative delirium can go for bright-light therapy (5000 lux) [33].

- Can use eye mask during sleeping time to protect eyes from stimulation [87].
- Try to switch off lights if not needed [88].
- Minimize nursing care activities during nighttime [87].
- Do light-level fluctuation according to natural day-night rhythm [88].
- Can raise curtains during daytime period [88].

36.5.1.5 Rescheduling of Patient Care Activities

- Critical care over 24 h can interrupt sleep up to 40–60 times per night which should be avoided. It may arise due to rostering of the staff but can be avoided by rescheduling of patient care activities and blood sampling between 5:00 AM and 6:30 AM and chest radiograph between 7:00 PM and 10:00 PM instead of midnight [33].
- Nasogastric tube feeding can be time restricted and keep it same as normal mealtime [33].

36.5.1.6 Motivation and Encouragement

Motivate the patient for good sleep hygiene and encourage for "out-of-bed" daytime nursing after assessing patient's condition [81].

36.5.1.7 Proper Communication

Proper information system can reduce patient's unnecessary stress factor, anxiety, and indirectly sleep disruption [81].

36.5.1.8 Raising Staff Awareness of Nursing and Medical Staff

To develop a culture for dealing with sleep disorders among critically ill patients, implementation of ICU sleep protocols and education of ICU physicians, nurses, and other ancillary staff are needed. Sleep quality assessment and promotion should be inculcated in curriculum, care plan should focus on multidisciplinary aspects, and team conference is much needed [47].

36.5.1.9 Possible Remedies to Improve Sleep with Mechanical Ventilation

- Try to avoid excessive pressure support and smaller tidal volumes. Be oriented and do surveillance for discomfort associated with endotracheal (ET) tube, ventilator dyssynchrony, and central apneas [31, 45, 53, 89].
- In case of disease-specific mode like noninvasive positive pressure in COPD, continuous positive-pressure or noninvasive positive-pressure ventilation in Cheyne-Stokes respiration is more applicable [46, 90].
- It has been observed that the effect size of nonmechanical ventilation is more than mechanical ventilation [91].
- Time mode is more beneficial for sleep rather than spontaneous mode [91].

36.5.1.10 Illness-Specific Management

- Transducer at the phlebostatic axis should be level with sleeping position [47].
- Do close monitor for pain or discomfort and give analgesic as prescribed but if analgesic and hypnotic are prescribed together then try to administer hypnotic once pain is relieved for better outcome [47].

36.5.1.11 Complementary Therapies

A combination of alternative therapies like massage, relaxation, and imagery therapies can be a good option for sleep promotion [92, 93].

- *Massage:* 3–10 min of effective massage probably activates the parasympathetic nervous system as well as decreases heart rate, blood pressure, respiratory rate, and stress level and helps in sleep [54]. Foot rubs are also found effective [92–94].
- Do practice different relaxation techniques [35].
- Reading books can stimulate sleep [31].
- Acupuncture/valerian acupressure: most effective with insomnia or elderly people.
- Do mobilization and optimizing comfort as needed [31].
- Music therapy and playing recordings of ocean sounds: Music therapy can reduce the degree of pain sensation and is good for sleep too. One RCT's results show that 45 min of classical type music can reduce heart rate, blood pressure, and respiratory rate; lengthen N3 sleep stage; and even increase subjective sleep score.
- Therapeutic touch can help the person to ventilate anxiety and worries whereas mental imagery reduces the levels of stress and anxiety and both induce sleep [39, 47].
- Aromatherapy, yoga, and biofeedback techniques are also applicable [39, 88].

36.5.1.12 Cognitive Behavioral Therapy (CBT)

In an ambulant setting for the treatment of insomnia CBT can be of use.

36.5.1.13 Other Interventions

- Any attachment, may be from monitor, different lines, or catheters, needs to be checked frequently so that it is not placed under the patient and does not create discomfort [50, 54, 95].
- Try to minimize activity (e.g., emptying trash).
- Maintain proper room temperature (too warm and too cool hamper sound sleep) [31].
- Include social support during sleep-promoting interventions (e.g., family support).
- Reduce or avoid daytime napping and it should be less than 45 min [49].

36.5.2 Pharmacological Consideration

Commonly used drugs for the management of sleep problem in critically ill patients are the following (Table 36.3):

Dexmedetomidine: It has been found that dexmedetomidine can induce sleep almost like natural stages [54].

Zolpidem, zopiclone, zaleplon, eszopiclone: A group of non-benzodiazepine agonists of the receptor of GABA pretended that they have less adverse effects than frequently used sedatives [89].

36.5.2.1 Antidepressant

Amitriptyline: The tricyclic antidepressant amitriptyline is normally considered as a nocturnal sedative and is used for increasing overall sleep time but also reduces sleep latency and REM sleep [89].

Table 36.3 Common drugs used to improve sleep in critically ill patients [92]

Drug	Suggested dose	Effect on sleep	Other benefits
Melatonin	3–10 mg	It decreases the time to fall asleep if suffering from insomnia but no clinical effect on time spent asleep. If sleep problem is due to any medical cause then melatonin does not show specific effectiveness	No other benefits for critically ill patients
Ramelteon	8 mg	Reduces the time to fall asleep and total duration of sleep increases	Lower incidence and duration of delirium, and fewer nighttime awakenings
Dexmedetomidine	0.1mcg/kg/h	Increases total sleep time and proportion of time spent in N2 (deeper) stage of sleep; reduces proportion of time spent in N1 (lighter) sleep. No change in REM sleep	Reduced postoperative delirium, reduced reported pain, improved reported sleep
Amitriptyline	10–50 mg	Shortens time to fall asleep and increases overall sleep time, but reduces REM sleep	No benefit has been proven in ICU patients when used for this indication
Mirtazapine	15–30 mg	Increases total slow-wave sleep and REM sleep, as well as improves insomnia scores	No other benefits for critically ill patients
Trazodone	50 mg	Increases total slow-wave sleep but reduces REM sleep. Improves subjective insomnia. No effect on total sleep duration or time to fall asleep	No other benefits for critically ill patients

Mirtazapine: This atypical antidepressant prominently causes somnolence mainly as a side effect and increases total slow-wave sleep as well as REM sleep unlike amitriptyline by blocking postsynaptic serotonergic and presynaptic alpha-2 negative feedback blockade and also by enhancing noradrenergic and 5HT1 neurotransmission [89].

Trazodone: Instead of benzodiazepines trazodone which is a tetracyclic antidepressant can be used for the treatment of insomnia mainly [89].

36.5.2.2 Antihistamines

Diphenhydramine, Doxylamine: These two medicines can be used for reducing sleep latency and increasing total sleep time [89].

Melatonin and Ramelteon: Melatonin plays a tremendous role in maintaining circadian rhythm and quality sleep and it has effects on the immune system and acts as neuroprotector, oxidant/antioxidant, anxiolytic, and analgesic [51, 96]. Exogenous melatonin when administered among critically ill patients with COPD has shown positive result as measured by actigraphy [80]. Use of synthetic melatonin agonist (ramelteon) was found to reduce delirium among elderly patients [33]. But still larger randomized controlled trial is recommended.

Different doses and preparations tried for effective result can be summarized as follows:

- Melatonin may be administered orally or I.V [51].
- Half-life of melatonin is 20–60 min [51].
- 10 mg of oral dose trial was found too high and has carryover effect on next morning; 1–2 mg trial shows less risk of daytime overdose and 3 mg has earlier pick concentration [51, 91].

36.6 Nursing Process in Management of Sleep Problems in Critically Ill Patients

Nursing Diagnosis: Impaired/disturbed sleeping pattern related to complex auditory environment, 24-h exposure to artificial light, general discomfort (i.e., pain, different monitoring equipment, different tubing, mechanical ventilation), absence of windows in ICU, frequent monitoring and time-sensitive patient care activities, presence of acute illness as evidenced by severely fragmented and brief sleep, reduced deeper stage of slow-wave sleep, dominance of lighter stages of sleep, excessive daytime sleeping, complaints of frequent awakening, and difficulty in falling asleep.

36.7 Desired Outcomes/Goal

36.7.1 Short Term

- Client will reduce daytime napping.
- Client will verbalize noise-free environment, reduced use of artificial light, proper management of care activities, and general comfort promoting nighttime sleep.

36.7.2 Long Term

- The client will verbalize less awakening at nighttime.
- The client will experience deepest stage of sleep.

36.8 Nursing Interventions

36.8.1 Environmental Management

- Minimize the unnecessary noise from family visits, bedside monitoring, equipment alarm sound, and conversations from the health team to allow the patient to obtain the much-needed NREM stage 3 and 4 sleep and REM sleep.
- Avoid bedside discussion after night dose of medication and force door closing.
- Do minimal use of telephone, TV, and pagers.
- Respond to the alarm within 1 min.
- Provide earplug or headphone to the patient if needed and try to use white noise.
- Dim the lights of hallway and nursing station and turn unnecessary lights out.
- Do effective use of a cycled lighting system which can promote patient's sleep and rest aligned with circadian rhythm.
- Can use light according to the day- and night-light fluctuation.
- Can provide eye mask to the patient.

36.8.2 Promoting Sleep Hygiene Activities

- Give proper positioning to promote comfort and do continuous surveillance for early identification.
- Establish standard operating protocol for sleep and rest.
- Involve family member when designing sleep hygiene for individual patients.
- Administer medication as prescribed (i.e., ramelteon 8 mg).
- After administering hypnotic, do the last round for the shift. Do assure freshwater and the call light should be within reach.
- Nursing care activities should be rescheduled and eliminate nonessential treatments during nighttime hours to allow uninterrupted sleep periods of at least 90 min so that one sleep cycle can be completed.

- Nursing care activities (i.e., maintaining personal hygiene, providing an extra pillow or blanket, arranging the pillows) can promote sleep but should be done in proper time preferably after 5:30 am for reducing sleep interruption.
- Monitor the discomfort regarding the disease process, tubing, and mechanical ventilation and focus on time mode of mechanical ventilation.
- Minimize unnecessary daytime sleeping.
- A back massage for 10 min should be provided with combination of foot rub, muscle relaxation, mental imagery, and music.
- Use therapeutic touch for reassurance and helping the patient to ventilate their feelings which can indirectly reduce anxiety.

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Part V

Sleep and Neuropsychopharmacology

Sleep in Patients with Schizophrenia or Unipolar or Bipolar Disorder: The Effect of Second-Generation Antipsychotic Drugs

37

Jaime M. Monti, S. R. Pandi-Perumal, David Warren Spence, and Pablo Torterolo

Abstract

In patients with unipolar (depressive) disorder, sleep disturbance generally takes the form of insomnia, whereas patients with bipolar disorder typically show a reduced need for sleep. Sleep impairment in these patients increases the risk for a major depressive episode and suicidal behavior. Insomnia is also a common trait in schizophrenia, with total sleeplessness being frequently detected during acute exacerbation of the psychiatric disease. The effects of a number of second-generation antipsychotic drugs (SGAs) on sleep variables in unipolar and bipolar disorder patients and in patients with schizophrenia have been characterized in sleep laboratories or by home-based sleep recordings. Administration of SGAs to patients with unipolar and bipolar disorder, including clozapine, risperidone, olanzapine, quetiapine, and ziprasidone, have been shown to improve sleep continuity. Additionally, the latter four drugs have been shown to ameliorate disturbed sleep architecture. In various studies of patients with schizophrenia, treatment with clozapine, olanzapine, quetiapine, and paliperidone is typically followed by a significant improvement of sleep induction and continuity in this patient group. Moreover, olanzapine and paliperidone improved sleep architecture. By contrast, quetiapine was associated with increased sleep disruption. No

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consistent effects were detected during the administration of risperidone. Taken together, this evidence supports the conclusion that several SGAs may ameliorate sleep in patients with schizophrenia and unipolar and bipolar disorder.

Keywords

Wakefulness · Non-REM sleep · Depression · Mania · Antipsychotic drugs

37.1 The Sleep-Wakefulness Cycle in Man

The pioneering sleep studies of Dement and Kleitman [1] and Rechtschaffen and Kales [2] produced an internationally adopted classification system of sleep stages which, with minor modifications, continues to be used today. This system recognized distinct sleep stages including a waking state, non–rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS). Relaxed wakefulness (W) is characterized by an electroencephalogram (EEG) profile which typically shows alpha-wave activity intermixed with lower amplitude irregular beta waves, slow or rapid eyelid blinks (as measured by the electrooculogram [EOG]), a relatively high tonic electromyogram (EMG), and movement artifacts. Concerning NREMS, the American Academy of Sleep Medicine [3] scoring manual recognized three stages (N1, N2, and N3). Stage 1 sleep is characterized by the transition from W to sleep and is typified by the presence of relatively low-voltage, mixed frequency waves with a prominence of activity in the theta range, slow and mostly horizontal eye movements, and a reduction of EMG activity. Stage N2 sleep is characterized by the appearance of sleep spindles and K complexes, while stage N3 sleep (slow-wave sleep) is associated with the occurrence of slow high-amplitude delta waves. During REMS, the sleeping subject's muscles are flaccid and he is even more unresponsive to environmental disturbances than during N3 sleep. Periodically, his eyes move rapidly under closed lids. If the subject is aroused, he might actually say that he was dreaming. The polysomnogram (which aggregates readings from the EEG, EOG, and EMG) is distinguished by the presence of low-voltage, mixed frequency EEG activity, which closely resembles that of stage N1 sleep. Often in this context are sawtooth waves in conjunction with bursts of REMs. In contrast, the muscles are completely relaxed (with the exception of the extraocular muscles and the diaphragm). Nevertheless, the flat EMG tracing can be frequently interrupted by muscle twitches.

Out of a typical night's sleep of 7–8 h, young adults spend 4–5% in stage N1 sleep, 46–50% in stage N2 sleep, 20–24% in stage N3 sleep, and 20–28% in REMS. A shortening in sleep duration, which progressively occurs with advancing age, is mainly related to the reduction in N3 sleep and REMS [4]. This is an important issue, and has implications for memory storage and recall, with research showing that different stages of sleep separately contribute to these critical functions. There is converging evidence that N3 sleep contributes to memory consolidation processes, while memory task performance is closely related to the amount of REMS [5, 6]. It

has been suggested that the decline in memory efficiency, which is often seen in elderly subjects, and which is sometimes attributed to organic brain deterioration, may in fact represent an age-related lessening of time spent in the sleep stages that are required for facilitating memory storage and retrieval [6]. These memory decrements, seen not only in the elderly but also in depressed patients, closely affect other cognitive/perceptual processes, such as the maintenance of attention, the ability to concentrate, and the capacity to sustain a logical chain of thoughts. All of these processes are affected in depressed subjects, and often more severely in patients with schizophrenia. The possibility that sleep disturbances have reciprocal and mutually facilitating effects on depressed mood is a major premise of a recently developed theory of the origin of mood disorders known as the circadian hypothesis of depression [7]. While this is not the only theory of how depressive disorders develop, it is nevertheless consistent with the more widely held view that mood disorders and disturbed sleep are closely associated.

37.2 Sleep Disturbances in Patients with Unipolar and Bipolar Disorder

Unipolar disorder (major depressive disorder) is characterized by: (a) depressed mood, (b) diminished interest in all activities, (c) sleep disturbance every day, (d) fatigue or loss of energy, (e) diminished ability to think or concentrate, and (f) recurrent thoughts of death [8].

Sleep alteration in patients with a diagnosis of unipolar disorder may take either the form of insomnia or hypersomnia, with the later condition occurring less frequently. Objective sleep changes include increased W and reduced sleep efficiency (SE). Sleep latency (SL) is augmented while N3 sleep and total sleep time (TST) are reduced. Rapid eye movement sleep latency is shortened while the duration of the first REMS episode and REM density are increased. Hypersomnia may be expressed as prolonged episodes of sleep at night or increased daytime sleep [8]. According to Breslau et al. (1996), the relative risk of developing a unipolar depressive disorder is four times greater in patients with an insomnia disorder as compared to patients with hypersomnia.

For the diagnosis of bipolar I disorder, the patient's symptoms must meet the following criteria for a manic episode: (a) elevated, expansive, or irritable mood; (b) inflated self-esteem; (c) decreased need for sleep; (d) pressure to keep talking; (e) flight of ideas; (f) increase in goal-directed activity; and (g) involvement in activities that have a high potential for painful consequences. For the diagnosis of bipolar II disorder, the patient has to satisfy the criteria for a current or past hypomanic episode and a major depressive episode. A common characteristic of bipolar I and bipolar II disorder is a reduced need for sleep without dissatisfaction with sleep quality. In contrast to patients with a unipolar disorder who are unable to sleep, patients with a bipolar I or a bipolar II disorder may awaken in the middle of the night or early in the morning feeling rested and full of energy [8]. Interestingly,

Colombo et al. [9] pointed out that disrupted sleep in patients with a diagnosis of bipolar disorder could be responsible for the occurrence of manic episodes.

37.3 Sleep Disturbances in Schizophrenia Patients

According to the American Psychiatric Association [8], schizophrenia is characterized by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. Additionally, sleep disturbances affect a considerable number of schizophrenia patients. This is of concern, because sleep disruption frequently aggravates the psychotic symptoms [10]. Delays in sleep onset and maintenance are the most frequently observed disturbances in schizophrenia patients, irrespective of their medication status (never medicated or previously treated) or the phase of the illness (acute or chronic). Further, other sleep disturbances including obstructive sleep apnea, restless legs syndrome, and periodic limb movement disorder are frequently diagnosed in patients with schizophrenia [11]. Objective changes of sleep induction and sleep maintenance in schizophrenia patients include increased SL, reduced TST, and SE. Changes in sleep architecture also occur. Schizophrenia patients show decreases in NREMS, N3 sleep, and REMS latency; however, REMS tends to remain unchanged [12]. Inconsistencies in interpatient comparisons of sleep architecture profiles are related mainly to age differences between patients and differences in pharmacological treatments or study techniques [13]. Of note, recent studies have described reduced sleep spindle activity and EEG power in schizophrenia patients, which could be tentatively related to a thalamic-reticular and thalamocortical dysfunction [14, 15].

37.4 Pharmacotherapy of Schizophrenia and Unipolar and Bipolar Disorder

Antipsychotic drugs are an essential component of the treatment of schizophrenia. Notwithstanding this, the advent of second-generation antipsychotics (SGAs) has brought with it an associated increase in the use of these compounds for treatment of other psychiatric disorders, including unipolar and bipolar disorder. The currently available SGAs comprise a diverse group of compounds that include the structurally related dibenzodiazepine derivatives clozapine, olanzapine, and quetiapine; the benzidoxasole derivatives risperidone, its active metabolite paliperidone (9-hydroxyrisperidone), and iloperidone; the benzisothiazolpiprazinylindolone, dibenzo-oxepinopyrrole, and quinolinone derivatives ziprasidone, asenapine, and aripiprazole, respectively; and lurasidone that belongs to the chemical class of benzisothiazol [16]. Compared to first-generation antipsychotics, the presently available SGAs have a reduced probability of producing acute extrapyramidal side effects. On the other hand, weight gain is frequently associated with prolonged treatment with clozapine and olanzapine, and less so with the other derivatives.

