Physiology of Sleep and Diagnosis: Basic Information for Dentists

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Abbreviations

AHI	Apnea-hypopnea index
ATP	Adenosine triphosphate
BZD	Benzodiazepine
CEMG	Chin electromyogram
CNS	Central nervous system
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GH	Growth hormone
GHB	Gamma-hydroxybutyrate
HRV	Heart rate variability
HSAT	Home sleep apnea test

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LAMF	Low-amplitude mixed frequency
LC	Locus coeruleus
LDT	Lateral dorsal tegmentum
MAO	Monoamine oxidase
NREM	Non-rapid eye movement
OC	Outer canthus
OSA	Obstructive sleep apnea
PCO_2	Partial pressure of carbon dioxide
PFR	Pontine reticular formation
PM	Portable monitor
PPT	Pedunculopontine nucleus
PSG	Polysomnography
RDI	Respiratory distress index
REM	Rapid eye movement
RIP	Respiratory inductance plethysmography
SCN	Suprachiasmatic nucleus
SEM	Slow eye movement
SH	Sleep hygiene
SpO_2	Oxygen saturation
SRBD	Sleep-related breathing disorder
SWA	Slow-wave activity
SWS	slow-wave sleep
THC	Marijuana
TSH	Thyroid-stimulating hormone
TST	Total sleep time
VLPO	Ventrolateral preoptic
WASO	Wake after sleep onset

2.1 Introduction

Normal sleep is a state of unconsciousness in which the brain is more responsive to internal and external environmental stimuli. The reversibility of this process distinguishes sleep from other states of unconsciousness. The human brain goes to sleep gradually and becomes less responsive to visual, somatosensory, auditory, and other environmental stimuli during the transition. During the sleep state, there is reduction of responsiveness to external sensory stimuli, associated with closed eyes, limited muscle activity, and recumbent position. During sleep, the body is in a rest and restoration state, while the brain is in a state of suspension of consciousness.

Sleep is a process for neuronal recovery and synaptic plasticity, which in turn is crucial for brain function and performance [1, 2]. Sleep is a reversible state of behavioral quietness and lack of responsiveness to normal stimuli. It is opposite to the state of wakefulness where there is an awareness of the surrounding environment and normal responsiveness to stimuli is present. There are three well-defined

states of being: wakefulness, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep [3]. Even though each of the states of sleep serves a vital role in the maintained function of all animals, as demonstrated by the physical deterioration and eventual death that some animals experience with sleep deprivation, there still remains a vast deficit in the fundamental understanding of sleep's purpose [4–6].

Sleep has its own unique effects on the body systems. It influences autonomic changes involving the cardiovascular, respiratory, and thermoregulatory systems. The cardiovascular physiological changes during sleep are a reduction in the heart rate, cardiac output, and blood pressure. Systemic vascular resistance and the stroke volume remain unchanged. Ten percent reduction in blood pressure is known as nocturnal dip. Only the metabolic system drives ventilation during sleep, as opposed to metabolic and voluntary drive during wake. Body temperature is linked to the sleep-wake cycle but is independent of the circadian rhythm. Sleep also promotes neuronal function, increases immune defense, and is essential for growth and development [7].

2.2 Generation and Maintenance of Sleep and Wakefulness

Cortical activation necessary to maintain wakefulness is supported by a network of subcortical structures and pathways. Major neurochemicals of this "ascending arousal system" include excitatory norepinephrine arising from the locus coeruleus (LC), serotonin from the midline raphe nuclei, histamine from the tuberomammillary nucleus, dopamine from the ventral periaqueductal gray matter, acetylcholine from the pedunculopontine tegmentum, and the laterodorsal tegmentum of the pons and orexin from the perifornical area. Despite their apparent redundancy, normal behavioral functioning may require all of these arousing systems.

Initiation and maintenance of sleep require suppression of activity in the ascending arousal systems. Inhibitory neurons of the ventrolateral preoptic (VLPO) area, which remain active throughout sleep, accomplish the maintenance of sleep [8]. The molecular "triggers" which activate the VLPO and initiate sleep onset have not been fully defined, but a substantial body of evidence points to extracellular adenosine as a candidate. Adenosine accumulates in the basal forebrain during wakefulness and diminishes with ongoing sleep [9]. Adenosine receptors are expressed in the VLPO, and adenosine activates VLPO neurons in vivo, making it a reasonable candidate for the "sleep switch." Caffeine and theophylline are potent adenosine receptor antagonists, which may form the basis for their well-known alerting effects.

