Introduction to Sleep and Sleep Disorders

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Introduction

Sleep is a brain state in which there is diminished responsiveness and motor inhibition, with associated recumbence and closed eyes. Sleep represents an important aspect of life, constituting about a third of our life. While the exact function of sleep is unknown, it is thought to be required for energy conservation, resetting of the body, and memory consolidation, with significant complications arising in those with sleep problems [1]. Due to challenges in daily living and the easiness of cutting back on sleep, it is thus not shocking to find 60 million Americans struggling from sleep disorders [2]. Some surveys suggest a continuous decrease in the average duration of sleep: in 1960 Americans slept 8–8.9 hrs on average, while in 1995 this number decreased to 7 hrs, with more than 30% of adults sleeping less than 6 hrs in 2004 [3, 4, 5]. Both direct and indirect economic burden as a consequence of sleep problems was estimated at $924 for young individual and $1,253 per geriatric patient compared to those without insomnia in a 2007 analysis of Americans [6]; a total of $13.9 billion in lost revenue was assessed in 1995, with $1.97 billion spent on hypnotics in the United States [7].

Disruption of sleep and the presence of sleep disorders can lead to and even worsen psychiatric (e.g., depression and anxiety), medical (e.g., diabetes mellitus [DM], strokes), and cognitive conditions (e.g., problems with memory consolidation) [1]. In addition, about 328,000 accidents occur yearly in the United States due to drowsiness and/or fatigue, with up to 21% involving fatalities [8]. Moreover, individuals with sleep problems have a 1.62 times higher risk of being injured than workers without sleep problems, with up to 13% of work injuries can be attributed to sleep problems [9]. To highlight the importance of sleep on cognition, the Accreditation Council for Graduate Medical Education (ACGME) changed their regulations for trainees in 2011 to cap their weekly working hours at 80 after a

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cornerstone study showed a higher number of errors among intensive care unit residents working continuous hours compared to those on a limited schedule [10].

While training of medical students and residents on sleep medicine tend to be minimal, many specialties are offering sub-specialization in the field. The American Board of Medical Specialties (ABMS) has sub-specializations in sleep medicine for residents in internal medicine, family medicine, psychiatry, neurology, and anesthesia. In addition, dentists can also specialize in sleep medicine given their significant role in the evaluation of oral causes of sleep apnea and management of dental devices to treat it. However, residency training in sleep medicine for all of these specialties is inadequate, leaving only a small number of practitioners knowledgeable about this field. Compared to a 1978 survey that found only 46% of surveyed medical schools offered education or training for sleep disorders, a slight increase to 55% was reported in 1995 [11, 12]. Internal medicine trainees had the highest exposure to sleep medicine (27.1%), followed by psychiatry (25.9%) and neurology (19.3%) residents, with only 7.2% of pediatrics residents receiving some training. However, the average duration of teaching for sleep medicine was only 2.1 hrs [13]. Another survey completed by neurology residency program directors conducted in 2010 found 81% of their programs had a formal sleep rotation [14]. In addition, in psychiatry 34% of chief residents reported having elective rotations in sleep available at their institution [15]. While previous studies showed improvement in sleep education among trainees, this later study suggested a possible decline in sleep medicine education among psychiatry residents over time. In addition, an international survey involving 12 countries in 2011 further suggested that the average sleep training is rather limited given the importance of sleep as less than 2.5 hrs of sleep education was provided in medical schools, with 27% not having any [16]. The United States and Australia were the only two countries with an average of more than 3 hrs of education.

In addition to the high prevalence of sleep problems and the often minimal education about them, it is important to note how sleep can affect the outcome of psychiatric conditions. In the past, it was thought that sleep problems would resolve once psychiatric conditions (e.g., depression) were treated. However, recent studies suggest that sleep problems, while often related to psychiatric disorders, are distinct from psychiatric disorders and that not directly addressing sleep problems can lead to relapse of psychiatric disorders or hinder recovery [14]. This was one of the reasons for removing subtypes of insomnia (e.g., insomnia due to psychiatric conditions, and insomnia due to substances) in favor of only acute and chronic insomnia as diagnostic criteria in the *International Classification of Sleep Disorders* – Third Edition (ICSD-3) [17]. While physicians tend to prescribe sedating psychotropic medications (e.g., the antipsychotic quetiapine for individuals with bipolar disorder or schizophrenia, and sedating antidepressants like trazodone or mirtazapine for depressed or anxious persons), studies suggest that these medications might not be sufficient to treat insomnia. Furthermore, some psychotropic medications can cause significant metabolic syndrome (including symptoms of weight gain), increasing the risk of obstructive sleep apnea. Similarly, some of the serotonergic agents might increase the occurrence and severity of restless leg syndrome (RLS) leading to sleep deterioration.