Other SGA-associated side effects include sedation, dyslipidemia, new onset or worsening of diabetes type 2, and hypertension [17]. Prescribing heuristics for the dosing, route of administration, and choice of the SGA should take into consideration the patient's disease state, the potential for drug interactions with other treatments, and the risk profile for side effects.

37.5 Receptor-Binding Affinity of Second-Generation Antipsychotic Drugs

Aside from aripiprazole which acts as a partial dopamine (DA) D2 receptor antagonist, all other SGAs are full DA D_2 receptor antagonists. Other actions of SGA's include the blocking of DA D_1, D_3, and D_4 receptors; serotonin (5-HT) 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors; noradrenergic (NE) α_1 and α_2 receptors; histaminergic (HA) H_1 receptors; and muscarinic cholinergic (ACh) m_1 receptors. These pharmacological agents can also interact with the DA, 5-HT, and NE transporters [18, 19] (Frangou and Murray 1996). Receptor interactions associated with SGA's are shown in Table 37.1.

Table 37.1 Relative receptor affinities of second-generation antipsychotic drugs

Receptor	D_1	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	α_1	α_2	H_1	m_1
Clozapine	+	+	−	+++	++	++	++	+++	+	+++	+++
Risperidone	+	+++	−	+++	++	−	+++	+++	++	+	−
Olanzapine	++	++	−	+++	++	+	−	++	+	+++	+++
Quetiapine	−	+	−	++	−	−	−	+++	−	++	++
Ziprasidone	+	+++	+++	+++	+++	+	++	++	−	+	−
Aripiprazole	−	+++	++	+++	+	+	++	+	+	+	−
Paliperidone	+	++	+	+++	+	−	−	++	++	+	−
Asenapine	++	++	++	+++	+++	+	+	++	++	++	−
Iloperidone	+	++	+	++	+	+	+	+++	+	+	−
Lurasidone	−	+++	+++	+++	+	−	+++	++	+++	−	−

From Kalkman et al. [20], Horacek et al. [19], Dolder et al. [18], Jarskog et al. [21], Ishibashi et al. [22], and Shin et al. [23]
+++ = high; ++ = moderate; + = low; − = minimal to none

37.6 Pharmacokinetics of Second-Generation Antipsychotic Drugs

Most SGAs are highly lipophilic and tend to accumulate in the central nervous system (CNS). The pharmacokinetics of each of the SGAs are briefly described in Table 37.2.

Clozapine's oral bioavailability is only 60–70%, owing to first-pass metabolism, while its peak plasma concentration (T_{max}) takes place in 2–5 h. The major metabolite norclozapine is pharmacologically active. The mean elimination half-life ($t_{½}$) of clozapine and its active metabolite amounts to about 12 h [24]. Risperidone is well absorbed, and its absolute bioavailability is 70%. The drug is metabolized to an active metabolite, 9-hydroxyrisperidone (paliperidone). Following oral administration of either the solution or tablet form, the T_{max} of the parent drug ensues at 1 h, while the T_{max} of the active metabolite takes place at about 3 h. The mean $t_{½}$ of both drugs total to 20 h [25]. Olanzapine is well absorbed, with approximately 40% of the therapeutic dose being metabolized before reaching the systemic circulation. The medication attains peak plasma levels (T_{max}) at about 6 h after oral administration, while its $t_{½}$ fluctuates between 21 and 54 h. Olanzapine is metabolized to inactive metabolites that are excreted in urine and feces [26]. Quetiapine is rapidly absorbed after oral administration and its T_{max} extends from 1 to 2 h. The compound is metabolized to its active derivative norquetiapine. Quetiapine and its active metabolite are eliminated with a $t_{½}$ of 7 h and 9–12 h, respectively [27]. Ziprasidone's activity is mainly due to that of the parent drug. Its systemic bioavailability amounts to 60%, and its T_{max} is 6–8 h. The $t_{½}$ of the compound extends from 2 to 5 h [28]. The T_{max} corresponding to aripiprazole is attained 3–5 h after oral administration. The antipsychotic drug displays linear kinetics and its $t_{½}$ amounts to 47–68 h. Moreover, it undergoes extensive hepatic metabolization and its active metabolite

Table 37.2 Pharmacokinetic parameters for second-generation antipsychotic drugs

Drug	Peak plasma Concentration (T_{max}, h)	Elimination Half-life ($t_{½}$, h)	Metabolism (active metabolites)
Clozapine	2–5	12	N-Desmethylclozapine
Risperidone	1	20	9-Hydroxyrisperidone (paliperidone)
Olanzapine	6	21–54	No
Quetiapine	1–2	7	Norquetiapine
Ziprasidone	6–8	2–5	No
Aripiprazole	3–5	47–68	Dehydroaripiprazole
Paliperidone	24	23	No
Asenapine	0.5–1.5	24	No
Iloperidone	2–4	18–33	P88 (hydroxyl metabolite)
Lurasidone	0.4	18	No

From Baldessarini and Tarazi [24], Heykants et al. [25], Callaghan et al. [26], DeVane and Nemeroff [27], Miceli et al. [28], Fleischhacker [29], Product Information - Saphris - Merck Sharp & Dohme [30], Citrome [31], and Leucht et al. [32]

dehydroaripiprazole shows a $t_{½}$ of 94 h [29]. Following sublingual administration, asenapine is rapidly absorbed with a T_{max} occurring within 0.5–1.5 h. The compound is rapidly distributed and extensively metabolized to inactive metabolites. Oxidative metabolism and direct glucuronidation are the primary metabolic pathways for the derivative. The $t_{½}$ of asenapine is approximately 24 h [30]. Iloperidone is well absorbed after administration of the tablet with peak plasma concentrations (T_{max}) occurring within 2–4 h. The $t_{½}$ of the compound ranges from 18 to 33 h. The metabolism of iloperidone generates two major metabolites, P88 and P95. The active metabolite P88 accounts for 19.5% of total plasma exposure in extensive metabolizers [31]. Orally administered lurasidone shows a bioavailability of 9–19%. The drug is metabolized in the liver and its T_{max} amounts to 0.4 h, while its $t_{½}$ totals 18 h [32].

37.7 Effects of Second-Generation Antipsychotic Drugs on Sleep Variables in Patients with Schizophrenia and Unipolar and Bipolar Disorder

The effects of SGAs on sleep variables in unipolar and bipolar disorder and in patients with schizophrenia have been investigated in the sleep laboratories or by home-based sleep recordings. Presently the evidence is restricted to clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and paliperidone. Available information on ziprasidone is exclusively related to patients with bipolar disorder, while findings regarding paliperidone are limited to schizophrenia patients. Future studies are expected to address the effects of ziprasidone, paliperidone, aripiprazole, asenapine, iloperidone, and lurasidone in patients with schizophrenia and/or unipolar and bipolar disorder.

37.7.1 Patients with Unipolar and Bipolar Disorder

Existing data on the effects of SGAs on sleep variables in patients with unipolar and bipolar disorder are briefly described in Table 37.3.

Armitage et al. [33] assessed the effects of clozapine on sleep variables in patients with a diagnosis of either bipolar I disorder ($n = 11$) or schizoaffective disorder bipolar type ($n = 3$) who were receiving antidepressants. When compared with baseline values, clozapine administration (370 ± 189 mg/day) resulted in a significant increase of SL, the number of awakenings, and TST. Values corresponding to NREMS stages and REMS latency and duration did not show significant changes.

Sharpley et al. [34] characterized the actions of risperidone administration (0.5–1.0 mg/day) on sleep in patients with unipolar disorder who failed to respond fully after administration of antidepressant drugs ($n = 8$). Compared with baseline values, the compound induced a significant decrease of WASO and REMS while N2 sleep was augmented.

Table 37.3 Effects of second-generation antipsychotic drugs on sleep variables in unipolar and bipolar disorder

Authors and treatment	SL	WASO	TST	SE	N1	N2	N3	REMSL	REMS
Armitage et al. [33]									
Clozapine (370 ± 189 mg)	↑*	–	↑*	n.s.	n.s.	n.s.	–	n.s.	n.s.
Sharpley et al. [34]									
Risperidone (0.5–1.0 mg)	n.s.	↓*	n.s.	n.s.	n.s.	↑*	–	n.s.	↓*
Sharpley et al. [35]									
Olanzapine (2.5–10 mg)	↓*	↓*	↑*	↑*	n.s.	n.s.	↑*	↓*	↓*
Moreno et al. [36]									
Olanzapine (15 mg)	n.s.	↓*	n.s.	↑*	n.s.	n.s.	n.s.	n.s.	n.s.
Lazowski et al. [37]									
Olanzapine (5–10 mg)	n.s.	–	↑*	↑*	n.s.	↑*	n.s.	n.s.	n.s.
Todder et al. [38]									
Quetiapine (300–800 mg)	↓*	–	↑*	n.s.	–	–	–	–	–
Gedge et al. [39]									
Quetiapine (155 mg	n.s.	–	n.s.	n.s.	n.s.	↑*	–	n.s.	↓*
Kim et al. [40]									
Quetiapine (300 mg – ER)	n.s.	↓*	–	↑*	–	–	–	–	–
Baskaran et al. [41]									
Ziprasidone (40 mg)	↓*	–	↑*	↑*	n.s.	↑*	↑*	↓*	n.s.

Abbreviations: *n.s.* nonsignificant, – not reported, *SL* sleep latency (min), *WASO* wake time after sleep onset (min), *TST* total sleep time (min), *N1, N2, N3*, NREMS stages (min), *REML* REM sleep latency (min), *REMS* REM sleep duration (min or %), *ER* extended release, ↑* – significant increase or ↓* – significant decrease as compared to baseline, placebo, or healthy subjects ($P < 0.05$)

Sharpley et al. [35] also measured the actions of olanzapine on sleep in patients with a diagnosis of unipolar disorder ($n = 12$) who did not respond adequately to treatment with antidepressant agents. The initial dose of the antipsychotic drug amounted to 2.5 mg/day and was increased to a maximum of 10 mg/day as required. Compared to baseline, SL and WASO showed significant decreases, while TST and SE were augmented during the drug treatment period. Concerning sleep architecture, N3 sleep exhibited an increase, whereas values corresponding to REMS latency and REMS duration changed in the opposite direction. Moreno et al. [36] studied the effects of olanzapine (mean dose 13.6 mg/day, range 5–20 mg) on sleep variables in bipolar patients during manic episodes ($n = 7$). In comparison to baseline, the antipsychotic drug reduced WASO and increased SE. Lazowski et al. [37] sought to characterize the effects on sleep of olanzapine in patients with a diagnosis of bipolar I or bipolar II disorder ($n = 15$) who were experiencing a major depressive episode, and who were receiving an antidepressant drug prior to enrolment, and found qualified evidence of its efficacy. Compared to patients on placebo ($n = 10$), olanzapine administration (mean dose 6.7 mg/day, range 5–10 mg) did not significantly modify SL. In contrast, TST and SE were augmented, while total wake time was decreased. Moreover, N2 sleep was significantly increased, while values corresponding to N3 sleep and REMS remained unaffected. Thus, the available evidence tends to indicate that olanzapine reduces WASO and increases TST and SE in antidepressant-resistant patients with a diagnosis of either unipolar or bipolar disorder who are experiencing a depressive episode and bipolar patients during manic episodes.

Gedge et al. [39] described the effect of adjunctive quetiapine therapy on sleep and W in patients with unipolar or bipolar disorder ($n = 11$) currently suffering a major depressive episode. The average dose of quetiapine was 155 mg/day (range 100–200 mg). In comparison to baseline, adjunctive quetiapine administration augmented N2 sleep while REMS was decreased. Kim et al. [40] characterized the effects of quetiapine extended release (ER) monotherapy (300 mg/day) on sleep and depressive symptoms in bipolar I and bipolar II disorder patients ($n = 12$) who were experiencing major depressive episodes at the time of drug administration. Compared to baseline, quetiapine ER produced significant reductions in WASO and increases in SE. Additionally, depressive symptoms became attenuated following administration of the antipsychotic drug. Todder et al. [38] assessed sleep in patients with unipolar or bipolar disorder ($n = 27$) who were given antidepressant treatment plus quetiapine (300 mg/day in the first week and 800 mg/day over the study period). Sleep latency was significantly reduced and TST was greater in the study patients as compared to healthy controls. Thus, according to Kim et al. [40] and Todder et al. [38], monotherapy or adjunctive quetiapine therapy mainly improved sleep continuity in patients with a diagnosis of unipolar or bipolar disorder. In contrast, Gedge et al. [39] found that quetiapine augmentation therapy only modified sleep architecture in unipolar or bipolar patients who were currently experiencing a major depressive episode as judged by the increase in N2 sleep and reduction in REMS.

Baskaran et al. [41] investigated the effects of ziprasidone on sleep in patients with bipolar disorder ($n = 8$) who were currently experiencing a major depressive

episode. The patients received ziprasidone at a starting dose of 40 mg twice daily to a maximum of 80 mg twice daily. Compared to patients on placebo ($n = 6$), the drug significantly reduced SL and REMS latency and augmented TST, SE, N2 sleep, and N3 sleep.

37.7.2 Patients with Schizophrenia

Available data on the effects of SGAs on sleep variables in patients with schizophrenia are briefly described in Table 37.4.

Wetter et al. [42] compared the nocturnal EEG recordings of drug-naïve schizophrenia patients with those of patients ($n = 12$) who were taking clozapine (348 ± 152 mg/day). In the patients receiving clozapine, significantly greater time values for N2 sleep, TST, and SE were found, while SL was reduced. By contrast, N3 sleep, REMS latency, and REMS duration showed no significant changes. Hinze-Selch et al. [43] conducted a study of clozapine effects in long-term drug-free schizophrenia patients ($n = 13$). Clozapine administration (170 ± 77 mg/day) significantly augmented N2 sleep, TST, and SE, while WASO and N3 sleep were decreased. In a study by Tandon [44] of sleep quality of schizophrenia patients ($n = 10$) who were receiving a stable dose of clozapine (amount not described), its effect was compared to that of drug-free patients. Clozapine produced a significant reduction of SL, whereas TST and REMS latency were increased. Lee et al. [45] studied the effects of clozapine (200–350 mg/day) on the sleep quality of schizophrenia patients ($n = 5$) who were drug free. Compared to healthy subjects, the values corresponding to the sleep parameters of N2 sleep, TST, and SE in the schizophrenia patients were significantly increased during clozapine therapy. In a study by Kluge et al. [46], the effects of clozapine (200–267 mg/day) on the sleep of patients with schizophrenia ($n = 15$) were compared to baseline. Administration of the compound was followed by significant increases in TST, SE, and N2 sleep, while N3 sleep was reduced.

Tandon [44] also characterized the sleep profile of patients with schizophrenia ($n = 7$) who were on a stable dose of risperidone (dose not specified). The only significant difference between drug-treated and drug-free patients was a reduction of SL. Haffmans et al. [47] characterized the effects of risperidone (5 mg/day; $n = 6$) and haloperidol (8.1 mg/day; $n = 9$) on the sleep of patients with schizophrenia. Compared to patients on haloperidol, the risperidone group showed an increase in the duration of N3 sleep. Yamashita et al. [48] also evaluated the effects of risperidone (6.4 ± 3.7 mg/day; $n = 5$) and haloperidol (7.5 ± 4.0 mg/day; $n = 5$) on sleep in schizophrenia patients. Their findings were similar to that reported by Haffmans et al. [47].

The effects of olanzapine on sleep variables in patients with schizophrenia have been compared to baseline values in a number of publications. In a study by Salin-Pascual et al. [49], olanzapine administration (10 mg/day) to drug-free patients ($n = 20$) was followed by a reduction of WASO and N1 sleep, while TST, N2 sleep, and N3 sleep were increased. REMS time and REMS latency exhibited no

Table 37.4 Effects of second-generation antipsychotic drugs on sleep variables in schizophrenia patients

Authors and treatment	SL	WASO	TST	SE	N1	N2	N3	REMSL	REMS
Wetter et al. [42]									
Clozapine (348 ± 152 mg)	↓*	–	↑*	↑*	n.s.	↑*	n.s.	n.s.	n.s.
Hinze-Selch et al. [43]									
Clozapine (170 ± 77/275 ± 122)	n.s.	↓*	↑*	↑*	n.s.	↑*	↓*	n.s.	n.s.
Tandon [44]									
Clozapine (dose not reported)	↓*	–	↑*	–	–	–	–	↑*	–
Lee et al. [45]									
Clozapine (200–350 mg)	–	–	↑*	↑*	–	↑*	–	–	–
Kluge et al. [46]									
Clozapine (200–267 mg)	–	–	↑*	↑*	–	↑*	↓*	–	–
Tandon [44]									
Risperidone (dose not reported)	↓*	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Haffmans et al. [47]									
Risperidone (5 mg)	–	–	–	–	–	–	↑*	–	–
Yamashita et al. [48]									
Risperidone (6.4 ± 3.7 mg)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	↑*	n.s.	n.s.
Salin-Pascual et al. [49]									
Olanzapine (10 mg)	n.s.	↓*	↑*	–	↓*	↑*	↑*	n.s.	n.s.
Müller et al. [50]									
Olanzapine (15–20 mg)	↓*	n.s.	↑*	↑*	n.s.	n.s.	↑*	n.s.	↑*
Kluge et al. [46]									
Olanzapine (15 mg)	↓*	–	↑*	↑*	n.s.	↑*	↑*	n.s.	↑*
Katshu et al. [51]									
Olanzapine (19 mg/15–25 mg)	n.s.	–	↑*	↑*	↑*	n.s.	↑*	n.s.	↑*
Keshavan et al. [52]									

(continued)

Table 37.4 (continued)

Authors and treatment	SL	WASO	TST	SE	N1	N2	N3	REMSL	REMS
Quetiapine (313 ± 229 mg)	↑*	↑*	n.s.	–	–	↑*	↓*	↑*	↓*
Luthringer et al. [53]									
Paliperidone (9 mg – ER)	↓*	n.s.	↑*	↑*	↓*	↑*	n.s.	n.s.	↑*

Abbreviations: *n.s.* nonsignificant, – not reported, *SL* sleep latency, *WASO* wake time after sleep onset (min), *TST* total sleep time (min), *N1, N2, N3* NREM sleep stages (min), *REMSL* REM sleep latency (min), *REMS* REM sleep duration (min), *ER* extended release, ↑* – significant increase or ↓* – significant decrease as compared to placebo, baseline, healthy subjects, drug-free patients, drug-naïve patients, or a first-generation antipsychotic drug ($P < 0.05$)

significant changes. According to Müller et al. [50], drug-free patients with schizophrenia ($n = 10$) given olanzapine (15–20 mg/day) showed a significant reduction of SL, while TST, SE, N3 sleep, and REMS were enhanced. In a study by Kluge et al. [46], olanzapine (15 mg/day) administration to schizophrenia patients ($n = 15$) induced a significant increase of TST and SE, while SL was reduced. Concerning sleep architecture, the antipsychotic drug significantly augmented N2 sleep and REMS. Katshu et al. [51] measured the effect of olanzapine (19 ± 3.9 mg/day) on sleep of drug-naïve or drug-free schizophrenia patients ($n = 15$). Olanzapine administration induced a significant increase of TST, SE, N1 sleep, N3 sleep, and REMS. Values corresponding to N2 sleep, SL, and REMS latency showed no significant changes.