Sleep is not a homogenous process. Two fundamentally distinct types of sleep exist, REM sleep, which is associated with active dreaming, and NREM sleep. Switching between NREM and REM sleep appears to be controlled by reciprocal inhibition between mono-aminergic neurons and a specific subset of cholinergic neurons within the brain stem. These "REM-on" cholinergic neurons exhibit reciprocal inhibitory connections to noradrenergic (LC) and serotonergic (raphe) neurons [10]. When REM sleep is triggered, REM-on cholinergic neurons become

maximally active, while noradrenergic and serotonergic neurons become virtually silent. The switching between activity and inhibition of these neurons results in characteristic cycling between NREM and REM during the sleep period.

2.3 Basic Mechanisms Coordinating and Governing Sleep and Wakefulness

Autonomic nervous system balance, homeostatic sleep drive, and circadian rhythms are mechanisms to maintain sleep and wakefulness in a dynamic balance. This active equilibrium provides the system with some extent of flexibility. Thus when the balance is upset, these mechanisms provide an avenue for the system to adjust and recover. This arrangement of regulatory mechanisms also provides a means by which an individual can adapt to sudden shifts in the time and duration of sleep.

2.3.1 Autonomic Nervous System Balance During Sleep

Basic physiology of the autonomic nervous system can be described as NREM sleep leads to autonomic balance to shift from sympathetic to parasympathetic dominance. Autonomic balance during REM sleep in general is similar to wakefulness. The autonomic nervous system regulates multiple body processes including blood pressure, body temperature, digestion, metabolism, water maintenance, production of body fluids, and rate of breathing. As the name suggests, this system functions automatically without the individual's conscious effort. It has two main divisions: sympathetic and parasympathetic. The system receives information about the body and external environment and responds by stimulating body processes to the sympathetic division or inhibiting through the parasympathetic division.

Autonomic system imbalance has been well studied. Sleep stages exert a significant effect on heart rate variability (HRV) by increasing sympathetic activity during NREM sleep and awake like sympathetic activity during REM sleep. These large interstage fluctuations are important to consider the possibility that an increase in synthetic activity due to sleep-disordered breathing can possibly trigger an arousal. Advances in the noninvasive autonomic system monitoring the HRV have revealed increased sympathetic drive in subjects suffering from obstructive sleep apnea. The effects of the physiologic response present episodes of airway obstruction on the heart rate variability suggesting an increase in sympathetic dominance compared with healthy controls.

2.3.2 Homeostatic and Circadian Regulation of Sleep

Normal human sleep and essential physiologic process comprises two phases or cycles, REM sleep and NREM sleep. Sleep is regulated by intricately interrelated activity and complex interplay at different anatomically identifiable centers and the

simultaneous occurrence of various behavioral and physiologic processes. Sleep-wake cycles are determined by synchrony between sleep homeostasis and circadian rhythms. Many models have been developed to explain the delicate interplay resulting in sleepiness or wakefulness, the most accepted among which remains the scheme originally proposed by Borbely et al. [11]. One of the major advances in the understanding of sleep physiology was the development of the two-process model of sleep regulation [11, 12]. It was originally described in a rat model and was qualitative in nature. The model consists of a homeostatic process termed process S and an intrinsic circadian pacemaker (process) termed process C.

Process S represents a putative drive for sleep that progressively increases in intensity during wakefulness and demonstrates a reduction during NREM sleep. Process C represents a nearly 24-h spontaneous oscillatory variation in the propensity for sleep. These two processes can be demonstrated to predict the timing and duration of sleep and the intensity of NREM sleep [13].

The two-process model of sleep regulation has been applied successfully to describe, predict, and understand sleep-wake regulation in a variety of experimental protocols such as sleep deprivation and forced desynchrony [14]. Much of the research on sleep homeostasis has been possible due to the recognition of the physiologic correlation of sleep propensity and slow-wave activity (SWA) on electroencephalogram (EEG). This has permitted measurement of sleep pressure under experimental conditions in both humans and animals [15]. Further, an inverse relationship between EEG SWA and brief awakenings during sleep has been observed and established [16]. Beyond the Borbely's model, the mathematical mechanisms and models that account for the complex interplay between circadian, ultradian (physiologic cycles with a periodicity of less than 24 h), and homeostatic aspects of sleep regulation have also been proposed [17].