Understanding normal sleep and screening for sleep disorders are an essential first step toward improving general health. The aim of this chapter is to provide knowledge about normal sleep, sleep evaluation, and an introduction to the treatment for sleep problems. Psychiatrists, psychologists, and other behavioral health professionals should incorporate screening of sleep problems in their patient assessments.

Functions of Sleep

While the functions of sleep are still not completely understood, disorders of sleep can lead to significant health consequences. Many of the assumed functions of sleep are derived from studies of the consequences of sleep deprivation.

Memory and Sleep Memory formation is divided into a stabilization stage occurring while awake (i.e., memory encoding) and an enhancement or consolidation stage that largely occurs during sleep [1]. The enhancement stage can help to restore lost memories and/or form new ones. Both slow wave sleep (SWS) and rapid eye movement (REM) sleep stages are essential for memory consolidation, with the former causing reactivation and redistribution of hippocampal memories (and consolidation of declarative memory) and the latter causing an increase in cortical synaptic memory consolidation (and consolidation of procedural and emotional aspects of memory) [18]. While longer durations of sleep (i.e., 8 hrs) showed the greatest positive effects on memory consolidation, short and ultrashort (e.g., 6 mins) sleep durations also showed improvements in memory consolidation compared to those with sleep deprivation. In addition, the closer the sleep onset is to the time of learning (e.g., within 3 hrs), the greater the consolidation effect was observed compared to when sleep onset occurred the next day [19]. Interestingly, some studies suggest that the psychopharmacological inhibition of REM, while expected to worsen memory, actually leads to better procedural memory consolidation in addition to an increase in non-REM (NREM) stage 2 spindle activity [19].

Process of Synapse, Circuit Maintenance, and Sleep Some researchers hypothesize that sleep has a role in achieving neuronal synaptic homeostasis by downscaling synapsis occurring during the day to the most important ones and eliminating unnecessary ones. This focused and preserved synapsis will lead to less energy consumption [20]. This can be understood perhaps more readily using the analogy of storing pictures on the cell phone, and deleting some of these pictures leading to energy conservation in the phone battery consumption. It is important to note that the downscaling of synapsis occurs mainly during SWS due to repeated depolarization–hyperpolarization states and an outcome of decrease in synapsis by 20% [20].

Attention and Working Memory Acute sleep deprivation worsens attention, with errors of omission (e.g., failing to identify a target letter) that are highly erratic (i.e., variable task performance) [21]. While sleep deprivation duration is correlated with the severity of attentional problems, some individuals might be more susceptible to this than others for unknown reasons [21]. Functional imaging has shown a reduction in the dorsolateral prefrontal cortex and intraparietal sulcus activity during sleep deprivation; the latter brain site has been associated with disorders of inattention and impulsivity such as attention deficit hyperactivity disorder and borderline personality disorder [21]. Neuronal network breakdown including the thalamocortical connections and amygdala to dorsolateral prefrontal cortex after sleep deprivation might explain some of these attentional problems [21].

Reward Processing, Dopamine, and Sleep Deprivation Sleep deprivation might lead to hypersensitization in the dopaminergic function of the mesolimbic rewards system, a connection mainly occurring between the ventral tegmental area and the prefrontal cortex. This leads to an incremental impairment of reward discrimination, with individuals sometimes even failing to discriminate between rewards and punishments. Thus, more risky decisions and higher reward sensitivity usually occur among sleep-deprived individuals. In addition, emotionally driven pleasure responses in the amygdala and striatum (including food intake) become impaired in sleep-deprived individuals leading to unhealthy decisions. Normally, during increased prolonged arousal, dopamine increases; however, a decrease in dopamine-2 (D2) and dopamine-3 (D3) receptor internalization occurs during sleep deprivation. An increase in dopamine-1 (D1) stimulation has been linked to increased risk for addictions ranging from overeating to substance abuse [21]. Some researchers have suggested that the presence of insomnia in childhood can lead to increased risk of addiction later in life [22] and increased risk of alcohol relapse following continued insomnia [23].

Brain Energy Conservation, Restoration, and Sleep During NREM, parasympathetic activity is usually increased (with a corresponding decrease in sympathetic activity). This slows heart rate and respiration as well as energy consumption, leading to energy conservation [24, 25]. Removing toxic waste from the brain during sleep has also been proposed as a function of sleep, including the removal of extracellular β-amyloid [25, 26].

Neuroendocrine Modulation, Obesity, Diabetes Mellitus (DM), and Sleep While growth hormone and prolactin increase during sleep, cortisol and thyroid stimulating hormone decrease [27]. Some studies suggest a neuroendocrinal and glucose control modulation function of sleep. In individuals with insufficient sleep duration, ghrelin (a peptide that leads to increased hunger) increases while leptin (a hormone causing satiety) decreases. This leads to dysregulation of appetite causing increased

hunger and increased risk for pathologies related to glucose metabolism and the development of DM [27]. Similarly, hormonal dysregulation (growth hormone, prolactin, and cortisol) has been found following sleep deprivation [27]. Obesity and DM have thus been partially attributed to the lack of insufficient sleep in children, adolescents, and adults [27].