Keshavan et al. [52] compared sleep variables of quetiapine-treated schizophrenia patients ($n = 20$) with those of drug-naïve patients. The compound (313 ± 229 mg/day) significantly augmented SL, WASO, REMS latency, and N2 sleep and decreased N3 sleep and REMS. Values corresponding to TST showed no significant changes.

Luthringer et al. [53] performed a placebo-controlled study in which the effects of paliperidone XR (9 mg/day) on sleep variables in patients with schizophrenia ($n = 17$) were evaluated. As compared to placebo, the compound significantly reduced SL and N1 sleep and increased TST, SE, N2 sleep, and REMS.

37.8 Conclusions

The effects of clozapine, risperidone, olanzapine, and quetiapine on sleep variables in unipolar and bipolar disorder and patients with schizophrenia have been characterized in the sleep laboratory or by home-based sleep recordings. Additionally, ziprasidone administration has been studied in patients with bipolar disorder, whereas paliperidone has thus far been characterized only in schizophrenia patients. Concerning patients with unipolar and bipolar disorder, the limited available evidence tends to indicate that the SGAs induced an improvement in sleep continuity as judged by the reduction in WASO and/or increase in TST and SE. Risperidone, olanzapine, quetiapine, and ziprasidone improved, in addition, sleep architecture as shown by increases in N2 sleep and N3 sleep. With respect to patients with schizophrenia, the administration of clozapine, olanzapine, and paliperidone was followed by a significant reduction of SL, while TST and N2 sleep showed an increase. Moreover, olanzapine and paliperidone enhanced values corresponding to SE, N3 sleep, and REMS. In contrast, the administration of quetiapine further disrupted sleep. The improvement of sleep induction and maintenance observed in the patients treated with the SGAs could be tentatively related to the moderate to strong blockade of several receptors, including the DA D_2, NE α_1, ACh m_1, and HA H_1 receptors. Moreover, the increase of N3 sleep is, in great measure, attributable to inhibition of the serotonin 5-HT_{2A} receptor.

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Effect of Antiepileptics on Sleep

38

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Abstract

This chapter focuses on discussing the effect of antiepileptic drugs on sleep to better understand the treatment effect, especially in patients of epilepsy and sleep problems. Chrono-epileptology is an emerging field of medical science which aims to explore the relationship between seizures and circadian rhythm. It targets to utilise these drugs in patients with epileptic disorders to maximise therapeutic effects and minimise adverse drug reactions.

Keywords

Sleep · Antiepileptics · Sleep-stages · Sleep-architecture

Quality of sleep is an important component for general health and wellbeing. It is particularly more essential in patients of epilepsy. Sleep architecture in patients of epilepsy is affected by seizure episodes, concurrent sleep disorder and antiepileptic drugs (AED). Sleep disorders are a part of complex interplay in epilepsy [1]. Sleep disorders are common in patients of epilepsy and two times more prevalent as compared to control population [2]. It is the most common comorbidity in childhood epilepsy [3]. The learning objective of this chapter is to identify the effect of antiepileptic drugs on sleep to better understand the treatment effect, especially in patients of epilepsy and sleep problems.

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38.1 Chrono-Epileptology

It is an emerging field of medical science which aims to explore the relationship between seizures and circadian rhythm. It targets to utilise these drugs in patients with epileptic disorders to maximise therapeutic effects and minimise adverse drug reactions [4].

Circadian rhythm, a 24-h cycle, under the influence of ambient time clues such as daylight and darkness at night, is a unique feature of most organisms. The pacemaker of this cyclical rhythm is located in the anterior hypothalamic suprachiasmatic nuclei (SCN) in mammals. It controls the physiologic, metabolic and behaviour changes associated with the rhythm. The circadian system determines the onset of the sleep cycle, quality and duration of various sleep stages. Projections from the SCN affect the thalamic and limbic systems (Please see Chaps. 1 and 3 for details). These integrated networks are frequently implicated in epileptogenic process and propagation of epileptic discharges.

38.2 Chronobiologic Changes of Sleep in Epilepsy

Sleep and epilepsy are inversely related with sleep disorders inducing epilepsy and viceversa. Sleep disorder is known to be a common problem in epilepsy patients (Please refer to Chap. 31 for details). Epilepsy patients are found to be twice more susceptible to sleep disorders than the normal individuals. Problems ranging from insomnia, sleepiness, obstructive sleep apnoea, periodic limb movement to restless leg syndrome (RLS) are commonly associated with epilepsy [5].

Epilepsy is seen to increase the latency period of sleep onset, decrease the sleep spindle density and alter stages of sleep with increased N1 and N2 nonrapid eye movement (NREM; light sleep) and decrease rapid eye movement (REM) sleep thereby [6]. Patients with epilepsy present with the predominant complaint of excessive daytime sleepiness. Obstructive sleep apnoea, a sleep disordered breathing, was found to cause daytime sleepiness in few epilepsy patients [7]. Seizure episodes interfere with the circadian rhythm affecting sleep pattern. They are also seen to affect quality and quantity of sleep.

On the contrary, antiepileptic therapy can have negative or positive effects on sleep. They are seen to either cause sedation or promote alertness. Hence, the effect of individual antiepileptics on sleep patterns is presented in this chapter. Most antiepileptic drugs target neurotransmission through the ion channels sodium, calcium and chloride (Na^+, Ca^{2+}, Cl^- respectively), γ -aminobutyric acid (GABA) and glutamate receptors or disrupt the release, inactivation and reuptake of excitatory or inhibitory amino acids.

38.3 Macro and Micro-Architectural Changes

Sleep can be defined as a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment. It consists of rapid eye movement (REM) sleep or dream sleep and non-REM (NREM) sleep. NREM sleep is further divided into stage N1, N2 and N3 sleep based on electroencephalography (EEG) patterns. In adult humans, sleep consists of about 5% wake, 5% N1, 50% N2, 15% N3 and 25% of REM sleep.

It is advocated to consider the possibility of a co-existing sleep disorder before attributing sleepiness in epilepsy patients on antiepileptic medication or uncontrolled seizures [8]. The macrostructural sleep and microstructural sleep indices could be evaluated to distinguish normal sleep from pathologic sleep that includes insomnia, sleep-related hypermotor epilepsy (erstwhile nocturnal frontal lobe epilepsy—NFLE), periodic leg movements and rapid eye movement (REM) behaviour disorder.

The macrostructural sleep indices include sleep latency (SL), total sleep time (TST), sleep efficiency (%SE), wake after sleep onset (WASO), sleep stage shifts/hour of sleep (SS/h), awakenings (AW), sleep stage of NREM and REM sleep and percent of total sleep time (Table 38.1).

The microstructural sleep indices include assessment of sleep spindles, K-complexes and cyclical alternating patterns (CAP). CAP is a sequence of alternating stereotyped EEG patterns forming a specific long-lasting periodic activity. Each CAP cycle consists of two components: phase A, consisting of transient EEG elements (aggregation of arousal-related phasic events) with different degrees of combination and complexity; phase B, consisting of a recurring period of background EEG activity (Θ/δ waves) that corresponds to the interval that separates two successive A phases. Each phase A or B lasts >2 and <60 s. Each CAP sequence includes at least two CAP cycles in succession and always begins with a phase A and ends with a phase B.

The noncyclic alternating pattern (non-CAP) is the NREM state characterised by sustained stability of EEG arousal level and muscle tone; the absence of a phase A for at least 60 consecutive seconds is scored as non-CAP. The microstructural sleep indices measure total CAP time, total non-CAP time, CAP rate, duration and number of A phases, duration and number of B phases and duration and number of CAP cycles (Table 38.2). There is a close association between sleep quality and sleep indices and are reported to follow a set pattern [9] (Table 38.3).

38.4 Impact of Antiepileptic Drugs on Sleep Indices

Most AED affects sleep architecture. Studies in healthy adult participants suggest that phenobarbital and levetiracetam reduce while gabapentin enhances REM sleep. Clobazam reduces, whereas levetiracetam, tiagabine and pregabalin enhance slow wave sleep (SWS). Carbamazepine increases SE/TST, while decreases SL, arousal and wake time.

Table 38.1 The sleep indices of macrostructure [9]

S. no.	Index	Definition
1.	Time in bed (minutes)	Total time in bed during the whole night
2.	Sleep period time (min)	Total sleep period time between the first time of falling asleep and last time of waking up
3.	Total real sleep time (min)	Total actual sleep time excluded all wakefulness time during the whole night
4.	Sleep onset latency (min)	Time delay between going to bed and falling asleep
5.	First REM sleep latency (min)	Time delay between going to bed and the beginning of the first REM sleep
6.	Stage shifts (number/hr)	The average number of all sleep stages per hour
7.	Awakenings (number/hr)	The average number of all awakenings per hour
8.	Sleep efficiency (%)	The ratio of total real sleep time to time in bed
9.	Time of wake stage after sleep onset (min)	Total time of all wakefulness after sleep onset during the whole night
10.	Time of N1 stage (min)	Total time of all N1 stages
11.	Time of N2 stage (min)	Total time of all N2 stages
12.	Time of N3 stage (min)	Total time of all N3 stages
13.	Time of REM stage (min)	Total time of all REM stages
14.	Percent of wakefulness (%)	Percent of all wakefulness time to sleep period time
15.	Percent of N1 stage (%)	Percent of all N1 stages time to sleep period time
16.	Percent of N2 stage (%)	Percent of all N2 stages time to sleep period time
17.	Percent of N3 stage (%)	Percent of all N3 stages time to sleep period time
18.	Percent of REM stage (%)	Percent of all REM stages time to sleep period time (%)
19.	Ratio of N3 to (N1 + N2)	Ratio of all N3 stages time to the sum time of N1 stages and N2 stages
20.	Ratio of N3 to NREM	Ratio of all N3 stages time to all NREM sleep time
21.	Ratio of REM to NREM	Ratio of all REM sleep time to all NREM sleep time
22.	Ratio of N3 to REM	Ratio of all N3 stages time to all REM sleep time
23.	NREM-REM cycle time (min)	The average time of all NREM-REM cycles
24.	Times of NREM-REM cycle (c)	The total number of all NREM-REM cycles
25.	Maximal sustained N1 time (min)	The maximal N1 stage time among all N1 stages
26.	Maximal sustained N2 time (min)	The maximal N2 stage time among all N2 stages
27.	Maximal sustained N3 time (min)	The maximal N3 stage time among all N3 stages
28.	Maximal sustained REM time (min)	The maximal REM stage time among all REM stages
29.	Maximal sustained wake time (min)	The maximal wake stage time among all wake stages excluded the wakefulness before the first falling asleep and the last waking up

Table 38.2 The sleep indices of microstructure [9]

S.no.	Index	Definition
1.	CAP time (min)	Total time of NREM sleep occupied by CAP sequences
2.	CAP rate (%)	Ratio between CAP sleep and total NREM sleep
3.	Total number of A1	Total number of phase A1
4.	Total A1 rate (%)	Percentage of phase A1 to all CAP A phases
5.	Total number of A2	Total number of phase A2
6.	Total A2 rate (%)	Percentage of phase A2 to all CAP A phases
7.	Total number of A3	Total number of phase A3
8.	Total A3 rate (%)	Percentage of phase A3 to all CAP A phases
9.	A mean duration (s)	Mean duration of all CAP A phases
10.	A total duration (min)	Total duration of all CAP A phases
11.	A1 mean duration (s)	Mean duration of all CAP A1 phases
12.	A1 total duration (min)	Total duration of all CAP A1 phases
13.	A2 mean duration (s)	Mean duration of all CAP A2 phases
14.	A2 total duration (min)	Total duration of all CAP A2 phases
15.	A3 mean duration (s)	Mean duration of all CAP A3 phases
16.	A3 total duration (min)	Total duration of all CAP A3 phases
17.	B mean duration (s)	Mean duration of all CAP B phases
18.	A index (c/hr)	Number of phase A per hour during NREM sleep
19.	A1 index (c/hr)	Number of phase A1 per hour during NREM sleep
20.	A2 index (c/hr)	Number of phase A2 per hour during NREM sleep
21.	A3 index (c/hr)	Number of phase A3 per hour during NREM sleep
22.	Total number of CAP sequences	Total number of CAP phase A-phase B sequences
23.	CAP sequences index (c/hr)	Number of CAP sequences per hour during NREM sleep

Table 38.3 Relation between sleep quality and sleep indices [9]

Type	The higher the index, the better the sleep quality	The lower the index, the better the sleep quality
Macrostructural Changes	Sleep efficiency Sleep continuity Amount and ratio of REM Sleep time Amount and ratio of deep sleep time Maximal sustained REM time	REM sleep onset latency Sleep onset latency Amount and ratio of wake time Amount and ratio of light Sleep time
Microstructural Changes		Number of arousals CAP rate, CAP time Number and ratio of A (A1, A2, A3)

Phenytoin exerts its antiepileptic properties by acting on voltage-gated sodium channels. It is associated with reduction in sleep efficiency, a decrease in sleep latency and shortening of light sleep stages (N1 and N2) as well as the REM phase of the sleep cycle. Slow wave sleep usually does not change or may occasionally increase. Acute effects of phenytoin administration include a decrease in sleep-onset latency and light stages of sleep with concomitant increase in slow wave sleep (SWS). On the other hand, chronic use may lead to an increase in the duration of light stages of sleep and a decrease in SWS. Prolonged use of phenytoin often showed reversal of these effects [10, 11].

Valproic acid acts by inhibiting GABA degradation, blocking voltage-gated sodium channels and reducing calcium currents. It increases the number of arousals, prolongs the light stages of sleep and NREM phase, decreases the length of the REM phase and decreases sleep efficiency [12].

Carbamazepine has been shown to act by inhibition of voltage-gated sodium channels. Subjective somnolence has been shown to be reported in 22–32% of patients. The drug also caused an increase in the number of sleep stage shifts, a reduction in REM sleep, increased fragmentation of REM sleep and a significant reduction in sleep latency when treatment is started with it [13].

Lamotrigine works by inhibiting voltage-sensitive sodium channels and impairment of glutamate release. Dose-dependent drowsiness is the most common side effect of the drug. Polysomnography demonstrated a statistically significant increase in N2 sleep stage and reduction in N3 sleep stage. Studies have shown that the patients experienced decreased sleep latency and improved consolidation of nocturnal sleep [14].

Ethosuximide selectively inhibits T-type calcium channels in thalamic neurons. It has been reported to reduce sleep wake cycle, increase REM sleep phase, enhance the light stages of sleep and increase the number of awakenings after sleep onset [15].

Levetiracetam acts by binding to synaptic vesicle protein 2A (SV2A), a transmembrane protein involved in calcium-dependent presynaptic neurotransmitter release. Studies where the drug was used as an add-on showed an increase in time spent in all NREM stages with a relative decrease in time spent in REM sleep [16]. Studies also showed an increase in total time spent in stages 2 and 4 of sleep and prolongation of REM latency period [17].

Benzodiazepines are associated with binding to $GABA_A$ chloride channels leading to increased neuronal inhibition. They have been frequently associated with enhanced sleep-onset latency, increased length of the light stages of sleep, decreased SWS, prolonged REM sleep latency and reduced overall REM sleep duration.

Tiagabine, a γ-aminobutyric acid (GABA) reuptake receptor (GAT-1) inhibitor, increased slow wave activity in the EEG power spectrum without increasing the amount of NREM stage 3 sleep or the arousal threshold compared to placebo in patients with obstructive sleep apnoea [18]. Lacosamide acts through selective enhancement of slow inactivation of voltage-gated sodium channels [19]. Usually, it does not negatively impact any objective sleep measures and has no substantial change in subject-rated daytime sleepiness or sleep quality [20].

In patients of epilepsy, slow wave sleep (SWS) is increased by pregabalin, carbamazepine and gabapentin whereas decreased by levetiracetam and ethosuximide. Sleep onset latency is reduced by phenobarbital, phenytoin and gabapentin. Phenobarbital and phenytoin reduce while ethosuximide and gabapentin increase REM sleep. There is no change in daytime sleepiness by topiramate, lamotrigine, zonisamide and vigabatrin but increased by phenobarbital. With this evidence, it is important to consider the effects of epilepsy treatments on sleep architecture in optimising management for patients with epilepsy (Table 38.4).

38.5 Prevalence and Risk Factors

Sleep disorders and epilepsy have a complex relationship. On one end of the spectrum, seizure can be exacerbated with sleep deprivation while on the other end, seizures can also occur during sleep. Epilepsy may aggravate certain sleep disorders. Sleep disorders may negatively impact epilepsy. Antiepileptics may interfere with normal sleep patterns and may cause excessive daytime sleepiness.

Subjective sleep disturbance is usually measured by Pittsburgh Sleep Quality Questionnaire (PSQI). It is designed to evaluate overall sleep quality, sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, medication use and daytime dysfunction with higher score indicating a worse sleep quality.

Prevalence of antiepileptic-induced sleep disorders is highly variable. In India, 24.6% patients with epilepsy have been found to have at least one sleep disorder. A study conducted in 302 patients on antiepileptics showed that 69.5% patients had sleep disorders [43]. Restless leg syndrome (RLS) is also a common feature of sleep disorder. Prevalence of RLS in patients on antiepileptic drugs ranges from 10% to 28.2% [44]. A study by Vendrame et al. showed 51% patients of epilepsy on treatment showed features suggestive of insomnia and poor quality of sleep. In a study done on 152 adult patients on antiepileptics, 55% reported insomnia and 70% were poor sleepers. It was also observed that number of antiepileptics significantly correlated with the insomnia and poor sleep quality [28]. Adult patients with partial epilepsy had two-fold significantly higher sleep disturbances than the controls [29]. Another study also demonstrated similar findings as 30% of patients with epilepsy had problems with sleep against 10% of controls [30]. Problems with induction and maintenance of sleep were more commonly reported among patients than controls. Sleep complaints in adult patients with epilepsy from different studies varied from 16.9% to 36% [31].

Sleep disturbances also affect children with epilepsy. A study has shown that 45% of children with first recognised seizure disorder had bedtime difficulties, daytime somnolence and parasomnias. Also the mothers of 14.2% children reported that their children exhibited day-time sleepiness of varied duration from 15 min–180 min [32]. A systematic review reported that excessive daytime sleepiness is seen in 10%–47.5% of patients with epilepsy [33].