During sleep, noradrenergic tone decreases especially during REM. In cases of insomnia or sleep deprivation, there is lack of this decrease in sympathetic activity. This increase in sympathetic activity can lead to heightened anxiety [21].

Immune Function and Sleep Infections are associated with increased sleep, although it is unclear whether this is due to a response to bacterial products. However, it is known that increased sleep during infection has been linked to lower morbidity and mortality [28, 29], perhaps due to sleep's role in energy conservation.

Normal Sleep and Sleep Architecture

An average adult sleeps 6–8 h, representing a third of our lives. Sleep is divided into two main stages based on findings from electroencephalogram (EEG) waves, eye movements, and chin electromyographic changes detected by polysomnography (PSG): non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is further divided into stages 1 through 3 sleep, with stage 3 (also called slow wave stage [SWS] or delta sleep) historically divided into stages 3 and 4, depending on the percentage of delta waves in each epoch that characterizes this stage. However, this distinction was removed as disorders occurring during stages 3 and 4 are similar. The sleep cycle in adults starts with N1, which highlights the person's drowsiness (sometimes in newborns, sleep can start with the REM stage), followed by N2, and a deeper stage of sleep, N3. REM usually occurs 90–120 min after sleep onset in adults, usually occurring briefly in the first cycle with a gradual increase in its duration as sleep progresses. Conversely, the reverse occurs for NREM sleep (i.e., the ratio of NREM/REM is high initially and decreases later in the night). There are usually four to five NREM/REM cycles during the night.

Non-Rapid Eye Movement Stages (NREM)

Brain waves help detect wakefulness and stages of sleep, with the highest in frequency occurring during wakefulness and slowly decreasing as sleep deepens. NREM sleep is divided into three major stages: a light stage of sleep (stage 1 or N1); a deeper stage (stage 2 or N2); and SWS (also known as stages 3 and 4, N3, or delta wave sleep). The arousal threshold, referring to how readily one is awakened, is lowest during NREM stage 1 and highest in NREM stages 3 and 4. Table 1.1 shows the changes occurring in different wake–sleep stages.

Table 1.1 Sleep characteristics and waves

	Duration	Respiration and HR	Chin activity	Type of waves	Blinking and REM
Wakefulness with eyes open	–	Regular unless controlled voluntarily	High	Beta and alpha	Might have REM due to reading; occasional blinking observed
Wakefulness with eyes closed	–	Regular unless controlled voluntarily	Normal or high	Alpha activity (8–13 Hz) in the posterior head regions	No blinking
N1	1–5%	Regular	Decreased compared to wakefulness	Theta (4–7 Hz)	Blinking and eye movements stop
N2	45–55%	Regular	Decreased compared to wakefulness	K complexes (0.5 s spike) and spindles (12–16 Hz)	No eye movement
N3	5–20%	Regular	Decreased compared to wakefulness	Delta waves (0.5–2 Hz)	No eye movement
REM	20–25%	Irregular and increased	Atonia; penile tumescence	Sew tooth waves (EEG desynchronization)	REM

HR heart rate, *EEG* electroencephalogram, *REM* rapid eye movement

Wakefulness Low-amplitude, high-frequency, desynchronous beta waves characterize brain activities in humans when alert with their eyes open. Synchronized, slower alpha waves (8–13 Hz) in the posterior head region replace beta waves when the person is drowsy and eyes are closed. As eye movements while reading can very easily be confused with the REM stage, it is important to detect the background EEG to confirm this staging. Normal or high chin activity as well as regular breathing is also observed during wakefulness.

Stage 1 (or N1) Stage 1 is the shortest in duration representing 0–5% of total sleep time (TST). It is characterized by theta waves (4–7 Hz), with a subtle slowing in frequency and relaxation of muscular activity (i.e., masseter muscle or chin tone and/or leg muscles) compared to the wake state. Hypnic jerks characterized by sudden muscle contraction, a non-pathological condition, can be observed during this stage and are brief.

Stage 2 (or N2) Stage 2 represents 45–55% of TST and is much more pronounced with the development of sleep spindles (short, rapid, and synchronized bursts of

brain activity with low amplitudes of 7–14 Hz) and K complexes (a brief 0.5 s, but large electric spike). The function of these waves is not clearly understood. No eye movement occurs in this stage.

Stage 3 and 4 (or N3) Stage 3 and 4 represents 20–25% of TST and is characterized by the large amplitude delta waves (large 75 microvolt or 0.5–2 Hz). The only difference between stages 3 and 4 is the percentage of the delta waves (i.e., delta waves span 20–50% of the epoch in stage 3 but more than 50% in stage 4). It is important to note that higher amplitude waves occur during N3 sleep when the person is younger (e.g., a 3-year-old child will have larger and more frequent delta waves than a geriatric individual). Memory consolidation (especially declarative memory) is believed to occur in both N3 stage and the REM stage.