Table 38.4 Antiepileptic drugs and effect on sleep architecture

Antiepileptic drugs	Dose	Sleep disturbances
Carbamazepine	400–700 mg/day	*Healthy adults* Reduction in sleep latency and arousals, increase in sleep efficiency and slow wave sleep (SWS) [21, 22] *Newly diagnosed epilepsy* Increased N3 [23]
Clobazam	10 and 20 mg doses	*Healthy adults* Reduced sleep latency, N1, SWS, WASO and increased N2 [24]
Ethosuximide	N/A	*Absence epilepsy* Increased N1 and REM Decreased SWS [25]
Gabapentin	600 and 900 mg	*Healthy men* Increase SWS [26]
	1800 mg	*As add-on in epilepsy patients* Increased REM sleep, reduced Awakenings and N1 [15]
	Minimum dose/drug Level	*Focal epilepsy* Increased SWS [10]
Lamotrigine	200 mg/day	*Add-on in drug-resistant focal epilepsy* Increased REM sleep, no change In daytime sleepiness [27] *Add-on in focal epilepsy* Increased N2 and reduced SWS [14]
Levetiracetam	2000 mg/day	*Healthy adults* Increased TST, SE, N2, SWS Decrease REM and WASO [16]
	Single dose, 1000 mg/day	*Epilepsy patients* Increased N2 [17]
	1000 mg/day	*Newly diagnosed partial epilepsy* Decreased WASO and increased SE [23]
	1000 mg/day	*Focal epilepsy* Reduced REM sleep [28]
Phenobarbital	80, 140 and 240 mg/day	*Healthy adults* Dose dependent decrease in REM sleep, awakenings Dose dependent increase in N2 [29]
	50 mg/day	*Epilepsy patients* Increased N2; decreased SL, REM and arousals [30]
Phenytoin	Minimum dose/drug level	*Focal epilepsy* Reduced SWS and REM and increased N1 [10]
	100 mg/day	*Epilepsy patients* Decreased N2 and SL Increased N1 and SWS [31]
	Dose to achieve 10–20 μg/ml drug level	*New onset epilepsy* *Acute (day 2):* Decreased SL *Short term (4–6 week):* Decreased SL, N1, N2; increased SWS *Long term (6 months):* Decreased SL [compared to baseline] [32]

(continued)

Table 38.4 (continued)

Antiepileptic drugs	Dose	Sleep disturbances
Pregabalin	150 mg/day	*Healthy adults* Increased SE, SWS and reduced Awakenings and REM sleep [33]
	300 mg/day	*Focal epilepsy* Reduced arousals and WASO [34] Increased N3, decreased N1 [35]
Tiagabine	5 mg/day	*Healthy adults* Increased SWS and SE [36]
	2, 4 and 8 mg/day	*Elderly (60–80 years) without sleep disorder* *At 2 mg:* No changes *At 4 mg:* Increased TST, SWS and reduced WASO *At 8 mg:* Increased SWS and reduced REM and calculated sleep fragmentation [37]
Topiramate	200 mg/day	*New onset focal epilepsy and controls* No significant changes in nocturnal sleep or daytime sleepiness on MSLT [38]
Valproic acid	500 and 1000 mg/day	*Healthy adults* No significant changes in nocturnal sleep on visual analysis [39]
	Taper dose	*Children with epilepsy* Reduced total sleep time (including naps) [40]
	Minimum dose/drug level	*Focal epilepsy* Increased N1 [10]
	N/A	*Epilepsy patients* Decrease SL and WASO, increased TST [31]
	N/A	*Absence epilepsy* Increased N1 and REM [25]
Vigabatrin	2–3 grams/day	*Focal epilepsy on CBZ monotherapy* No significant changes in nocturnal sleep or daytime sleepiness (compared to baseline) [41]
Zonisamide	200–300 mg/day	*Focal epilepsy* No significant changes in nocturnal sleep or daytime sleepiness [42]

N1 stage N1, *N2* stage N2, *N3* stage N3, *N4* stage N4, *SWS* slow-wave sleep, *REM* stage REM, *TST* total sleep time, *SE* sleep efficiency, *WASO* wakefulness after sleep onset

Sleep disorders in epilepsy patients also vary according to the antiepileptics being taken. A review reported varied rates of insomnia in epilepsy patients on different antiepileptics as 2.2% (Carbamazepine), 2.3% (Topiramate), 3.4% (Valproic acid), 5% (Pregabalin), 4.9–6.4% (Lamotrigine), 4.2–6.3% (Levetiracetam) and 6.6% (Vigabatrin) [34]. Also, first-generation antiepileptics (barbiturates, benzodiazepines, phenytoin and phenobarbital) have more impact on sleep architecture. They tend to reduce the amount of time spent in REM and slow wave sleep. They decrease the night time sleep and increase day time sleepiness [35]. According to a study, factors as currently employed, presence of at least one sleep disturbance

and antiepileptic polytherapy individually correlated significantly with excessive day-time sleepiness [36]. A review study depicted that insomnia in adult patients with epilepsy was inconsistently related to female gender, poor seizure control and antiepileptic drug polytherapy. In children, associated risk factors were developmental delay, focal epilepsies and poor seizure control [37]. Poor seizure control was also the strongest risk factor independently affecting sleep quality in patients on antiepileptics according to another study. In the study, poor sleep quality was found in significantly higher proportions in patients of partial seizure, non-seizure-free and polytherapy groups [38].

38.6 How to Manage

Sleep disorders are common in the general population and so, concurrent sleep disorders frequently occur in patients of epilepsy. Attention to these sleep disorder could be helpful to safely choose AED as these drugs are proven to be useful [45]. Drugs like barbiturates (phenobarbital) and benzodiazepines (clonazepam, clobazam) could be helpful in patients of insomnia. These long-acting drugs could be administered at bedtime. Long-acting benzodiazepines are indicated in patients of anxiety and epilepsy. Patients of anxiety disorder have difficulty in sleep initiation. Drugs increasing slow wave sleep like gabapentin and tiagabine could help to consolidate in patients with frequent or early awakening. Lamotrigine could be a good choice in patients of insomnia with mild depression. Carbamazepine and gabapentin are effective in restless leg syndrome and gabapentin in periodic limb movement. Therefore, treatment with agents could be considered in patients of epilepsy with either of these conditions (Table 38.5).

Table 38.5 Use of antiepileptic drugs (AEDs) in sleep disorders and comorbid conditions that can affect sleep [45]

Conditions	Potentially useful AED	Potentially harmful AED
Insomnia	Barbiturates, Benzodiazepines, Gabapentin, tiagabine	Felbamate
Restless leg/periodic limb movements of sleep	Gabapentin, Carbamazepine, Benzodiazepines	
Obstructive sleep apnoea		Benzodiazepines, barbiturates
Depression	Lamotrigine	
Anxiety	Benzodiazepines	
Migraine	Valproic acid, gabapentin, Topiramate	
Neuropathic pain	Carbamazepine, gabapentin, lamotrigine, topiramate	

38.7 Summary and Conclusion

The choice of antiepileptic drugs for patients of epilepsy should always be initiated with the most effective agents for seizure type, keeping in mind concurrent sleep disorder. With a large pool and therefore, more effective options available for AED now-a-days, the drug of choice is one that is individually selected and suited for the patients. It is important to consider potential association of AED and sleep indices while treating a patient of epilepsy (Table 38.6).

Table 38.6 Summary of the effects of antiepileptic drugs (AEDs) on sleep [45]

AED	Sleep latency	Sleep efficiency	Stage 1 sleep	Slow wave sleep	REM sleep	Daytime drowsiness
Barbiturates	Decrease	No effect	No effect	No effect	Decrease	Increase
Benzodiazepines	Decrease	No effect	No effect	Decrease	Decrease	Increase
Carbamazepine	No effect	No effect	No effect	No effect	Decrease	Increase
Phenytoin	Decrease	No effect	Increase	No effect	Decrease	Increase
Valproic acid	No effect	No effect	Increase	No effect	No effect	Increase
Felbamate	Not known	Not known	Not known	Not known	Not known	Decrease
Gabapentin	No effect	No effect	Decrease	Increase	Increase/ no effect	Not known
Lamotrigine	No effect	No effect	No effect	Decrease	Increase/ no effect	Not known
Levetiracetam	Not known	No effect	No effect	No effect	No effect /increase	Not known
Oxcarbazepine	Not known	Not known	Not known	Not known	Not known	Not known
Tiagabine	No effect	Increase	No effect	Increase	No effect	Not known
Topiramate	Not known	Not known	Not known	Not known	Not known	Not known
Vigabatrin	Not known	Not known	Not known	Not known	Not known	Increase
Zonisamide	Not known	Not known	Not known	Not known	Not known	Not known

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Sleep During Hypnotic Therapy

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Manisha Bisht

Abstract

Insomnia is a significant public health burden with a prevalence rate of 5–50% in the general population. Evidence indicates that histaminergic, cholinergic, serotoninergic and adrenergic neurons are more active during waking and excite thalamocortical pathways thereby inhibiting GABA-ergic neurons. The medications or classes of medications approved to treat insomnia are benzodiazepines, non-benzodiazepine hypnotics, melatonin agonists, doxepin and suvorexant. These medications have certain limitations urging the clinicians to prescribe off-label drugs like antidepressants [e.g. trazodone, amitriptyline, olanzapine and mirtazapine), anxiolytics (e.g. alprazolam and clonazepam), antipsychotics (e.g. quetiapine), antiepileptics (e.g. pregabalin, gabapentin) and agomelatine. The purpose of this review is to compile the clinical evidence of pharmacological treatments of insomnia, including off label medications used in insomnia.

Keywords

Insomnia · Hypnotics · Benzodiazepines · Pharmacological treatment of insomnia · Clinical evidence for hypnotics

Insomnia is a significant public health burden in a large proportion of the population. Studies have reported a large variability in prevalence rate of insomnia in the general population ranging from 5% to 50% [1]. Insomnia is associated with symptoms like irritability, daytime sleepiness, impaired cognitive functioning and reduced quality of life [1, 2]. Epidemiologic studies have revealed that approximately one-third of

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adults (30–36%) have experienced at least one symptom of insomnia, like difficulty initiating sleep or maintaining sleep at least once in life time [1]. Recently, a study has reported an increase in the number of prescriptions for any sleep medication by 293% [3].

Sleep is divided into two states known as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Previously, based on electroencephalogram (EEG) patterns, NREM sleep was subdivided into four stages (stages 1, 2, 3, 4) [4]. According to the recent classification released by American Academy of Sleep Medicine in 2007, NREM sleep is now divided into three progressively deeper stages of sleep, namely, stage N1, stage N2 and stage N3 (formerly stages 3 and 4) [5]. REM sleep is now referred to as stage R. Table 39.1 represents various stages of sleep occurring in physiological conditions. The EEG pattern in NREM sleep is synchronous and presents characteristic waveforms: Stage N1 accounts for 2–5% of total sleep time and is the phase of transition between the awake states and is characterized by a decrease inthe frequency of the EEG trace paralleled by an increase in its amplitude. Stage N2 accounts for 45–55% of total sleep time, occurs throughout the entire sleep period and is characterized by the occasional occurrence of a series of high-frequency waves (8–14 Hz) known as sleep spindles and K-complexes. Stage N3, which corresponds to deep or delta-wave sleep and reflects slow-wave sleep (SWS), occurs mostly in the first third of the night and accounts for 5–15% of total sleep time. Stage R or REM sleep is defined by low-amplitude desynchronized theta EEG activity and represents 20–25% of total sleep time. It occurs in four to five episodes throughout the night and is characterized by cortical and hippocampal activation and rapid eye movements. Many drugs acting on central nervous system (CNS) can disturb sleep architecture to variable extent [6].

The activity of brain during the sleep proceeds from waking through the three stages of NREM sleep and then REM sleep. NREM sleep and REM sleep alternate through the night in a cyclical fashion, usually with four to five sleep cycles throughout the night. As the sleep progresses, the time spent in stage 3 is reduced, while the time spent in REM is increased. The REM stage of sleep is shortened from frequent interruption of sleep resulting in increased irritability and restlessness during the daytime. Sleep restoration is dependent on maintaining both sleep quality (sleep latency and duration of sleep) and architecture (cyclical, non-REM sleep stages and REM).

The physiological mechanisms regulating sleep-wake rhythm are not completely elucidated. Figure 39.1 lists some of the neurotransmitters involved in maintaining sleep and waking. Evidence indicates that during waking, histaminergic, cholinergic, serotoninergic and adrenergic neurons are more active and excite thalamocortical pathways via their ascending thalamopetal projections thereby inhibiting γ-aminobutyric acid (GABA-ergic neurons. During sleep, input from the brain stem decreases, causing diminished thalamocortical activity and disinhibition of the GABA neurons. Drugs currently approved to treat insomnia mainly act on specific receptors like γ-aminobutyric acid (GABA), histamine, melatonin or orexin (OX)/hypocretin located in specific brain areas. All are based on well-established

Table 39.1 Stages of sleep and their characteristics

Earlier classification	Newer classification	Total sleep time	Occurrence	EEG pattern	Can be associated with
NREM					
Stage 1	Stage 1	2–5%	Transition between the awake state and sleep	Decrease inthe frequency of the EEG trace paralleled by an increase in its amplitude	Hallucinations
Stage 2	Stage 2	45–55%	Throughout the entire sleep period	Theta waves Occasional occurrence Sleep spindles K-complexes	Sleep talking
Stage 3	Stage 3	5–15%	First third of the night	Deep or delta-wavesleep and reflects slow-wave sleep (SWS)	Sleep walking, bed wetting
Stage 4					
NREM	Stage R	20–25%	Four to fiveepisodes throughout the night	Low-amplitudedesynchronized theta EEG activity	Paradoxical sleep, dreams

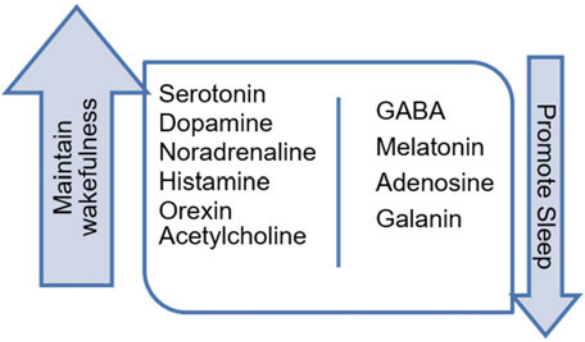

Fig. 39.1 Neurotransmitters modulating sleep wake cycle

neurotransmitter effects on sleep and waking [7]. Each receptor modulates different characteristics of sleep and hence has variable effect on sleep cycle.

39.1 Types of Insomnia

Insomnia is a subjective complaint like pain. It is commonly defined as recurring problems in sleep initiation (sleep onset insomnia), frequent nocturnal awakening or waking up too early (sleep maintenance insomnia) or sleep thatis chronically poor in quality and is associated with some daytime impairment. The sleep onset insomnia is also called initial insomnia, and sleep maintenance insomnia can be either middle or terminal insomnia. International classification of sleep disorder (ICSD-3) classifies insomnia disorder, because of its duration into short-term or transient (lasting only a few days to 3–4 weeks) and chronic (persisting for more than 3 months). Clinically (as well as using polysomnographic criteria), insomnia is defined as a sleep latency of more than 30 min, remaining awake after sleep onset for more than 30 min, sleep efficiency of less than 85% or less than 6–6.5 h total time asleep, occurring on three nights per week or more [8].

39.2 Management of Insomnia

The goal of treatment for insomnia is to improve sleep and alleviate distress or dysfunction caused by the disorder. It can be managed by behavioural therapy, pharmacologic therapy or a combination of both. Combined behavioural therapy is recommended as initial therapy for management of insomnia for majority of the patient by most of the clinical practice guidelines [9–12].

Combined behavioural therapies for insomnia include sleep hygiene education, stimulus control, relaxation, sleep restriction therapy, cognitive therapy and cognitive behavioural therapy [13]. However, there is limited access to behavioural therapy in some regions and patient groups. Therefore, preferred therapy for insomnia in many patients is use of hypnotic medications. The choice of treatment should

be individualized according to the severity and impact of the insomnia, the availability of advanced behavioural therapies, the patient's preferences, potential benefits versus the risks and finally the cost of the treatment.

39.3 Historical Aspect of Hypnotic Drugs Use

Prior to twentieth century, various herbal preparations, bromide salts, alcohol and opioids were the primary agents used for inducing sleep. Before the introduction of barbiturates, chloral hydrate, paraldehyde, urethane and sulphonal were used as alternative to hypnotics. In early twentieth century, after the advent of barbiturate and related compounds, they became the preferred agents for management of sleep disturbance. By mid-century, owing to their lethal overdose potential and dependence liability, their use was curtailed. The first benzodiazepine (BZD) indicated for hypnotic use, flurazepam, was approved by the Food and Drug Administration (FDA) in 1970 and thereafter BZD rapidly superseded the use of other agents for treatment of insomnia. In 1992, first nonbenzodiazepine, benzodiazepine receptor agonist (non-BZD or Z compounds) hypnotic, Zolpidem, was introduced and till date, it is the most widely prescribed hypnotic medication [14]. In last two decades, three more agents acting on other receptors than γ-aminobutyric acid (GABA) are approved by FDA for insomnia. These include a melatonin agonist (ramelteon) in 2005, a low dose tricyclic antidepressant doxepin in 2010 and most recently in 2014, an orexin receptor antagonist (suvorexant).

39.4 Properties Required in Ideal Hypnotic Agent

Figure 39.2 enlists the properties needed in an ideal hypnotic agent. Based on their pharmacokinetic profile, some medications improve sleep onset or sleep maintenance, whereas others improve both variables.

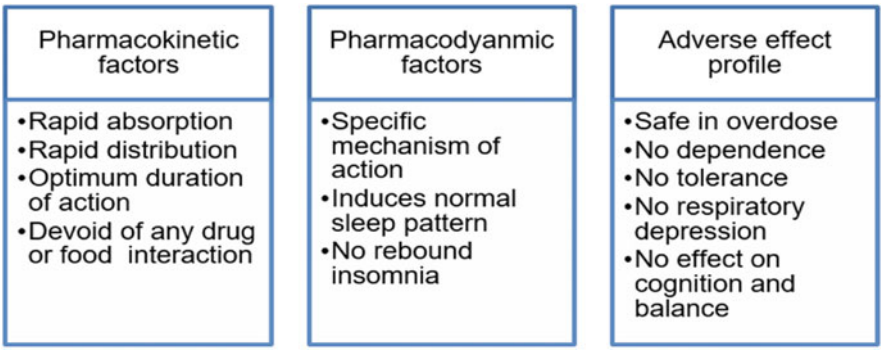

Fig. 39.2 Properties of an Ideal Hypnotic

The pharmacokinetic properties like rate of absorption and distribution are important as they determine onset of sleep. The faster the hypnotic is absorbed and distributed to the brain, the quicker it induces sleep. Some agents like temazepam have a poorer bioavailability and slower absorption and are not effective for inducing sleep. On the other hand, drugs like zolpidem that enter the brain very quickly need to be taken in the bedroom or even in bed. The dose and the elimination half-life of the drugs determine its duration of action and are responsible for ease of waking and the tendency to cause daytime carryover ("hangover") effects.