Rapid Eye Movement Stage (REM)

In the REM stage, all muscles except for the ocular, heart, and breathing muscles are in complete atonia. Although dreams occur in all stages of sleep, it is during REM that vivid dreams occur. Individuals who lack atonia during REM and who act on their vivid dreams will sometimes injure their bed partner due to their movements (i.e., REM behavior disorder [RBD]). While most individuals have a lag time of 90–120 min before initiating REM, individuals with a short REM latency (as in narcolepsy) will present with hypnagogic hallucinations (i.e., they initiate dreaming while awake, which the individual may perceive as hallucinations). The classic sleep paralysis in narcoleptics occurs when they wake in the morning but cannot move their muscles due to continued atonia while in the REM stage. Similarly, the sudden loss of muscle tone (i.e., cataplexy) that occurs with emotional stimulation in narcolepsy is due to the rapid onset of REM with its atonic state. It is important to note that REM starts during the first 60–120 min of sleep initiation (depending on the individual's age), with shorter durations of REM occurring in the initial phases and longer durations toward the second half of the night. In addition, REM density, defined as the number of eye movements/time, increases in the second half of the night. Thus, disorders elicited during REM occur more often in the second half of the night (an important question to ask patients or their partner is "when does the disorder occur in the night?"). Vital signs including breathing are usually irregular and variable during the REM stage. Electroencelphalogram (EEG) shows irregular wave amplitude (also known as saw teeth activities) of the brain during this stage. Phasic waves are observed during rapid eye movements occurring in the pons, lateral geniculate thalamus, and occipital cortex [30]. Both penile tumescence in males and vaginal engorgement in females occur during this stage. In addition, brain metabolism increases during this stage. The REM stage duration significantly decreases in individuals prescribed serotonergic agents, stimulant medications, and/or benzodiazepines (BNZs).

Process C and Process S

In the early 1980s, the Swiss sleep researcher Alexander Borbely proposed that sleep depends on two processes: Process C, involving circadian rhythms, and Process S, involving sleep/wake homeostasis [31]. Process S is the propensity to feel sleepy with longer periods of wakefulness. However, after sleeping, the propensity to sleep decreases to its lowest point, slowly increasing as the person stays awake. There is a neurochemical basis for Process S as adenosine increases in the basal forebrain and inhibits A1 receptors, subsequently leading to an inhibition of wakefulness. In addition, A2 receptors induce Fos expression leading to sleepiness. Coffee and caffeinated beverages are adenosine receptor antagonists, thus leading to increased alertness.

Process C involves our internal clock (circadian oscillator), centered in the suprachiasmatic nucleus in the anterior hypothalamus, and stimulates sleep to occur at certain times and wakefulness at others. Although it depends in part on time cues that include light exposure and social cues (e.g., food intake, going to work/school, presence of a clock; these are usually referred to as Zeitgebers), [32] its duration typically exceeds the 24-hour day in the absence of cues (average around 24.9 h). Studies suggest that during sleep deprivation, the frontoparietal area is sensitive to sleep pressure (Process S), while the thalamus and basal ganglia are more affected by circadian rhythms (Process C) [33].

Understanding the effects of photoentrainment and sleep becomes very important. When light stimulates certain retinal cells containing melanopsin, through the retinohypothalamic tract, it leads to stimulation of the suprachiasmatic nucleus of the hypothalamus to inhibit melatonin secretion (which helps to control body temperature, hormones including cortisol, and vital sign variation during sleep). Through the preganglionic sympathetic neurons in the lateral horn of the spinal cord, light/darkness affects the superior cervical ganglia (through norepinephrine), which have their postganglionic neurons in the pineal gland, which secretes melatonin. The pineal gland increases the enzyme *N*-acetyltransferase to form *N*-acteyl-5-methoxytryptamine from tryptophan leading to the increased formation and secretion of melatonin. Thus, with gradual onset of darkness, melatonin is secreted. Dim light melatonin onset (DLMO) refers to the slow increase in melatonin secretion (until a level causing sleepiness is reached) as a response to darkness. DLMO occurs 2 hrs before the onset of sleep time, and when melatonin reaches a certain level, individuals start feeling sleepy. It is thus not surprising to find delayed sleep onset (circadian rhythm phase delay) among people who are exposed to late night light exposure from cell phones, computer screens, TV, or other devices.

Over the counter melatonin, which stimulates melatonin 1 and 2 receptors in the brain, and melatonin agonists (Rozerem) have been used to treat certain forms of insomnia. Three possible mechanisms of melatonin or its agonist exist: it is theorized to work by either causing a shift in circadian rhythm phase, reduction in body temperature, or by directly acting on sleep centers causing sleepiness [34]. In addition, agomelatine has been suggested to regulate circadian rhythm and also act as an antidepressant. Thus, some researchers recommend the use of much lower melatonin

doses (i.e., 0.3–0.5 mg) 3–5 hrs before the target bedtime as a way to stimulate a melatonin surge (or DMLO). Calcification of the pineal gland in the geriatric population can lead to circadian rhythm problems and thus cause deficiency in melatonin production. Due to the overlap between Process C and Process S, the lowest alertness levels occur at 4–6 a.m. and, to a lesser extent, around 2–4 p.m.

Sleep Changes Over Life Stages

Sleep Duration and Age Sleep duration varies significantly depending on the age of the individual, with a gradual decrease as the individual ages. According to the National Sleep Foundation, recommended sleep durations are as follows: newborns (<3 months) are expected to sleep 14–17 hrs a day; infants (3–11 months) 12–15 hrs; toddlers (1–2 years) 11–14 hrs; preschoolers (3–5 years) 10–13 hrs; school-aged children (6–13) 9–11 hrs; teenagers (14–17) 8–10 hrs; younger adults (18–25) 7–9 hrs; adults (26–64) 7–8 hrs; and geriatric population 7–8 hrs [35, 36].

Sleep Architecture and Children In newborns, due to the lack of typical waves that characterize sleep stages (i.e., sleep spindles and K complexes that characterize stage 2 NREM sleep develop at 3 and 6 months after birth, respectively), a different type of sleep staging is observed. Sleep at this age is divided into an active stage (equivalent to REM sleep), "non-active" stage (equivalent to NREM), intermediate stage (having characteristics of both previous stages), and indeterminant stage (cannot be characterized as either of the first three stages). Spindles occur at 2–3 months after birth, K complexes at 4–6 months, and delta waves at 4–5 months [37, 38]. Thus, waves characteristic of sleep stages in older children and adults emerge by 6 months, when sleep is divided into NREM and REM sleep.

In newborns, sleep usually starts with the onset of an active sleep stage (or what is equivalent to REM in adults) and its sleep percentage starts to gradually decrease at 3 months [38]. This is in comparison to older children and adults in which it is pathological if REM occurs within the first 15 min of sleep and might signify insomnia or narcolepsy. In adults, REM latency (time from sleep until the first occurrence of REM sleep) is 90–120 min. However, REM latency and sleep cycles tend to be shorter in infants (45–60 min cycles) and older children (60–90 min cycles). In addition, active sleep (REM equivalent) constitutes 50% of the infant's sleep, 30% at age two, and only 20–25% in older children and adults.

Consolidation of Night Sleep and Napping. In newborns, sleep is usually interrupted every 2–4 hrs due to their frequent need for nutrition. Consolidation of nighttime sleep usually occurs around 6 months, at which time parents can sleep better [38]. Sleep is further consolidated at night as napping gradually becomes less frequent, with most children ceasing to nap by 5 years of age. In some cultures, however, adults usually continue to have an afternoon nap (around 4–5 p.m.). In the

geriatric population, daytime napping can occur at a higher frequency due to daytime fatigue and the interruption in their nighttime sleep.

Sleep Architecture and Geriatrics Compared to younger adults, geriatric individuals have the same sleep latency (SL) and REM duration, but exhibit a decrease in SWS stage duration, total sleep time (TST), and sleep efficacy (SE). In addition, increased waking after sleep onset (WASO) occurs as well as a possible albeit slight increase in stages 1 and 2 sleep. Aging and associated neuropathological processes affecting the suprachiasmatic nucleus, medical issues (e.g., pain, frequent urination, polypharmacy), comorbid sleep problems (e.g., increased prevalence of sleep apnea), and psychiatric problems (e.g., depression and anxiety) can further affect sleep among geriatric individuals.

Circadian Rhythm and Age During the adolescent period, there is a tendency for the development of circadian rhythm delay. This means that adolescents usually go to sleep and wake up at later times than normal, with maintenance of sleep duration if given the opportunity. This often becomes problematic as youth get older and school start time becomes earlier. In addition, exercising relatively late at night might increase the risk of such phase delay. The use of electronics (especially with schoolwork necessitating computer use) can further complicate adolescent sleep. Thus, sleep deprivation and daytime sleepiness is not uncommon in this age group. A growing number of school districts, however, are starting school somewhat later in the morning as research indicates that later starting times are associated with longer sleep durations [39]. Additionally, later start times were associated with less daytime sleepiness [40]. In contrast to adolescents, geriatric individuals often develop circadian rhythm advance (i.e., early sleep onset and early morning awakening) with fragmented sleep [41]. Due to the decrease in delta waves, N3 usually is significantly shorter in this older population compared to their younger counterparts.