Drugs with half-lives of more than 6 h, such as nitrazepam tend to leave sufficient residual drug in the brain to cause daytime sedation and falls [15]. The advent of the Z-drugs like zaleplon was due to efforts to design shorter half-life drugs with minimal carry-over effects [16]. It can be taken 5 h before the desired time of arising, without the risk of next day hangover. But a very short half-life decreases the drug's duration of action and limits its ability to maintain sleep throughout the night like in the case of zaleplon and to some extent zolpidem. Individual difference in rate of drug metabolism or sensitivity to drug actions may play a role in variation in the susceptibility to hang over, which can vary as much as twofold between subjects [17].

So in nutshell the "perfect" hypnotic should induce sleep with normal sleep architecture. It should be devoid of next-day effects like rebound anxiety or day time sedation. It should be devoid of interaction with other medications. Most importantly, it could be used chronically without causing dependence or rebound insomnia on discontinuation.

39.5 Medications Used in Insomnia

Table 39.2 summarizes the medications or classes of medications that are approved to treat insomnia, namely, benzodiazepines, non-benzodiazepine hypnotics, melatonin agonists, doxepin and suvorexant [18–20]. Even though agents acting on GABA like benzodiazepines (BZDs) and non-benzodiazepines (Z-drugs) are approved for insomnia with a strong clinical evidence, they have numerous problematic effects. The problems with these agents have led clinicians to prescribe other medications that are perceived to be less harmful or to be less liable to addiction. Therefore, the clinical use of newer off-label drugs with diverse mechanism of action is increasing for the management of insomnia. The medications approved for other indication but which have not been evaluated for either efficacy or safety in subjects with insomnia are indicated as "off label" medications. These off label medication used in insomnia include antidepressants (e.g. trazodone, amitriptyline and mirtazapine), anxiolytics (e.g. alprazolam and clonazepam) and antipsychotics (e.g. quetiapine). One study assessing the prescription of hypnotic medication revealed that off label drugs prescription is very common in the treatment of insomnia [14].

The purpose of this review is to compile the clinical evidence of pharmacological treatments of insomnia, including off label medications used in insomnia.

Table 39.2 Clinical indication of medications approved for treatment of insomnia

Agent	Adult dose	Half-life (hours)	Clinical indication
Benzodiazepine immediate release			
Estazolam	1–2 mg	Intermediate (10–24)	Sleep onset or sleep maintenance insomnia
Flurazepam	15–30 mg	Long (40–114)	Sleep onset or sleep maintenance insomnia
Quazepam:	7.5–15 mg	Long (39 h drug; 73 active metabolite)	Sleep onset or sleep maintenance insomnia
Lorazepam	0.5–2 mg	Intermediate (10–14)	Sleep onset or sleep Maintenance insomnia
Temazepam	7.5–30 mg	Intermediate (8–15)	Sleep onset or sleep maintenance insomnia
Triazolam	0.125–0.25 mg	Short (2–5)	Sleep onset insomnia
Nonbenzodiazepine immediate release			
Eszopiclone	1–3 mg	Intermediate (6)	Sleep onset or sleep maintenance insomnia
Zaleplon	5–20 mg	Short (1)	Sleep onset insomnia
Zolpidem	5–10 mg	Short (1.4–4.5)	Sleep onset insomnia
Nonbenzodiazepine extended release			
Zolpidem ER	6.25–12.5 mg	Intermediate (1.6–4.5)	Sleep onset or sleep maintenance insomnia
Nonbenzodiazepine alternate delivery			
Zolpidem oral spray	5–10	Short (1.4–4.5)	Sleep onset insomnia
Zolpidem sublingual tablet	5–10	Short (1.4–4.5)	Sleep onset insomnia
Zolpidem sublingual tablet (middle of the night)	1.75 mg/ 3.5 mg	Short (1.4–4.5)	Sleep maintenance insomnia
Selective melatonin receptor agonist			
Ramelteon	8	Short (1–2.6 drug; 2–5 active metabolite)	Sleep onsetinsomnia
Selective histamine receptor antagonist			
Doxepin (low dose)	3–6 mg	Long (15 drug; 31 active metabolite)	Sleep maintenance insomnia
Dual orexin receptor antagonist			
Suvorexant	10–20 mg	Intermediate (12)	Sleep onset or sleepmaintenance insomnia

39.6 Currently Approved Hypnotic Agents

39.6.1 Benzodiazepines (BZD)

Benzodiazepines are defined by their characteristic benzodiazepine structure (benzene and diazepine rings). They are positive allosteric modulators of GABA responses at the $GABA_A$ receptor complex. Several benzodiazepines such as estazolam, temazepam, triazolam, flurazepam and quazepam are FDA-approved for the treatment of chronic insomnia. Other agents such as lorazepam, oxazepam, clonazepam or diazepam can also be used as hypnotics in absence of approved agent. The choice of a BZD should be based on the desired onset and duration of action. The approach is to use a short and intermediate-acting agent for sleep onset and maintenance insomnia, respectively, while long-acting benzodiazepines are preferred if comorbid anxiety is present. BZDs also decrease anxiety and have anticonvulsive properties.

Pharmacokinetics: Benzodiazepines are relatively rapidly absorbed and metabolized by hepatic cytochrome P450 (CYP) 3A4 pathway. The elimination half-lives of benzodiazepine medications vary considerably and range from approximately 3.5–24 h. The elimination half-life approximately correlates with the duration of action and risk for next-day residual sedation and impairment.

39.6.2 Adverse Effect Profile

The more common side effects associated with benzodiazepine receptor agonists (BZRA) hypnotics include somnolence, dizziness, headache, fatigue, ataxia, anterograde amnesia and confused behaviours. The intensity and incidence of central nervous system (CNS) toxicity generally increase with age [21]. They are associated with next-day hangover effects, cognitive or memory impairments, psychomotor and balance problems, rapid development of tolerance, rebound insomnia upon abrupt discontinuation, car accidents or falls [22]. Most importantly, they can also cause significant risk of abuse and dependence [23]. A large proportion of people who are prescribed BZD become chronic users. Sudden withdrawal of the benzodiazepine can cause symptoms like temporary intensification of insomnia or anxiety, dysphoria, irritability, sweating, unpleasant dreams, tremors, anorexia and faintness or dizziness also may occur. Hence, therapy should be discontinued by gradually tapering the dosage [21]. Benzodiazepines may sometimes cause paradoxical or disinhibition reactions which appear to be dose related. Euphoria, restlessness, hallucinations, sleep-walking or talking and increased nightmares are some paradoxical effects occurring with use of various benzodiazepines. Bizarre disinhibition or dyscontrol reactions like hostility and rage have also been seen in some users. Hence, it is prudent to taper the dosage gradually when therapy is to be discontinued.

39.6.3 Drug Interactions

Benzodiazepines have additive effects with other sedative or hypnotic drugs. Ethanol increases both the rate of absorption of benzodiazepines and the associated CNS depression. Valproate and benzodiazepines used in combination may cause psychotic episodes.

39.6.4 Clinical Indication

BZD are indicated for use in sleep onset or sleep maintenance insomnia depending on the pharmacokinetic profile of the individual agent. The dose, elimination half-life and clinical indication of individual agent is summarized in Table 39.2.

39.7 Nonbenzodiazepine BZRA

Nonbenzodiazepine benzodiazepine receptor agonists are structurally different from the benzodiazepines and have more targeted action at GABA type A receptor containing the α1 subunit, leading to greater specificity as hypnotic and have less anxiolytic and anticonvulsant activity. Hypnotics in this class are commonly referred to as "Z compounds." They include zolpidem, zaleplon, zopiclone and eszopiclone, which is the S(+) enantiomer of zopiclone. Z compounds have mostly replaced benzodiazepines in the treatment of insomnia, over the last decade.

39.7.1 Pharmacokinetics

These agents are mainly available as immediate release tablet or capsule formulations, with the exception of zolpidem which is additionally available in an extended-release bedtime use tablet, oral dissolvable doses for bedtime or middle-of-the-night use and an oral liquid spray formulation. They are primarily metabolized in liver, eszopiclone is metabolized by CYPs 3A4 and 2E1, while zaleplon is metabolized to a lesser extent by CYP3A4.

The nonbenzodiazepine medications have half-life ranging from 1 h for zaleplon to 6–9 h for eszopiclone. The differential effect of gender on zolpidem metabolism led to the recommendation to reduce the dosage of some formulations of this agent by 50% in females. Also, plasma half-life of zolpidem may increase twofold or more in patients with cirrhosis and in older patients requiring adjustment of dosage [21].

39.7.2 Adverse Effect Profile

Initially, Z compounds were promoted as having less potential for dependence and abuse than traditional benzodiazepines. However, postmarketing clinical experience

with Z-drugs revealed that they can also produce tolerance and physical dependence as well as next-day cognitive, memory, psychomotor and balance impairments and risk of motor vehicle accident [21–23].

39.7.3 Clinical Indication

A summary of the effects of Z drugs on sleep architecture is presented in Table 39.2. Based on the type of formulation and elimination half-life, individual Z drugs are indicated for use in sleep onset or sleep maintenance insomnia.

39.8 Low-Dose Doxepin

Doxepin is a tricyclic antidepressant with most potent antihistaminic effects among other agents of this category. The standard antidepressant dose of doxepin ranges from 75 to 150 mg/day at which it inhibits the reuptake of serotonin and norepinephrine and antagonizes cholinergic, histaminergic and alpha-adrenergic activity. Whereas the doses approved for insomnia are 3–6 mg/day wherein it affects only the histamine receptor.

39.8.1 Pharmacokinetics

Doxepin should be taken within 30 min of bedtime, and it should not be taken within 3 h of a meal to minimize the risk of next day effects, as food delays its absorption and increases its exposure. It is mainly metabolized in liver by cytochrome P-450 2D6 and 2C19; thus, coadministration of inhibitors of these isozymes may increase its concentration and therefore require lower dose not exceeding 3 mg [24].

Adverse Effect: The most frequently reported adverse events with low-dose doxepin were somnolence and headache which were not dose-related [24]. Next day, residual sedation/impairment, withdrawal effects and rebound insomnia were also absent. Low-dose doxepin does not produce physical tolerance or dependence or is associated with abuse potential. Moreover, anticholinergic effects which were predominant with normal dose of doxepin were also absent [24].

39.8.2 Clinical Indication

Low-dose doxepin is FDA approved for the treatment of insomnia characterized by difficulties with sleep maintenance to a maximum dose of 6 mg/day. It could be considered as first-line therapy for adults and older people with sleep maintenance insomnia.

39.9 Melatonin Receptor Agonist

Melatonin is a hormone synthesized in the pineal gland under control of the circadian system responsible for facilitating sleep onset. Currently, ramelteon is the only melatonin receptor agonist approved by FDA for treatment of insomnia. It is a potent and highly selective agonist at the metallothionein (MT1) and MT2 receptors with 3–16 times higher affinity than that of melatonin [18]. Other agents acting as melatonin agonist are melatonin used as dietary supplement, tasimelteon approved for treatment of non–24-h circadian rhythm sleep-wake disorder and agomelatine which act on multiple receptor including melatonin receptor and approved as an antidepressant [18].

39.9.1 Pharmacokinetics

Ramelteon is rapidly absorbed from the gastrointestinal (GI) tract and its absorption is affected by high-fat meal hence it is not recommended to take it after a high-fat meal. It undergoes rapid, high first-pass metabolism and shows substantial intersubject variability in maximal serum concentration and area under the concentration curve [18]. It is metabolized mainly by CYP1A2 and forms a less potent active hydroxylated M-II metabolite which has longer half-life. Ramelteon has a half-life of about 1–2.6 h while that of M-II is 2–5 h. Coadministration of ramelteon with fluvoxamine, a potent CYP1A2 inhibitor is a specific contraindication [18].

39.9.2 Adverse Effect

It is generally well tolerated by patients and does not impair next-day cognitive function. Even after 6 months of drug administration, no evidence of tolerance, rebound insomnia or withdrawal effects were present [25]. Most importantly, unlike most hypnotic agents, ramelteon is not a controlled substance.

39.9.3 Clinical Indication

Ramelteon is approved for the treatment of sleep onset insomnia. It is efficacious in combating both transient and chronic insomnia.

39.10 Orexin/Hypocretin Receptor Antagonist

Orexins/hypocretins are neuropeptides secreted from the lateral hypothalamus neurons which regulate various wake-promoting neurotransmitters with a net effect of enhancing and stabilizing the waking state. There are two orexin neuropeptides,

orexin-A (OXA) and orexin-B (OXB) which act through two G-protein coupled receptors, OX1R and OX2R [26].

Suvorexant is reversible selective dual (OX1R and OX2R) orexin receptor antagonist approved recently. It binds reversibly with both the orexin receptors and inhibits the activation of the arousal system, thus, facilitating sleep induction and maintenance.

39.10.1 Pharmacokinetics

Suvorexant is available as an immediate-release tablet. Median time to peak levels under fasting conditions is 2 h and ingestion of the drug with high-fat meal delays it by approximately 1.5 h. It is mainly metabolized by the CYP3A4 system and has a plasma half-life of about 12 h. Dosage adjustments may be necessary for CYP3A inducers and inhibitors.

39.10.2 Adverse Effect

The most common adverse reaction is daytime somnolence. The higher doses (>20 mg) cause motor impairment and can affect driving skills significantly and there is a possibility of the worsening of depression or suicidal ideation. There are no reports of physical dependence and withdrawal syndrome on discontinuation even after 1 year of chronic therapy.

39.10.3 Clinical Indication

Suvorexant is approved for sleep onset or sleep maintenance insomnia. One 10-mg dose should be taken within 30 min of going to bed if at least 7 h remain until the projected time of awakening. It is also Schedule IV controlled substance.

39.11 Alternate Medications Prescribed for Sleep

Most medications prescribed "off label" for insomnia have not been evaluated for either efficacy or safety and have not been studied in subjects with insomnia. There is limited evidence for the use of antidepressants (e.g. trazodone, amitriptyline, olanzapine and mirtazapine), anxiolytics (e.g. alprazolam and clonazepam), antipsychotics (e.g. quetiapine), antiepileptics (e.g. pregabalin, gabapentin) and agomelatine. The available clinical evidence for the use for these agents is summarized in Table 39.3 [18]. The ideal situation for prescription of these agent for insomnia is a patient with comorbid condition requiring these medications. These drugs may improve sleep while successfully treating comorbid disorders like mirtazapine can treat insomnia as well as depression in a depressed individual.

Table 39.3 Available evidence for off label agents used in insomnia

Pharmacological agent	Studies conducted for			Evidence for use in	
	Effect on sleep in healthy volunteer	Efficacy in primary insomnia	Efficacy in secondary insomnia	Insomnia disorder	Secondary insomnia
Agomelatine		No studies	1 systematic review 2 double-blind RCT	Weak	Weak
Tasimelteon		I unpublished data	2 double blind RCT	Weak	FDA approved – non-24 sleepwake Disorder
Prolonged release melatonin		4 RCT 1 open label trial	1 RCT	Strong evidence adults >55 years	Weak
Trazodone	2 studies	1 RCT	2 reviews 9 RCT 1 open label	Weak	Strong SSRI-induced insomnia
Amitryptiline	1 study	No studies	1 RCT trial I retrospective study	Weak	Weak
Mirtazapine	1 study	1 case series	4 open label 1 RCT	Weak	Weak
Quetiapine		1 RCT 1 open label trial	1 review, 5 open label RCT, 3 randomized, placebo-controlled trials, 1 naturalistic study, 1 post hoc analysis, 1 retrospective study	Weak	Strong—evidence Insomnia associated with depression
Olanzapine		No studies	5 studies Open label RCT, cross over RCT	Weak	Moderate evidence – posttraumatic stress disorder, paradoxical insomnia
Gabapentin	1 study			Weak	

(continued)

Table 39.3 (continued)

Pharmacological agent	Studies conducted for			Evidence for use in	
	Effect on sleep in healthy volunteer	Efficacy in primary insomnia	Efficacy in secondary insomnia	Insomnia disorder	Secondary insomnia
		1 open label trial 1 RCT	1 RCT, 2 open label trial		
Pregabalin	1 study	No studies	2 systematic reviews	Weak	Strong evidence – insomnia in generalized anxiety disorder, fibromyalgia

The unique mechanism of action and a different side effect profile than the BZDs and Z-drugs of these agents can facilitate personalized and targeted medical management of insomnia. But unfortunately, evidence is scarce to guide the use of these medications for insomnia.

39.12 Newer Agents in Pipeline

39.12.1 Lemborexant

It is a newer orexin receptor antagonist which is submitted to US FDA for review as new drug application for the treatment of insomnia after completing two key Phase 3 studies of lemborexant – SUNRISE 1 (Study 304) and SUNRISE 2 (Study 303).

39.12.2 Lumateperone

It is a novel antipsychotic agent with a unique mechanism of action with high 5-hydroxytryptamine 2A (5-HT2A) blocking activity. A Phase 2 study in treatment of insomnia revealed strong evidence of efficacy, with no impairment of next-day cognition.

39.12.3 Piromelatine

It is a novel investigational agent that has agonist activity at MT1 and MT2 along with agonism at 5-HT1A/1D receptors. A phase II randomized clinical trial ($N = 120$) in primary insomnia resulted in significant improvement in insomnia symptoms.

39.12.4 Lorediplon

It is a novel, longer acting non-BZD hypnotic drug that acts on $GABA_A$ receptor. Currently, the drug has completed Phase II clinical trial. Results indicated strong efficacy in sleep maintenance with an acceptable safety profile. It also seems to preserve natural sleep architecture.

39.13 Hypnotic Medications and EEG Changes

Any medication which can cross the blood-brain barrier has the potential to alter the sleep. Medication-induced changes in sleep may be therapeutic or can lead to sleep disturbances or may be benign. Medication can affect the sleep quality and/or the sleep architecture. The effect of drug on sleep quality can be assessed by latency until sleep onset, wakefulness after sleep onset and/or the duration of sleep. Sleep architecture is the structure of sleep and consist of cyclical, rapid eye movement (REM) and several non-REM sleep stages. It is assessed primarily by electroencephalography (EEG) during polysomnography. Most of the pharmacological agents currently approved as hypnotics, disturb sleep architecture to variable extent. Table 39.4 summarizes the effect of hypnotics on sleep architecture.