Neurobiology and Neuroanatomy of Sleep

While aspects of sleep continue to be a mystery, there has been a significant increase in knowledge about the neurobiology of the sleep–wake cycle. Table 1.2 reviews specific brain areas and neurotransmitters involved in sleep–wake cycles. Wakefulness is promoted by activity in the pons, midbrain, and posterior hypothalamus through the monoamine neurotransmitters including acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin. Damage to the posterior hypothalamus causes a coma-like state [42]. NREM sleep, on the other hand, depends on activity in the preoptic area in the anterior hypothalamus and forebrain through gamma-aminobutyric acid (GABA) and galanin neurotransmitters. Thus, damage to these centers will lead to loss of the major inhibitory neurotransmitters leading to insomnia [42]. REM initiation depends on pontine and midbrain

Table 1.2 Brain areas and neurotransmitters involved in the sleep–wake cycle

	Brain centers	Neurotransmitters	Function	Pathology	Medications
Wakefulness	Lateral and posterior hypothalamus stimulate dorsal raphe (orexin A/B), locus coeruleus (orexin A), and tuberomammillary nucleus in posterior hypothalamus (orexin B)	Orexin		Deficiency of orexin leads to narcolepsy	Suvorexant is an orexin antagonist that helps elicit sleep
	Dorsal raphe nucleus (orexin A/B)	Serotonin	Causes wakefulness and decreases REM sleep		Stimulation by SSRIs causes insomnia; however, agomelatine blocks 5-HT2 receptors inducing NREM sleep
	Locus coeruleus (orexin A)	Norepinephrine	Highest in wakeful state, less in NREM, and lowest in REM sleep		Stimulation by SNRIs cause insomnia; alpha-1 antagonist (prazosin) help decrease nightmares/PTSD symptoms, while alpha-2 antagonist (clonidine) causes sleepiness
	Reticular formation (lateral dorsal tegmentum and pedunculopontine tegmentum)	Acetylcholine	Discharge during wakefulness and REM-On (which induces REM onset) and inactive in NREM	Decreased acetylcholine in dementia patients is often associated with excessive sleepiness	
	Substantia nigra and ventral tegmental nucleus	Dopamine	Causes wakefulness	In parkinsonism, damage to SN leads to sleepiness	Stimulants increase dopamine, causing wakefulness; antipsychotic medications cause sedation; ropinirole and pramipexole induce sleepiness by auto-activation of inhibitory D2/D3 receptors

(continued)

Table 1.2 (continued)

	Brain centers	Neurotransmitters	Function	Pathology	Medications
	Tuberomammillary nucleus (orexin B) in posterior hypothalamus	Histamine projections to cerebral cortex, amygdala, substantia nigra	Active in wake, less in NREM, and silent in REM	Lesions of the posterior hypothalamus cause coma-like state [23]	Antihistaminic medications (Benadryl or diphenhydramine) cause sedation
NREM	Ventrolateral preoptic area in anterior thalamus Forebrain	GABA Galanin	Inhibited by monoamines and acetylcholine		Benzodiazepines and gabapentin cause sedation
REM [22]	Subcoeruleus nucleus Dorsal paragigantocellular reticular nucleus Pontine Caudal midbrain	REM-On: – acetylcholine, glutamate, GABA, and glycine REM-Off: – noradrenaline, adrenaline, serotonin, histamine, and GABA.	Monoamines are least active during REM		SSRIs and SNRIs inhibit REM duration; norepinephrine is inactive during cataplexy; thus, venlafaxine has been used to treat cataplexy

REM rapid eye movement, *SSRIs* selective serotonin reuptake inhibitors, *NREM* non-rapid eye movement, *SNRIs* selective norepinephrine reuptake inhibitors, *PTSD* post-traumatic stress disorder, *SN* substantia nigra, *GABA* gamma-aminobutyric acid

structures, with acetylcholine, glutamate, and glycine being important for REM initiation. It is thought that the subcoeruleus nucleus (in the mesopontine junction) is the main REM generating center, with stimulation causing REM atonia (mainly through GABA/glycine in ventromedial medulla) while damage to it causes a reduction in REM sleep [43].

Sleep Disorder Classifications

Three major classification systems exist and are often used to classify sleep disorders: the *Diagnostic and Statistical Manual of Mental Disorders* – Fifth Edition (DSM-5) [44], the *International Classification of Sleep Disorders* – Third Edition (ICSD-3) [17], and the *International Statistical Classification of Diseases and Related Health Problems* – Tenth Edition (ICD-10 [40]; see Table 1.3). Within the

Table 1.3 Classification of sleep disorders according to the *Diagnostic and Statistical Manual of Mental disorders* – Fifth Edition (DSM-5), *International Classification of Sleep Disorders* – Third Edition (ICSD-3), and *International Statistical Classification of Diseases and Related Health Problems* – Tenth Edition (ICD-10)

Classification	Types
DSM-5 (Sleep–wake disorders)	Insomnia Hypersomnia Narcolepsy Breathing-related sleep disorders: obstructive sleep apnea–hypopnea, central sleep apnea, sleep-related hypoventilation Circadian rhythm sleep–wake disorders Parasomnia: Non-rapid eye movement (NREM) sleep arousal disorders, nightmares, REM behavior disorder (RBD) Restless leg syndrome (RLS) Substance- or medication-induced sleep disorders Others: other specific insomnia, unspecified insomnia, other specified hypersomnolence, unspecified hypersomnolence, other specified sleep–wake and unspecified sleep–wake disorders
ICSD-3	Insomnia Sleep-related breathing problems Central disorders of hypersomnolence Circadian rhythm sleep–wake Parasomnias Sleep-related movement disorders (i.e., restless leg syndrome, nocturnal seizures) Other sleep disorders
ICD-10	Insomnia Hypersomnia Circadian rhythm problems Sleep-related breathing problems Sleep-related movement disorders (i.e., restless leg syndrome, nocturnal seizures) Parasomnias Other sleep category and drug-induced sleep disorders

United States, DSM-5 is the primary manual used to diagnose psychiatric disorders, whereas in most other countries ICD-10 is used. Sleep specialists, especially in the United States, usually use ICSD-3.

In DSM-5, sleep disorders were divided into ten major categories: insomnia, hypersomnia, narcolepsy, breathing-related sleep disorders (obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation), circadian rhythm sleep–wake disorders, non-rapid eye movement (NREM) sleep arousal disorders, nightmares, REM behavior disorder (RBD), restless leg syndrome (RLS), and substance- or medication-induced sleep disorders.

In contrast, the ICSD-3 has divided sleep disorders into seven major categories depending on the associated signs and symptoms. If the duration of sleep is affected, this can lead to either insomnia (sleeping less than expected) or hypersomnia (sleeping longer than expected). If the individual's sleep–wake cycle does not match the expected sleep–wake cycle, then circadian rhythm problems occur. One of the most frequently used diagnostic categories is sleep-related breathing problems that include obstructive sleep apnea. In addition, sleep-related movement disorders include neurological issues (i.e., restless leg syndrome, nocturnal seizures). Parasomnias are often encountered in children and include sleep walking and sleep talking. A final sleep category falls under the terminology of "other sleep category" for those problems that do not meet diagnostic criteria elsewhere.

The ICD-10 classification system for sleep disorders is similar to that of ICSD-3, with the addition of drug-induced sleep disorders as a diagnostic category. While the aim of these classification systems is to bring uniformity and consistency in diagnoses, differences in diagnostic criteria exist across systems (see Chap. 2). As such, we will focus on the use of the ICSD-3 classification because it focuses on sleep disorders in a more comprehensive manner, while highlighting differences from the other two classification systems.

Effects of Psychotropic Medications on Sleep

Total Sleep Time and Sleep Efficacy Sedating psychotropic medications that work through histamine and alpha-1 blockage (i.e., trazodone, mirtazapine, doxepin, risperidone, quetiapine, and olanzapine) can lead to increases in TST [45]. Among psychotropic medications (even the sedating ones), low-dose doxepin is the only medication approved by the Food and Drug Administration (FDA) to treat insomnia. Other psychotropic medications have not shown significant efficacy in treating insomnia, with a growing concern that the use of second-generation antipsychotics can increase risk of metabolic syndrome and extrapyramidal side effects [46]. However, benzodiazepines and Z-drugs (i.e., zolpidem, zopiclone, eszopiclone, and zaleplon) increase TST and sleep efficacy while decreasing REM, and thus can be helpful in treating insomnia and REM behavior disorder (RBD). In comparison, monoamine oxidase inhibitors (MAOIs) can lead to insomnia by prolonging sleep latency (SL) and increasing arousals [45].

REM Stage In addition, psychotropic medications can also lead to inhibition of REM duration due to their stimulation of serotonin and norepinephrine (thus masking narcolepsy signs during polysomnography [PSG] and mean sleep latency test [MSLT] results through stimulation of 5-HT1A) and to sleep fragmentation (through 5-HT2 agonist and alpha-2 inhibition effects). It is important to note the presence of eye movements, which can be confused with REM, during NREM sleep in individuals taking selective serotonin reuptake inhibitors (SSRIs), especially fluoxetine. Since the omnipause neurons in the brain stem inhibit saccadic eye movements, the increase in serotonin from SSRIs will lead to inhibition of the "omnipause" neurons causing the occurrence of saccadic eye movements (also known as "prozac eyes"). This latter phenomenon was found in 48.8% of individuals treated with fluoxetine compared to only 5.8% of individuals on tricyclic antidepressants [46].

Movement Disorders Serotonergic agents (i.e., antidepressants and/or atypical antipsychotic medications) have been shown to often increase the occurrences of RLS (with an onset before sleep, but can also lead to an interruption in sleep), periodic leg movements (PLMS), and/or bruxism (teeth grinding). The antidepressant bupropion has the least negative impact on these side effects and might theoretically improve RLS due to its dopaminergic stimulation. Similarly, gabapentin and BNZs have been used off-label to treat RLS.