39.14 Conclusion

The current generation of medications approved for the treatment of insomnia includes a wide variety of compounds with distinct pharmacodynamic and pharmacokinetic features. Although there is a major advance in safety profile as compared with earlier pharmacologic agents like barbiturates used for insomnia, still the need of better agents continues. In parallel, preclinical research has identified various neurotransmitters affecting the sleep wake cycle, which in turn can facilitate the

Table 39.4 Effect of FDA approved drugs for insomnia on sleep efficiency and architecture

Drugs	Effect on sleep quality		Effect on sleep architecture				
	Sleep latency	Sleep efficiency	Effect on NREM			Effect on REM	Dependence liability
			N1	N2	N3		
Benzodiazepines	↓	↑	↓	↑	↓	↓	High
Z drugs	↓	↑	↔	↑	↔	↔	Moderate
Melatonin agonist	↓	↑	↔	↑	↓	↔	Low
Suvorexant	↓	↑	↔	↑	↔	↑	Low
Low dose doxepin	↓	↑	↔	↑	↔	↔	Low
Trazodone	↔	↔	↔/↓	↔/↓	↔/↑	↔/↓	Low

↑ increase, ↓ decrease, ↔ no change

identification and discovery of novel hypnotics. BZDs and Z-drugs continue to be widely prescribed although they are associated with an increased risk of falls, fractures and emergency hospitalizations especially in elderly. Owing to these limitations, clinicians often resort to prescribe off-label drugs, although these compounds often lack a strong evidence base for their use. Newer agents with comparable efficacy and improved long-term safety would be preferred over current first-line therapies.

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Stimulants and Sleep

40

Ravindra Rao and Richa Tripathi

Abstract

Psychostimulants are considered as the most widely used psychotropic substances globally. These substances cause excitation, elevated mood, increased alertness, and arousal by their effect on the central nervous system (CNS). Some of the substances are widely and legally available such as nicotine and caffeine, while others are used as recreational drugs such as 3,4-methylenedioxymethamphetamine (MDMA). Plant products such as khat are also used in some parts of the world. Stimulants are also one of the common compositions of newer psychoactive substances and their use is increasing day by day. These substances have been found to have profound effect on sleep architecture, including changes in Nonrapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep patterns. During acute intoxication, nicotine and other stimulants increase REM latency, sleep onset latency, and NREM-2 sleep. Similarly, chronic abstinence from stimulants is also associated with sleep disorders, including drowsiness or hypersomnia. Subacute withdrawal from cocaine may lead to "occult insomnia." The use of stimulants may also obscure underlying sleep disorders. These substances when used in pregnancy can have deleterious effects on fetal development. There are few studies on the management of stimulant-dependent sleep disorders.

Keywords

Stimulants · Sleep · Caffeine · Methamphetamine · Cocaine · Nicotine · Ecstasy · MDMA

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40.1 Introduction

Psychostimulants are considered as the most widely used psychotropic substances over the world. Psychostimulants can be defined as psychotropic substances with the capacity to stimulate the central nervous system. CNS stimulants can be classified as sympathomimetic (amphetamine and cocaine) and nonsympathomimetic (caffeine or theophylline). These substances cause excitation, elevated mood, increased alertness, and arousal. Caffeine and nicotine are legally available substances in most parts of the world and are used widely throughout the world. On the other hand, illicit psychostimulants such as cocaine, methamphetamines, ecstasy, etc., are used more in specific subgroups or cultures. Psychostimulants are also used for the treatment of obesity and ADHD (attention deficit hyperactivity disorder). Stimulants, either as medications or as drug of abuse, have adverse effects on sleep architecture, causing insomnia and hypersomnia. Use of stimulants may also obscure underlying sleep disorders.

Caffeine is the most consumed socially acceptable stimulant, with approximately 90% of the world's population consuming it daily in the industrialized countries. Nicotine can be considered as the most used legal stimulant, with about 20.5% of the world population aged more than 15 years [1]. As per the recent World Drug Report, 2019, 29 million (0.6% of global population aged 15–64 years) used amphetamines and prescription stimulants, 21 million (0.4% of global population aged 15–64 years) used ecstasy, and 18.1 million people (0.4% of global population aged 15–64 years) used cocaine in the past year [2]. There is considerable variation in the prevalence of the stimulants across regions. For example, it is reported that the use of ecstasy is mainly associated with recreational nightlife settings, with higher levels of use among younger people.

Stimulant-dependent sleep disorder was originally defined as a "reduction of sleepiness or suppression of sleep by CNS stimulants and resultant alterations in wakefulness following drug abstinence." The International Classification of Sleep Disorders, third edition (ICSD-3) mentions all sleep disorders caused by drugs under "sleep disorders resulting from a drug or substance" in the following categories: (a) central sleep apnea; (b) sleep-related hypoventilation; (c) central disorders of hypersomnolence; (d) insomnia; (e) parasomnia; and (f) sleep-related movement disorders [3]. The current chapter will focus on changes in sleep profile in psychostimulant use. The association of sleep with each group of stimulants will be discussed separately in the subsequent sections.

40.1.1 Nicotine

Nicotine is the primary psychoactive component of tobacco in both smoking and smokeless form of tobacco use. It is not normally considered among the "harder" stimulant drugs such as cocaine or methamphetamine, but its cessation is difficult [4]. Smoking has been ranked in the top three risk factors for global burden of disease [5]. It is also a major cause of preventable morbidity and mortality. Although

the medical hazards of smoking have been studied for decades, its effects on sleep, generally, and on sleep architecture, specifically, are not well characterized.

There are various distinct mechanisms through which cigarette smoking can alter nocturnal sleep architecture. First, nicotine from cigarette smoke can stimulate the release of several key neurotransmitters that are key regulators of the sleep-wake cycle. Second, habitual smokers often experience acute withdrawal during sleep as the intake of nicotine is curtailed [6]. The medical consequences associated with cigarette smoking, such as chronic obstructive pulmonary disease, also can disrupt sleep continuity [7, 8]. According to the reciprocal interaction model of McCarley and Hobson [9], REM sleep results from cholinergic stimulation of neurons in the gigantocellular tegmental field, and their activity inhibits non-REM sleep (For details, please see Chaps. 1 and 23). Nicotine stimulates nicotinic acetylcholine receptors (nAChRs) in the brain, which results in the release of a variety of neurotransmitters, most importantly dopamine (DA) [10]. Based on these effects, nicotine interacts with sleep regulating mechanisms and thus affects sleep. Epidemiologic investigations indicate that, compared with never smokers, current smokers experience greater difficulty in initiating and maintaining sleep and are generally more dissatisfied with their sleep quality [11]. Disturbed sleep has been seen even with smokeless tobacco and passive smoking [12].

40.1.1.1 Sleep Findings in Acute Administration and Intoxication of Nicotine

Laboratory-based studies in smokers have reported extended sleep latency, decreased total sleep time, extended REM sleep latency, and decreased slow wave sleep following nicotine administration; these effects mirrored in subjective reports of smokers who report problems with falling asleep and daytime sleepiness [6, 13]. Studies examining the effect of acute nicotine intoxication on sleep using transdermal nicotine application in nonsmokers reported a dose-dependent reduction of REM sleep, slow wave sleep, and total sleep time [14, 15]. During acute intoxication, nicotine, similar to other stimulants, increases REM latency, sleep onset latency, and NREM-2 (NREM stage 2) sleep [15].

40.1.1.2 Sleep Findings in Nicotine Dependence

Studies have also found that compared to nonsmokers, smokers have longer sleep latency, longer REM latency, greater time awake during the night, shorter total sleep time (TST), lesser slow wave sleep (SWS), and reduced sleep efficiency [13, 16]. The effects of nicotine on sleep architecture depend not only on the dose but also on the timing of exposure. Long-term administration of low-dose nicotine increases REM sleep, whereas chronic administration of nicotine in high doses reduces REM and total sleep time [17, 18]. Nicotine also seems to suppress ponto-geniculo-occipital (PGO) spikes, which are a key feature of phasic REM sleep. This effect may be mediated by nicotine-induced stimulation of serotonergic neurons in the dorsal raphe nucleus of the pons, which in turn inhibits pedunculopontine and laterodorsal tegmental cholinergic neurons, the main generators of ponto-geniculo-occipital spikes [19, 20].

40.1.1.3 Sleep Findings in Nicotine Withdrawal

During nicotine withdrawal, sleep quality is decreased with increased numbers of night-time awakenings and poor affect and REM rebound (a phenomenon in which increased frequency and length of REM sleep occur) on polysomnography (PSG) studies [14, 15]. The effects of withdrawal on sleep are dose dependent, but usually begin 6–12 h after cessation of nicotine, reach a maximum within 1–3 days, and can continue for up to 3 weeks [14]. Effects also include an increase in REM sleep and a decrease in REM latency as well as sleep onset latency [14, 15]. A correlation has been observed between plasma nicotine concentration and sleep disturbances—sleep disturbances are commonly found to begin from the quit day. It is also seen that sleep disturbance observed during transdermal nicotine therapy appeared to be associated with tobacco withdrawal rather than with nicotine excess [21, 22]. Jaehne et al. (2015) assessed sleep during smoking, in withdrawal, and after 3 months and found that compared with the smoking state, there was an increase in arousal index and wake time during nicotine withdrawal [23]. Also, smokers who later relapsed presented a greater degree of nicotine dependence and more withdrawal symptoms than those who remained abstinent. The group who relapsed also had less REM sleep, a longer REM latency as well as more intense sleep impairments in the subjective sleep rating during the withdrawal.

Spectral analysis of sleep electroencephalograms (EEGs) showed an increase in alpha-frequencies (8–12 Hz) and a reduction in delta-frequencies (4–7 Hz) in smokers, indicating intrusion of wakefulness along with a reduction of the deeper sleep stages [24]. Smokers also had a higher spectral electroencephalographic (EEG) power in the gamma-frequencies compared with nonsmokers, indicating a greater cortical processing during sleep [24].

40.1.1.4 Factors Affecting Sleep in Nicotine Use

Sleep disturbance is caused not only due to nicotine but may also be caused by comorbid conditions commonly associated with nicotine. For example, sleep can be disturbed by sleep apnea and restless legs syndrome (RLS), which are found more frequently in smokers [25, 26]. Sleep bruxism (tooth grinding) may also lead to disturbed sleep. Few data are available, however, to confirm an association between smoking and these disorders [25, 27, 28]. In a study by Ohayon et al. (2002), a significant association was seen between cigarette smoking (>20 cigarettes per day) and restless leg syndrome [25]. Similarly, Philips et al. (2000) found significant association between daily use of one pack of cigarettes and restless leg syndrome [27].

40.1.1.5 Smoking Cessation and Sleep Disturbances

Available data on the effects of smoking cessation and nicotine-replacement therapy on sleep have yielded conflicting results. Some studies show that nicotine-replacement therapy was, in large part, responsible for the sleep disturbances typically associated with smoking cessation [29, 30]. Cessation of smoking and nicotine withdrawal itself, however, may also contribute to disturbed sleep. Nicotine-replacement therapy objectively improves sleep parameters, decreasing

arousal frequency and increasing slow wave sleep. Studies on nicotine patches have reported improvements in measures of sleep quality, including reduction in sleep fragmentation and increased levels of slow wave sleep, compared to nonmedicated quitting and pre-cessation measures, although no significant effect on REM sleep was observed [6]. Salin-Pascual et al. [17] found that transdermal application of nicotine increased REM time in both smokers and nonsmokers. Gillin et al. [18] found that transdermal nicotine applied to nonsmoking volunteers was associated with early morning awakening and reduced REM sleep time in a dose-dependent fashion (across placebo, 7-mg and 14-mg patches). Page et al. [31] observed increased sleep fragmentation, less REM sleep, and increased REM dream quality in participants on 24-h transdermal patch.

Bupropion, an atypical antidepressant, is frequently prescribed as a smoking cessation aid. Bupropion is believed to act on dopaminergic and noradrenergic transmission to relieve the symptoms of nicotine withdrawal and craving. Bupropion improves the cessation rates of smoking, with higher doses producing greater benefits than lower doses. However, a sizeable proportion of patients discontinue the drug because of adverse effects [32]. Insomnia, which occurred in a dose-related fashion, nightmares and abnormal dreams were the most commonly reported sleep complaints by patients taking bupropion [32]. A recent report also noted somnambulism and sleep-eating during bupropion therapy for smoking cessation [33]. It is difficult, however, to distinguish the sleep-related effects of bupropion from those of nicotine withdrawal. Although the effects of bupropion on sleep architecture have not been studied in normal human subjects, its effects on depressed persons demonstrated possible dose-related changes in sleep stages. Low-dose bupropion increased slow wave (stages 3 and 4) sleep at the expense of stage-2 sleep and higher doses produced the opposite effects [34, 35]. In contrast to other antidepressants, bupropion did not suppress REM sleep. In fact, it increased REM density, activity, and percent in patients with unipolar depression. Prolongation of REM onset latency was observed in depressed patients who responded to bupropion therapy, whereas decreased REM latency was noted in those patients who failed to respond [34, 36].

Varenicline (VCL) is another medication used to treat nicotine dependence. A study conducted by Polini et al. [37] found that the participants receiving varenicline had good sleep quality, as expressed by a more than 90% sleep efficiency index similar to placebo. However, there were increased number of awakenings and a tendency for a longer time to stay awake after sleep onset and changes in dream measures. McClure and colleagues [38] reported that 39–46% of treatment seeking smokers using varenicline reported difficulty sleeping, while 56–68% reported a change in dreaming. These sleep disturbances were retained till 21 days after cessation of smoking. Two meta-analyses of clinical trials that compared the efficacy of varenicline to placebo show that disturbed sleep, specifically difficulty falling and staying asleep, as well as the incidence of abnormal dreams were between 50% and 70% higher in varenicline recipients [39, 40]. Prospective studies suggest that insomnia-related symptoms peak in the first week of quitting and then progressively decline until pretreatment levels are achieved at 2–12 weeks [41].

Nicotine has been shown to readily cross the placenta and accumulate in both the placenta and amniotic fluid, thus exposing the fetus to a high level of nicotine compared with the exposure level found in the mother [42]. Studies indicate that the amount of nicotine found in breast milk is about three times greater than that found in maternal blood plasma [43]. As for changes in sleep and wake patterns, a considerable change has been observed in sleep and wake patterns when children were breastfed immediately after their mother smoked. Mennella et al. (2008) tested mother-infant pairs on 2 days separated by 1 week and found the total sleep time to vary from 53.4 min when their mothers smoked (one to three cigarettes for 20 min) to 84.5 min when they did not smoke [44]. Another study observed that infants of smoking mothers have sleeping disorders [45].

40.1.2 Caffeine

Caffeine is the most widely used psychoactive drug in the world, with 80% of the world's population estimated to have used caffeine [46]. It is also the most common beverage used by adolescents. It is estimated that almost 30% of American adolescents consume caffeinated beverages on a daily basis [47]. Soda appears to be the beverage of choice, followed by coffee and energy drinks [48, 49].

Caffeine is primarily ingested via dietary sources including beverages such as coffee, tea, and soft drinks. Caffeine dosages in commercially available products have increased since the mid-1990s [50]. Moderate caffeine consumption is often considered benign [51, 52]. However, caffeine is an addictive substance that is used for its rewarding properties including to promote alertness [53–55]. While consumption of caffeine in low-moderate doses (equivalent to 3.6 mg/kg body weight) is considered safe, high doses of caffeine intake (>6 mg/kg body weight) can lead to negative health consequences, including cardiovascular changes. Caffeine is known to produce dependence in vulnerable individuals, recognized as a disorder both in the International Classification of Diseases (ICD), version-10 as well as in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [56, 57].

Laboratory-based studies have demonstrated that caffeine has alerting and performance enhancing properties [58]. Various studies on caffeine consumption have showed that subjective sleep is poorer in high (> 500 mg/d) than in low (< 500 mg/d) "habitual" caffeine consumers [59].

40.1.2.1 Sleep Findings in Acute Administration of Caffeine

Acute administration of caffeine close to normal bedtime results in increased sleep latency, and decreased total sleep time, including decreased slow-wave sleep [60]. The timing of administration influences the magnitude of effect on sleep, such that administration close to habitual bedtime has the greatest potential for disruption [61–63].

40.1.2.2 Sleep Findings in Chronic Administration of Caffeine

Similar to acute caffeine administration, sleep findings have been reported following repeated administration of caffeine (400 mg, three times per day for 7 days) with reduction in total sleep time and slow wave sleep, and tolerance to the effect developing over the course of a week [63]. In addition, there is some evidence that caffeine consumption earlier in the day will also affect sleep on subsequent nights by reducing total sleep time and reducing sleep efficiency [64]. Dependence on caffeine is found to cause poor sleep quality, daytime dysfunction, and increased sleep disturbances.

40.1.2.3 Laboratory Studies of Sleep Disturbance with Caffeine Use

The sleep disturbances are also confirmed in laboratory studies with EEG or actimetry measures of sleep [61, 62, 65]. These studies show that sleep latency and wakefulness after sleep onset (WASO) were prolonged and sleep duration was reduced. Only one actimetry study has reported no effect of caffeine on any sleep variable [66]. The study was conducted in 10 college students who were not habitual coffee users with an aim to see the effect of evening coffee abstinence on sleep parameters. The nonsignificant result was attributed to possibly small sample size and on the fact that the participants were not habitual coffee users. Sleep efficiency (i.e., percentage of total time asleep divided by total time in bed) was reduced in most of the studies. There is a dose-response relationship between caffeine use and sleep parameters. Studies have shown progressive worsening of sleep quality with increasing dose, as quantified by sleep latency, WASO, sleep duration, and sleep efficiency [60, 62, 67].

The duration and frequency of wakefulness, arousals, and stage-1 sleep increase earlier in the night at the expense of slow wave sleep (SWS; i.e., NREM sleep stages 3 and 4), which is reduced in duration and occupies proportionately less of sleep time, especially within the first 6 h [64, 68, 69]. Increased arousals and awakenings at the expense of reductions in both stage-2 and stage-4 sleep have also been observed [63]. It has been seen that slow wave sleep (SWS) over the entire sleep episode reverts to baseline levels the night after cessation of caffeine, although stage-2 sleep was still found to be decreased [64]. Caffeine has not been found to affect sleep structure in the recovery night after sleep deprivation [70]. Recovery sleep during the biological day after a night of sleep deprivation contained less SWS compared to baseline [68, 71].

There is some evidence for a dose-response relationship between caffeine and sleep structure. Progressively higher bedtime doses reduced the percentage of SWS, which initiated later, whereas lower doses increased latency to stage-2 sleep [60]. The time spent in SWS decreased with progressive dose increase, whereas the duration of wakefulness in the first 6 h of the sleep episode progressively increased [61]. Studies have found no clear dose-response relationship with REM sleep [72]. The study by Karacan et al. [60] suggested that after large doses (4.6 mg/kg), the proportion of REM sleep was increased in the first third of the night, whereas in the final third of the night, this effect on REM sleep occurred after comparatively moderate doses (2.3 mg/kg).

40.1.2.4 Individual Sensitivity to Effect of Caffeine on Sleep Architecture

Not only individuals of different ages, but also those of a similar age are differently sensitive to sleep disruption by caffeine. Genetics influence the caffeine consumption and the physiological response to caffeine in humans [73]. Few genes have been found to modulate differences in individual caffeine sensitivity such as adenosine A2A receptor gene (ADORA2A), adenosine deaminase (ADA) with SNPrs6575353 of the gene encoding PRIMA1 (proline-rich membrane anchor 1) located on chromosome 14, with SNP rs521704 of the gene coding for GBP4 (guanylate-binding protein 4) located on chromosome 1, SNP rs10830964 near the MTNR1B (melatonin receptor 1β) gene, and polymorphisms of the gene CYP1A2 [74].

40.1.2.5 Perinatal Effects of Caffeine on Sleep

Maternal caffeine consumption, even in large amounts during gestation and lactation, had no consequences on sleep of the infant at 3 months of age [75]. An experimental study by Mulder et al. (2010) revealed that in comparison with caffeine-naive fetuses, fetuses that were regularly exposed to caffeine had a differential performance in active wakefulness, general movements, and heart rate variation before and after maternal coffee loading, suggesting fetal tolerance in response to maternal habitual coffee ingestion and no change in sleep parameters [76]. In clinical settings, studies in which caffeine was used to treat apnea of prematurity revealed that caffeine did not modify either the duration of active sleep or the total sleep time or the sleep stage durations of preterm infants [77, 78].

40.1.3 Cocaine

Cocaine use and use disorder are prevalent across the world; however, the prevalence is much higher in some regions. High prevalence is reported in Oceania, North America, Western and Central Europe, and South America [2]. Evidence-based ranking of addictive substances, using categories such as physical harm, dependence, and social stigma, has also listed cocaine as the second most harmful drug, after heroin [79]. Cocaine causes competitive inhibition of presynaptic dopamine transporters in the nucleus accumbens and prefrontal cortex, leading to an increase in dopamine availability [80]. Acute subjective effects of cocaine intake are euphoria, orgiastic feelings, restlessness, motor activation, and increased alertness. Trouble sleeping is a frequently cited adverse effect of cocaine intake [81].

40.1.3.1 Acute Effects of Cocaine on Sleep

Acute cocaine administration causes longer sleep latency, reduced total sleep time, and suppression of REM [82]. It has also been observed that smaller doses of cocaine administered in the morning may improve sleep in cocaine-dependent subjects, probably by attenuating withdrawal effects.

40.1.3.2 Sleep in Cocaine Withdrawal and Abstinence

Cocaine abusers often experience hypersomnia and a propensity for REM sleep during periods of acute and subacute withdrawal from cocaine [83]. Studies have reported conflicting findings as both insomnia and hypersomnia have been observed during cocaine withdrawal, depending on time lag between the last dose of cocaine and the conduct of the study as can be seen below.

Acute withdrawal in cocaine-dependent individuals is often characterized by depressed mood, psychomotor agitation or retardation, increased appetite, fatigue, sleep disturbances, and unpleasant dreams [84]. It has been shown that during acute cocaine withdrawal, the total sleep time is significantly reduced [82, 85]. Sleep onset latency is prolonged and sleep efficiency is decreased [82, 86]. An increase in REM sleep percentage and reduced REM latency are also seen [82, 87]. These changes in REM sleep are consistent with the subjective withdrawal symptom of increased dreaming [84].

During the subacute phase of cocaine withdrawal, PSG parameters of sleep continuity deteriorate further. Total sleep time, sleep latency, and sleep efficiency reduce further [85, 87]. REM latency is also significantly reduced. It has been shown that cognitive performance also deteriorates during subacute cocaine withdrawal [85, 87]. Reaction time on vigilance task increases, which is a sensitive measure of growing sleep pressure in the context of sleep deprivation [87–89]. Also, the sleep-dependent performance on motor sequence task is compromised and correlates with an individual's total sleep time during withdrawal [88]. These findings are most notable in view of the fact that subjective sleep quality remains unchanged or improves during subacute withdrawal [87, 88, 90]. This phenomenon is the exact opposite of the distorted sleep perception in patients with insomnia, who typically underestimate their sleep quality.

Coincidence of improving self-reported sleep quality with poor and worsening sleep was termed "occult insomnia" to reflect the relative lack of awareness of what appears to be severely disrupted sleep [88]. It is not known why cocaine-dependent subjects do not recognize this deterioration of sleep during subacute withdrawal. A possible explanation is that although slow wave sleep (SWS) percentage is low both during acute and subacute withdrawal, delta spectral power (which denotes deep sleep) may increase during subacute withdrawal [88]. An increased delta spectral power is associated with better self-reports of sleep quality [91].

It has also been found that sleep disturbances contribute to the reduction in striatal D2/D3R availability in cocaine abusers. Cocaine abusers also exhibit longer time spent in total sleep and REM sleep during acute withdrawal than during subacute withdrawal [92]. PSG studies of mixed (cocaine or amphetamine) stimulant-dependent individuals also report poorer sleep later in abstinence during inpatient treatment [18, 92]. Using an experimental, inpatient model of the binge and abstinence cycle, Pace-Schott et al. [93] presented evidence for progressive sleep quality deterioration from binge to abstinence, which reaches clinically significant levels by 15 days of abstinence. In addition, abstinence-related sleep quality declines were accompanied by declines in cognitive performance [93] (Fig. 40.1).

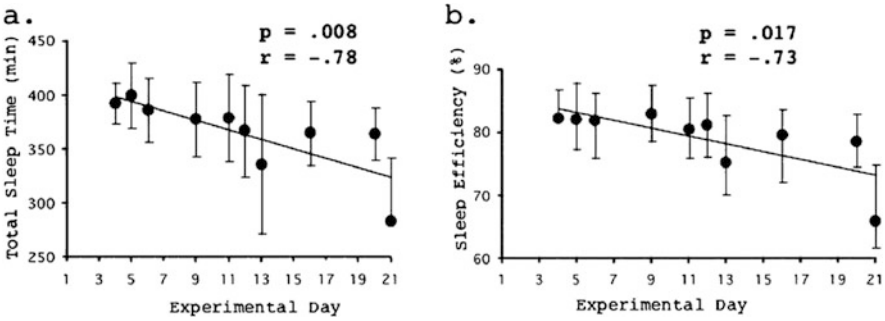

Fig. 40.1 Changes in objective polysomnographic (PSG) and subjective sleep quality as a function of experimental day analyzed using simple regression across a simulated cocaine binge and abstinence sequence. (**a**) Changes in PSG total seep time. (**b**) Changes in PSG-measured sleep efficiency. (From: Pace-Schott EF, Stickgold R, Muzur A, Wigren PE, Ward AS, Hart CL, et al. *Sleep quality deteriorates over a binge-abstinence cycle in chronic smoked cocaine users.* Psychopharmacology (Berl). 2005 Jun;179(4):873–83)

However, despite prior research on subjective and objective sleep abnormalities in chronic cocaine users, no work, to date, has associated sleep parameters during the initial abstinence period with later cocaine use or relapse.

40.1.3.3 Mediating Factors for Sleep Disturbance in Cocaine Users

The consequence of repeated cocaine use is an increase in extracellular adenosine in the ventral tegmental area [94]. A growing body of evidence has supported the role of the purine nucleotide, that is, adenosine as a mediator of sleepiness following prolonged wakefulness [95–98]. Basheer and co-workers [99] have advanced the hypothesis that during prolonged wakefulness, adenosine accumulates selectively in the basal forebrain and promotes the transition from wakefulness to slow wave sleep (SWS) via adenosine receptor activation. Adenosine A_1 and A_{2A} receptor subtypes are most likely to mediate physiological effects of adenosine on sleep, and these effects appear to be site- and receptor-dependent [100]. A_1 receptor activation promotes delta activity in the NREM stage. A1 receptor expression is increased following withdrawal from chronic cocaine treatment [96]. Manzoni et al. [98] have observed that 1 week of withdrawal from chronic cocaine augments adenosine uptake to decrease the potency of adenosine-mediated inhibition of glutamate release. This enhanced adenosine uptake ultimately increases glutamate release to increase the excitability of neurons. Also adenosine A_{2A} receptors have been suggested to be linked to cocaine-mediated behaviors such as relapse, hyperlocomotion, and reinforcement [98, 101]. Activation of A_{2A} receptors in the nucleus accumbens promotes sleep. Repeated administration of cocaine has also been shown to increase adenosine A_{2A} receptor subtype expression in nucleus accumbens [95, 102].

40.1.4 Methamphetamine

Among the substances which have a significant effect on the sleep condition are stimulants, including amphetamines. It has been seen that D-methamphetamine (D-Meth) and other amphetamines have profound effects on sleep-wake cycles. Amphetamines are used for curbing appetite, increasing attention and concentration, increasing energy, and also as an illicit recreational substance. The acute effect of amphetamine administration in rodents and canine narcolepsy models and humans is a protracted period of wakefulness with a high level of arousal [103–106].

40.1.4.1 Acute Use

Limited research has been conducted to assess the effects of acute amphetamine administration on sleep-wake cycle. It has been suggested that consuming amphetamines usually leads to insomnia immediately after usage. Rechtschaffen et al. [107] showed that a small amount of amphetamine can increase sleep latency and decrease REM sleep.

40.1.4.2 Amphetamine Withdrawal and Sleep

Amphetamine withdrawal in humans results in a broad spectrum of deficits in attention, motivation, and mood [108]. It can also lead to hypersomnia in the early withdrawal states [109]. Some of the cognitive deficits may be secondary to the hypersomnolence that occurs because of amphetamine withdrawal. It has been seen that amphetamine users undergo withdrawal-sleep twelve or more hours per day, even when given antidepressant pharmacotherapy [108]. Antidepressants are usually given during amphetamine withdrawals to treat apathy and low mood seen in amphetamine withdrawal state. Nonimprovement of sleep disturbance despite antidepressants shows that sleep disturbance is not secondary to depression. Preclinical studies on amphetamine withdrawal in experimental rodents subjected to D-Meth exposure show hypersomnolence. This acute hypersomnolence is characterized by increased duration of total sleep time and proportion of NREM [110]. Mitler et al. [111] reported that methamphetamine can decrease sleep efficiency in low doses (10 mg), although sleep increases for 3–5 days after withdrawal. There are also reports of delayed sleep in users attempting to quit amphetamine after long-term use during the 3–5 initial days [112].

McGregor et al. [113] pointed out that the subacute phase of methamphetamine withdrawal syndrome is characterized by similar symptoms of the acute phase syndrome, but of reduced intensity [113]. In another study by Ardani et al. (2016), who measured sleep quality using Pittsburgh Sleep Quality Index (PSQI) in the first, second, and fourth week of methamphetamine withdrawals, the prevalence of improper sleep quality reduced from the first week to the fourth week [114]. Yet, the prevalence of improper sleep quality was 52% in the fourth week of methamphetamine withdrawals. It is possible that there is extensive neuronal damage in those who suffer from methamphetamine-induced hypersomnolence, resulting in a slow recovery phase.

It has also been suggested that quitting methamphetamine use may increase the daytime drowsiness [115].

The disturbed sleep (hypersomnolence characterized by increase in TST and proportion of NREM sleep) lingering for more than a month after quitting methamphetamine showed that in methamphetamine dependents, behavioral symptoms attributed to withdrawal from methamphetamine are not simply an opposite form of behavioral symptoms which are present in the course of using these drugs. It seems that a kind of adaptation is developed in sleep-wake cycle-related systems in brain while abusing amphetamine and amphetamine-like substances, so withdrawal from methamphetamine is not simply an opposite form of using it. According to some studies, this adaptation is caused by the formation of a secondary pacemaker as an opponent process to regulate sleep-wake cycle out of the suprachiasmatic nucleus. As a result, quitting amphetamines, while activation of the opponent processes remained in this system, results in some more durable symptoms in patients' sleep-wake cycle [116].

40.1.4.3 Mediating Factors for Sleep Disturbance in Methamphetamine Users

Amphetamines are known to have longer half-life (9–15 h) in comparison to other stimulants. They have proven neurotoxic effects through reactive oxygen species and hyperthermia, causing axonal injury, especially in synaptic terminals [117, 118]. They also lead to significant changes in neurotransmission of glutamate, dopamine, serotonin, and norepinephrine causing major behavioral changes [119–121].

Increased wakefulness during consumption and other psychostimulant effects of amphetamines are due to the elevation of extracellular monoamine concentrations caused by blockade of the dopamine (DA) transporter and possibly other monoamine transporters [104, 122–124]. The mechanisms underlying amphetamine withdrawal hypersomnolence remain ill defined. Increased sleep drive in response to sleep deprivation is manifested electroencephalographically by elevation of total sleep time relative to baseline sleep amounts [125]. To an extent, methamphetamine-induced wakefulness during consumption is likely to increase sleep drive during abstinence in the same way that wakefulness induced by any other means increases sleep drive.

40.1.4.4 Amphetamines and Mood Disorders

Amphetamine exposure in vivo or in vitro induces biochemical changes [126, 127]. There is also impact of anxiety and depression on sleep quality while on amphetamines. Stimulant use can lead to anxiety states soon after consuming, and depressive states in long-term use, while patients usually develop depressive symptoms soon after quitting them [128]. It has been seen that depression and anxiety could also have deteriorating effects on sleep quality [129, 130].

40.1.5 Ecstasy

3,4-Methylenedioxymethamphetamine (MDMA) is the main psychoactive constituent of ecstasy. Ecstasy has stimulant and hallucinogenic effects and has often been described as an entactogen. It is a drug that is frequently used by visitors of raves or techno parties in large dance clubs. MDMA induces rapid release of serotonin via interaction with presynaptic serotonin uptake carriers. MDMA also induces rapid dopamine release and binds to a variety of neurotransmitter receptors, especially serotonin 5-HT2 receptors. MDMA users commonly report restless, disturbed sleep during the 48 h following MDMA intake [131, 132]. 3,4-Methylenedioxy-N-ethylamphetamine (MDE; "eve") has similar effects as MDMA.

40.1.5.1 Effects of Ecstasy Use on Sleep

Heavy MDMA use is associated with persistent neuropsychiatric including sleep disturbances [131, 133]. A number of different models of sleep-ecstasy interrelationships are possible. First, ecstasy might impair sleep directly via psychopharmacological effects. Second, lifestyle differences might also result in a person obtaining less sleep or suboptimal sleep. Previous research in ecstasy users has found that users of the drug report disturbed sleep both as a primary subjective effect and as a longer lasting psychobiological complaint [132, 134–136]. Insomnia has been reported even after 2 years of stopping MDMA, suggesting that the effects of MDMA may be prolonged [137].

In a study by Baylen and Rosenberg (2006), between 9% and 85% of participants reported "sleeplessness" as a subjective effect of ecstasy [134]. Huxster et al. (2006) reported that this sleeplessness persists for 48 h after use [132]. Chronic use of ecstasy causes insomnia and sleep deprivation [135]. MDMA users have significantly longer sleep latency, less total sleep time and less NREM time, and short REM latency than control subjects [138–140, 142, 143]. During NREM periods, they have less stage-2 sleep and more stage-1 sleep in comparison with control subjects [137, 139–143]. Even in sleep-deprived subjects, MDMA was not associated with increased daytime sleepiness. The sleep disturbances (insomnia and poor quality of sleep) although may be a primary subjective effect of ecstasy due to its stimulant-like properties, studies in ecstasy users also report that these effects may be longer lasting.

40.1.6 Khat

Khat (*Catha edulis*) is an evergreen flowering shrub that grows at high altitudes in East Africa and the southwest of the Arabian Peninsula. The young tender leaves are used as a psychoactive stimulant. The major active compounds are alkaloids, of which cathinone and cathine are the most active ones. They are similar in structure and pharmacological activity to amphetamines and stimulate the central nervous system. The global consumption of khat is increasing. Cathinone activates dopaminergic pathways involved in the regulation of sleep [144]. Khat use is associated

with poor sleep as well as other conditions implicated in precipitating sleep problems, that is, anxiety, depression, and stress [144–148].

40.1.6.1 Sleep Problems in Khat Users

There are limited studies on khat use and sleep problems. Khat has been found to affect sleep and to be associated with sleep onset insomnia [149–151]. The prevalence of sleep onset insomnia and nightmares was very high in khat users (65%), with 31% reporting moderate-to-severe level of disturbances [149–153]. After immediate use of khat, the user usually experiences depressed mood, irritability, anorexia, and difficulty to sleep [153]. There is lethargy and sleepy state the next morning. In chronic khat users, sudden discontinuation results in withdrawal symptoms such as sleeping disturbances, depression, and intense cravings during the first day [151]. It has been seen that sleep gradually improves on discontinuation of khat [153, 154]. Since depression and sleep deprivation are both common in pregnant patients, khat consumption may further aggravate both symptoms [155, 156]. Table 40.1 provides a summary of the effect of psychostimulants on sleep.

40.1.6.2 Management of Sleep Problems in Psychostimulant Users

In general, the drug class of choice for insomnia treatment in patients without comorbid alcoholism is the benzodiazepine receptor agonists. However, there are concerns about the use of benzodiazepines for the treatment of insomnia in the case of patients with substance use disorders due to fear of dependence on benzodiazepines. Sedating antidepressant medications such as trazodone or doxepin are often used to treat insomnia and insomnia comorbid with depression. Cognitive-behavioral treatment for insomnia (CBT-I) is an alternative to medications [157].

Literature on treating sleep disturbance in stimulant abuse is limited. Currently, there are no evidence-based recommendations on the strategies to face the negative impact of stimulants on sleep. However, some general recommendations can be taken from patients of ADHD with sleep problems such as to wait and watch as insomnia due to stimulants attenuates in 1–2 months, avoiding evening stimulant dose and adding antihistaminics, mirtazapine, trazodone, melatonin, or clonidine [158, 159]. Nonpharmacological interventions, such as sleep hygiene and cognitive-behavioral therapy, also help patients with ADHD having sleep problems [160].

A placebo-controlled trial of modafinil 400 mg/d in cocaine-dependent individuals has been found to improve the latency and sleep staging of sleep and reduced daytime sleepiness [161]. In a study conducted in China, Tai-chi intervention, which includes training in sustained attention focusing and multitasking, was found to be effective in ameliorating sleep problems over a period of 6 months (significant reduction in Pittsburgh Sleep Quality Index scores) in amphetamine-type stimulant (ATS)-dependent females [162]. Melatonin receptor agonists, especially Ramelteon, may be beneficial in curbing sleep deficits caused by smoking cessation [163].