Obstructive Sleep Apnea Many psychotropic medications, especially antipsychotic drugs, can lead to weight gain and increased risk of OSA. Some studies suggest this increased risk is independent of the antipsychotic medication's weight gain effects, possibly acting through reduction in the hypoglossal nerve activity during inspiration [47, 48].

Interaction Between Sleep Disorders, Psychiatric Complications, and Medical Problems

Although the function of sleep is yet to be fully understood, a direct bidirectional relationship between sleep disorders and both medical and psychiatric disorders are well delineated. For example, in children with obstructive sleep apnea (OSA), attention deficit hyperactivity-like symptoms [49, 50] and depression [51] have been reported. Similarly, a bidirectional relationship is observed in manic individuals with a lack of sleep precipitating the onset of mania and manic episodes leading to a decreased need for sleep. Accordingly, studies suggest that sleep disorders need to be addressed during the treatment of psychiatric disorders to better attain remission to euthymia. Chapter 17 discusses this relationship in more detail.

Similarly, a higher prevalence of diabetes mellitus (DM), cardiovascular complications (i.e., hypertension, strokes, and heart disease), obesity including high (HDL) and low-density lipoprotein (LDL) levels [52], and even cancer have been linked to

untreated OSA. In addition, OSA severity is associated with an increased prevalence of hypertension, leaving some to suggest treatment resistance to such medical and psychiatric complications if OSA is not addressed [53, 54].

Sleep Assessment Measures

The assessment of normal sleep can include clinical interviews, questionnaire-based self-report scales, and the use of equipment (e.g., to conduct polysomnography). Clinical interviews may inquire about one's sleep pattern including naps, work/academic schedule, food intake, and screening for specific sleep disorders including OSA. Self-report questionnaires include sleep logs (recording when the person went to sleep, how often and how long they had arousals, and what time s/he woke up during a 1–2 week period), the 7-item Insomnia Severity Index (ISI) to screen for insomnia, and the 8-item Epworth Sleepiness Scale (ESS) to screen for daytime sleepiness.

Similarly, there are objective measures, some of which are less sensitive compared to polysomnography (PSG), including actigraphy (a sensor worn to measure movement, based on the assumption that the person is asleep if they do not move) and pulse oximetry (measuring oxygen saturation), while others measure autonomic activities that have been correlated to sleep. Nocturnal pulse oximetry has been used to detect any decrease in oxygen during sleep, suggesting the occurrence of respiratory events. Home sleep testing (HST), which measures airflow, chest expansion (or lack of), and nocturnal oximetry, has been increasingly used due to its easy accessibility, especially for individuals with developmental disorders or those with anxiety disorders who might not tolerate polysomnography, and the lower cost (compared to PSG). However, PSG (i.e., a "sleep study") remains the gold standard method for diagnosis of sleep disorders. PSG records brain waves, blood oxygen levels, heart rate, breathing, and eye and leg movements to assist in identifying sleep disorders. Thus, for certain populations (e.g., people with significant metabolic syndrome and/or pulmonary complications), a HST is not preferred because it is less sensitive in detecting respiratory events. PSG is the standard of practice for pediatric populations as well, given the lower scoring cutoff used in this population, and thus any missed events by HST (compared to PSG) might lead to less accurate classification of the respiratory events (see Chap. 7), while many insurance companies require the PSG study to be used initially for diagnosis.

PSG includes EEG leads around the eyes to depict the eye movements (i.e., to diagnose rapid eye movements [REM] stage), around the masseter muscle (to detect teeth grinding and helps in staging of sleep including atonia during REM), and around the bilateral limb to diagnose periodic leg movements (i.e., individuals might move their limbs often during sleep, interrupting it). In individuals suspected of having seizure activity, extra EEG leads are used to better detect abnormal brain activity (i.e., epileptic activity). Airflow sensors include pressure and thermal flow to both the nose and mouth (to diagnose apnea–hypopnea index, which is the number of respiratory events per hour and is critical to the diagnosis of apnea). A snoring microphone is

available to detect snoring. Two chest and abdominal belts are available to assess the extent of breathing and chest/abdominal expansion. Oximetry (and in pediatrics, end tidal carbon dioxide detection) is available to detect oxygen level. In comparison, HST has limited recording capabilities, which include nasal sensor for airflow detection, one abdominal belt, and pulse oxygenation (variable forms of equipment and information leads are available). A newer form of in-home sleep study (WatchPAT) depends on the vascular sympathetic activity and involves attaching fewer leads. Chapter 7 discusses respiratory descriptors in detail.

Conclusion

Sleep is a very complex process that is necessary for living organisms. While its exact function is not completely understood, its abnormalities can lead to significant medical and psychiatric complications. The overlap in neurotransmitters between sleep and psychiatric conditions further highlights the importance of addressing sleep disorders in individuals with psychiatric complications.

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