Table 40.1 Summary of the effect of psychostimulants on sleep

Stimulant	Acute	Chronic use	Withdrawal
Cocaine	↑ Sleep latency	↑ Sleep latency	*Acute*
	↓ TST	↓ TST	↑ TST
	↓ REM	↓ REM	↑ REM (rebound)
	↑ REM latency	↑ REM latency	↓ Sleep latency
			↓ REM latency
			Subacute
			↑Sleep latency
			↓ Sleep efficiency
			↓ TST
			↓ REM
			↑ SWS
Nicotine		↓ Sleep efficiency	↑ WASO
	↑ REM latency	↑ REM latency	↑ REM
	↓ Slow wave sleep	↓ Slow wave sleep	↓ REM latency
	↓ TST	↓ TST	↓ TST
	↑ Sleep latency	↑ Sleep latency	↓ Sleep latency
Caffeine		↓ Sleep efficiency	↑ WASO
	↑ REM latency	↑ REM latency	↑ REM
	↓ Slow wave sleep	↓ Slow wave sleep	↓ REM latency
	↓ TST	↓ TST	↓ TST
	↑ Sleep latency	↑ Sleep latency	↓ Sleep latency
Methamphetamine	↑ Sleep latency	↑ Sleep latency	*Acute withdrawal*
			↑ TST
			↑ REM (rebound)
			↓ Sleep latency
			↓ REM latency
	↓ REM	↓ REM	*Subacute-chronic withdrawal*
			↑ TST
			↑ REM (rebound)
			↓ Sleep latency
			↓ REM latency
MDMA	↑ Sleep latency	↑ Sleep latency	↓ REM latency
	↓ TST	↓ TST	↓ TST
	↓ NREM	↓ NREM	

↓ decreased, ↑ increased, *TST* total sleep time, *NREM* nonrapid eye movement, *REM* rapid eye movement

40.2 Conclusion

Sleep is often an understudied phenomenon in psychostimulant use, but it is an important concern. It can be a pointer toward their initiation or escalation of drug use. Psychostimulants have a substantial effect on sleep, which can be seen in

different phases including acute use, withdrawal, and abstinence. The change in sleep pattern is also documented objectively in terms of alteration in both NREM sleep and REM sleep. The sleep disruptions reflect alterations in brain monoaminergic systems. Currently, there is no recommended treatment for psychostimulant-induced sleep disorder. There is still a need for increased understanding of the etiology of sleep disturbances. Understanding the degree to which these sleep and alertness disturbances persist and the underlying neurobiologic changes accompanying these disturbances could lead to more effective treatments.

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Effect of Dopamine Agonists on Sleep

41

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Abstract

Dopamine agonists are the mainstay of symptomatic treatment of idiopathic Parkinson's disease and restless leg syndrome. Both diseases are associated with significant sleep dysfunction. Both ergot and non-ergot dopamine agonists have a significant influence on sleep architecture. Various pharmacological studies have revealed that they exert their actions on sleep via D2 and D3 receptors. Long-term therapy with dopamine agonists in Parkinson's disease and restless leg syndrome is associated with excessive daytime sleepiness and sleep attacks, which can further complicate the pre-existing sleep dysfunction among these patients. In this chapter, we discuss the effect of dopamine agonists on sleep architecture, the prevalence of sleep disorders associated with them and their management.

Keywords

Dopamine · Dopamine agonists · Dopamine receptors · Sleep · Excessive daytime sleepiness · Sleep attack

Abbreviations

cAMP	Cyclic adenosine monophosphate
DA	Dopamine

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EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness score
ICSD	International classification of sleep disorders
MSLT	Multiple sleep latency test
OSA	Obstructive sleep apnea
PD	Parkinson's disease
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
RBD	REM sleep behaviour disorder
REM	Rapid eye movement
RLS	Restless leg syndrome
SWS	Slow-wave sleep

41.1 Introduction

Dopamine (DA)containing neurons are localized primarily in the substantia nigra and ventral tegmental area of the midbrain [1] and both these areas of the brain have been associated with wakefulness [2, 3]. The neurons in these nuclei send projections to the striatum, basal forebrain and cerebral cortex [4, 5]. The dopaminergic neurons in the ventral tegmental area demonstrate the highest activity both during waking and REM sleep [6], while the release of dopamine in the frontal cortex is higher in wakefulness [7].

The central dopamine receptors belong to the G-protein-coupled receptor superfamily and are activated by DA as an endogenous ligand [8, 9]. The activation of DA receptors has been associated with several neurobiological processes such as cognition, learning, motivation and sleep [9–11]. DA receptors have been a key target for treatment of diseases like Parkinson's disease (PD) and there has been an equally significant expansion in the knowledge of this field in the last few years. Increasingly, there is considerable attention on the effect of DA agonist on sleep. In subsequent paragraphs, we make an attempt to improve our understanding of this emerging topic.

41.2 DA Receptor Family and Sleep

Dopamine receptors have been broadly divided into two groups based on their physiological properties: the D1-like receptors and the D2-like receptors [10, 12]. The D1-like receptors are further subdivided into D1 and D5 dopamine subtypes, whereas the D2-like receptors consist of D2, D3 and D4 subtypes. D1-like receptors are located on the postsynaptic side of the synaptic cleft and are coupled to the G protein ($G_{s\alpha}/G_{olf}$) [10, 12]. They stimulate the activity of adenyl cyclase and the production of cyclic adenosine monophosphate (cAMP). In contrast, the D2-like

receptors are coupled to the G protein ($G_{i\alpha}$) and inhibit the production of cAMP by inhibiting adenyl cyclase [9, 10]. All these receptors modulate several physiological functions of dopamine including sleep.

41.3 Dopamine Receptor Agonists and Sleep: Evidence from Animal Model Studies

Most of the pharmacological studies of D1 receptor agonists have demonstrated that these receptors function as wake promoters [13–15] and have been shown to suppress rapid eye movement (REM) sleep [16–18]. Isaac and Berridge reported that D1 receptor agonist SKF 82958 increased the wakefulness time, suppressed slow-wave sleep (SWS) and REM sleep in a dose-dependent manner [19].

On the contrary, bromocriptine, a D2 receptor agonist, has been found to decrease wakefulness and increase SWS in rats [16]. The effect of D2 receptor agonists could vary from one molecule to another, and may be dependent upon the doses and state of sleep and wakefulness. For example, another D2 receptor agonist, Quinpirole, diminished wakefulness at low doses but promoted sleep at higher doses [20]. Similarly, Python et al. reported a dose-dependent increased waking with RO 41–9067 [21]. Another selective D2 agonist, Piribedil, has been shown to increase wakefulness and reduce REM sleep in the rebound period after 96 h of REM sleep deprivation in rats, thus showing the effect on specific sleep state [22]. Cabergoline has been reported to block the ability of restraint stress to increase the amount of REM sleep and it also reduced REM sleep [23]. These effects could have been attributed to their effects on other receptors, besides D2 receptors.

Limited evidence is available about the role of D3, D4 and D5 agonists in sleep. In a study among rats, pramipexole, a D3 receptor agonist, has been shown to increase the SWS as well as REM sleep and reduce wakefulness in low doses. However, in higher doses, it enhanced the waking time [24]. Contrarily, Ro 10–5824 and A-412997, D4 agonists, have been shown to increase waking and reduce non-REM sleep in rats [25].

41.4 Dopamine Agonists and Sleep in Humans

Dopamine agonists are the mainstay of treatment for Parkinson's disease (PD) and restless leg syndrome (RLS), and both these conditions are associated with a host of sleep-related issues. DA agonists are often utilized as a first-line drug for symptomatic treatment of young-onset PD, since they have been found to delay motor complications, dyskinesia and the need for levodopa (L-Dopa) initiation [26–31]. Patients with PD experience frequent nocturnal awakenings due to akinesia, dystonia, painful muscle cramps and tremors (Please see Chap. 29). DA agonists and their sustained release formulations such as extended-release ropinirole and rotigotine transdermal patch have shown significant improvements in these motor functions, thereby improving the overall sleep in them. Similarly, DAs are used

frequently in RLS for symptomatic management which improves sleep quality. However, the use of these agents is associated with several sleep disorders like excessive daytime sleepiness (EDS), sleep attacks and hallucinations.

41.4.1 Excessive Daytime Sleepiness and Sleep Attacks

The international classification of sleep disorders, third edition (ICSD-3) defines excessive daytime sleepiness (EDS) as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least 3 months [32, 33]. Studies before ICSD-3 defined sleep attacks as "an event of overwhelming sleepiness that occurs without warning or with a prodrome that is sufficiently short or overpowered to prevent the patient from taking appropriate protective measures" [34] (For details, please see Chap. 6). Patients with EDS are more likely to suffer from 'sleep attacks' which are episodes of sudden onset of sleep without prodrome. These episodes may mimic narcolepsy without cataplexy.

The exact prevalence of EDS and sleep attacks varies significantly in different studies [34–37]. An earlier review by Homann et al. reported a 6.6% of patients taking dopamine agonists have sleep events and an unspecified proportion had sleep attacks [38]. However, a recent systematic review by Yeung et al. reported the prevalence of sleep attacks as 13% in patients with dopaminergic medications [39].

Occurrence of sleep attacks varies among different dopamine agonists as well as depends upon the number of dopamine agonists prescribed. Sleep attacks are more prevalent in patients taking a combination of levodopa and multiple dopamine agonists (9.2%), followed by levodopa with a single dopamine agonist (7.3%). Patients with dopamine agonist alone accounted for 5.3% and those with levodopa alone reported a 2.9% prevalence of sleep attacks [40]. Among the dopamine agonists, sleep attacks have been reported in 50% of patients with pramipexole, 23.1% with ropinirole and 15.4% with pergolide [39, 41–43]. However, another study by Kang et al. reported no significant association of ropinirole with EDS in Korean patients [44].

41.4.2 Risk Factors for EDS and Sleep Attacks with DA Agonists

Genetic predisposition has been implicated in developing sleep attacks. A study by Rissling et al. showed a significant association between D2 receptor gene polymorphism, Taq IA, and the sudden onset of sleep in patients with PD [45]. Another study showed an association of sleep attacks without warning signs with the dopamine receptor D4*2 (short)allele [46]. Similarly, a strong association has been demonstrated between variant allele T of (−909 T/C) preprohypocretin polymorphism and sudden sleep attack in patients with PD [47].

Choice of a dopamine agonist in isolation or combination with levodopa is a risk factor for developing EDS. Several studies have demonstrated that the combination

of levodopa with dopamine agonist has got the highest risk of EDS and sleep attacks [40]. Pramipexole has been found to have the highest potential for EDS [34, 40]. The EDS associated with dopaminergic therapy is also dose-dependent [40, 42]. A study by Hauser et al. reported moderate-to-severe sleepiness among patients with a mean pramipexole dose of 4.0 mg per day [42]. The EDS improved after reduction in the dose or discontinuation of pramipexole. PD patients taking higher doses of dopaminergic therapy have also been found to be more prone to irresistible sleep attacks [34]. There has been a trend for a higher dosage of bromocriptine and pergolide in patients experiencing sleep attacks [40].

In addition to these dose-related effects of DA agonists on sleep, there are several other patient and disease-related factors that can predispose PD patients to sleep attacks. Age [40], male sex [36], disease duration [36, 40], disease severity [36, 48], co-existent depression [48], higher baseline Epworth sleepiness score (ESS) [40], early arousals and daytime napping [43] have also been considered as risk factors for developing sleep attacks. Daytime napping and use of benzodiazepines could have a protective role in preventing sleep attacks [43].

41.4.3 Evaluation of Sleep Dysfunction Due to DA Agonists

Patients taking DA agonists presenting with EDS should be evaluated in detail by obtaining information related to clinical problems, sleep patterns and disturbances, along with an enquiry into medications, family and psychosocial backgrounds. Physical examination must be done and if necessary, an objective sleep assessment with polysomnography (PSG) and multiple sleep latency test (MSLT) should also be done. Various subjective sleep assessment scales should be used to assess the magnitude and category of sleep dysfunction. Epworth sleepiness scale (ESS) is a commonly used scale to assess the severity of sleepiness. Most of the studies use a score of 10 as a cut-off to determine excessive sleepiness. Stanford sleepiness scale, Pittsburgh sleep quality index (PSQI) and PD sleep scale are few other scales to assess sleepiness [49]. (Please see Chap. 9 for details).

Objective assessment with PSG might be required in selected cases to identify underlying sleep disorders such as obstructive sleep apnea (OSA), chronic unexplained insomnia, periodic limb movement disorder, parasomnia and REM sleep behaviour disorder (RBD). They cause night sleep fragmentation and might be a contributing factor for the EDS. Although not routinely practised, MSLT and maintenance of wakefulness test may be done when PD patients exhibit narcolepsy-like behaviour. In a study by Arnulf et al., 21 of 54 patients with PD treated with levodopa (L-dopa) met the PSG criteria of narcolepsy [50]. A sleep diary or an actigraphy can also be used to diagnose EDS.

The scales used in subjective assessment have their advantages and disadvantages. In a study by De Cock et al., the high frequency of self-reported EDS in PD patients was not corroborated by short sleep latency in the MSLT [51]. At present, however, there are no uniform assessment criteria for EDS and a more standardized assessment of EDS is necessary.

41.4.4 Management of EDS and Sleep Attacks

Management of EDS and sleep attacks is complex because of the heterogeneous causes associated with patients with PD. Treatment must be individualized and directed towards any specific cause if found. Any primary sleep disorder identified during evaluation should be treated accordingly.

41.4.5 Pharmacological Measures

41.4.5.1 Modification in Dopaminergic Therapy

The European Federation of Neurological Societies and Movement Disorder Society recommendations highlight the need to improve nocturnal sleep quality by reducing akinesia, tremor and urinary frequency with appropriate medications; reducing or discontinuing sedative drugs; and reduction of dose or switching to other dopamine agonists to reduce sleep attacks [52].

DA agonists can be given as monotherapy, with a reduced dose, or maybe successfully discontinued altogether. If however, switching of therapy is required, then DA agonists may be replaced by selegiline, amantadine or entacapone which have got no effect on EDS [53, 54]. In a small study by Asai et al., switching treatment to pergolide, a selective dopamine D1/D2 agonist, completely resolved sleep attacks in four patients with PD treated with other DA agonists [55]. Long-acting dopaminergic stimulation may be considered for nocturnal akinesia resulting in subjective improvement in sleep quality [53]. In view of the associated risk, benzodiazepines should be avoided for the treatment of RBD in patients with PD. A practical approach to EDS in patients on DA agonists is illustrated in Fig. 41.1.

41.4.5.2 Specific Pharmacological Agents

A Movement Disorder Society evidence-based review has concluded that there are insufficient data to recommend any specific drugs for long-term management of EDS in PD patients [56]. Limited data exist for the use of drugs like modafinil [57], methylphenidate [58], caffeine [59, 60], sodium oxybate [61, 62] and istradefylline [63] for EDS in PD patients. All these drugs are currently under investigation and further studies are required for establishing their role in the long-term management of EDS.

41.4.6 Non-pharmacological Approach

Supplementary exposure to bright light (i.e. light therapy) has been found to be beneficial in reducing ESS in PD patients [64]. It has been postulated that light therapy improves daytime alertness, nighttime sleep quality and reduces sleep fragmentation by influencing the circadian system and promoting dopamine release [64, 65]. However, further studies are required to determine its optimal timing, dosage and treatment duration.

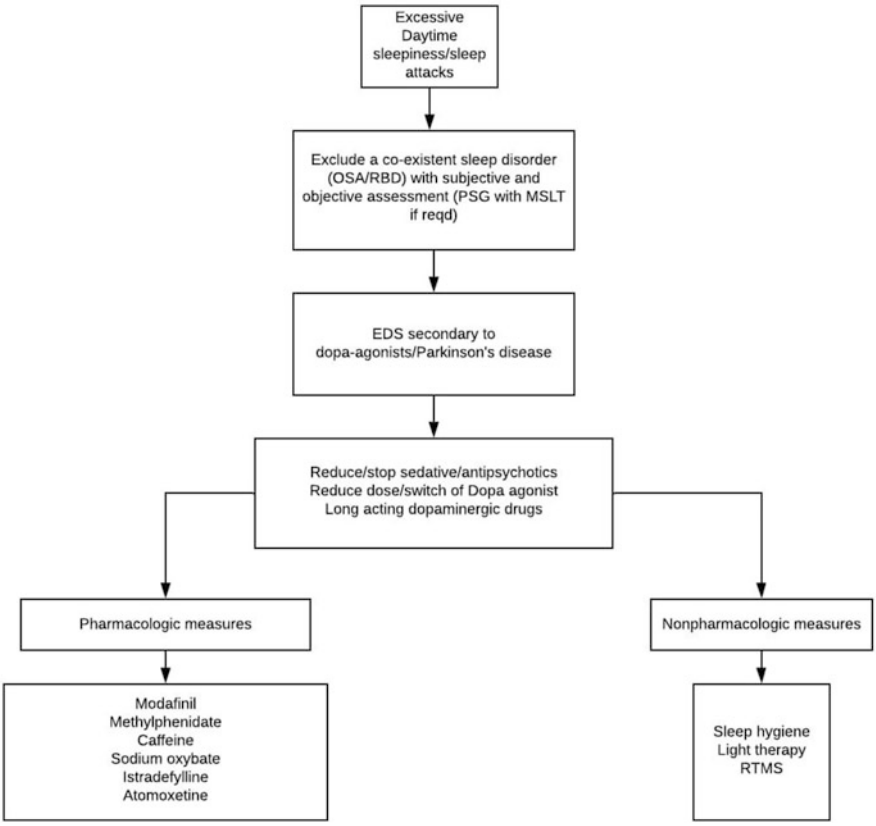

Fig. 41.1 Approach to management of excessive daytime sleepiness in patients with dopamine agonists. *OSA* obstructive sleep apnea, *RBD-REM* sleep behaviour disorder, *PSG* polysomnography, *MSLT* multiple sleep latency test, *EDS* excessive daytime sleepiness, *RTMS* repetitive transcranial magnetic stimulation

41.4.6.1 Hallucinations

Drug-induced hallucinations are encountered in about 40% of PD patients, with sleep disturbances being the strongest predictor [66]. Patients using DA agonists have an increased risk of hallucinations. In advanced PD patients, about 6% of the patients on prolonged release rotigotine [67] and over 10% of patients using pramipexole had hallucinations [68]. In cases of significant hallucination and sleep disturbances, dopamine agonist can be given in reduced dosage or switched to alternative therapy.

41.5 Conclusion

Dopamine agonists have been shown to have a significant effect on sleep in animal studies. They improve the motor symptoms, reduce the "off" periods and alleviate pain as well as dyskinesia in patients with PD. These effects are beneficial for subjective improvement in sleep quality. However, many sleep-related adverse effects emerge with their chronic usage mainly such as excessive daytime sleepiness and sleep attacks, which can cause severe deterioration in the quality of life of PD patients. Proper evaluation of sleep complaints of PD patients, proper choice of DA agonists and the optimal dosage can address the sleep-related adverse events. Some pharmacological interventions have shown promising results in addressing the EDS, however further studies are warranted before they can be approved for clinical use.

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