Nevertheless, the Borbely's two-process model is still the most accepted theory, which describes the orchestrated balance necessary to achieve a normal sleep-wake cycle [18]. The original Borbely's two-process model was qualitative, while a quantitative version was established later, based on this. In the latter, process S varied between an upper and a lower thresholds that in turn were modulated by a fixed circadian process C. This model has, thus, been able to explain phenomena like recovery from sleep deprivation, circadian phase dependence of sleep duration, sleep in shift workers, sleep fragmentation during continuous bed rest, and internal desynchronization in absence of cues [11]. The processes which underlie sleep regulation are homeostasis, circadian process, and ultradian process:

1. Homeostatic process S: Mediates the rise in "sleep pressure" during waking and the dissipation of "sleep pressure" during sleep.
2. Circadian process C: Operates independently of the duration of wakefulness, cycling in a fixed and rhythmic pattern to promote alertness. Most circadian models assume that multiple oscillators underlie the differences in period and entrainment properties of the sleep/wake cycle and other rhythms (e.g., body temperature).

3. Ultradian process: Simulates the cyclic alternation of NREM and REM sleep by assuming a reciprocal interaction of two cell groups. These occur within sleep and represented by the alternation of the two basic sleep states NREM and REM sleep. Described as part of a model of ultradian variation of slow-wave activity, herein, the change of S, not the level of S, corresponds to slow-wave activity. A REM sleep oscillator triggers the decline of slow-wave activity during REM sleep.

2.3.3 Interplay Between S and C Processes

The homeostatic sleep drive is directly determined by the duration of wakefulness. In the morning, with an adequate amount of sleep, process S is at its nadir. As the day proceeds and the duration of wakefulness grows in length, process S or the drive/pressure to sleep increases linearly until the person goes to sleep, effectively working to reduce the S drive. The circadian process C operates independently of the duration of wakefulness. This process cycles in a fixed and rhythmic pattern to promote alertness (Figs. 2.1, 2.2, and 2.3). During the day, when the homeostatic sleep drive is mounting, wakefulness is maintained because the circadian process works to offset this rising drive toward sleep.

The timing of circadian rhythm and the homeostatic sleep drive normally align to achieve a fixed and consolidated sleep-wake cycle. However, individuals can experience a dip in their circadian alerting drive in the late afternoon, which explains the common after-lunch dip or siesta in alertness [19]. Under conditions of sleep deprivation, the interplay between the homeostatic and circadian process becomes less coordinated and the sleep-wake state becomes unstable [20]; sleep-deprived individuals demonstrate evidence of involuntary sleep intrusions [21]. The circadian after-lunch dip in alertness is amplified in loss of sleep [22, 23].

The circadian models have been found to be variously dependent on light, split or non-split sleep pattern, sleep timing, temperature rhythm, melatonin, and pineal regulation [24–26]. Studies published as early as the 1970s established the suprachiasmatic nucleus of the hypothalamus as the central circadian pacemaker in mammals [27]. This pacemaker is composed of individual cells that, when isolated, can oscillate independently within a near 24-h period.

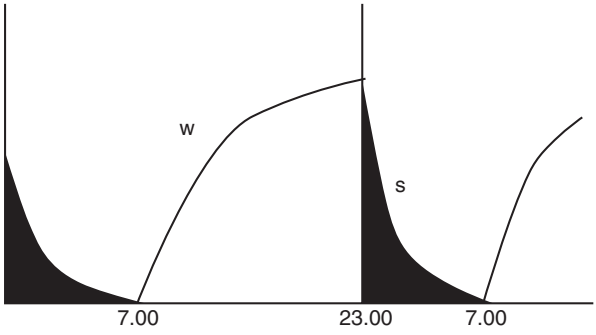

Fig. 2.1 Diagrammatic representation of the basic process of sleep regulation: Process S (homeostatic). (Image supplied by Deepak Shrivastava)

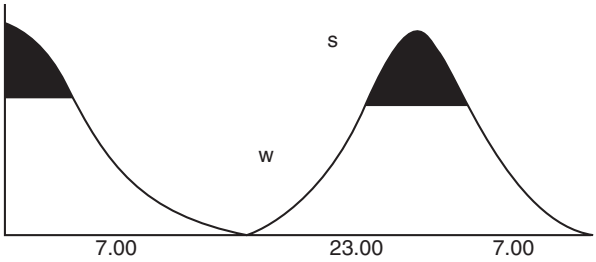

Fig. 2.2 Diagrammatic representation of the basic process of sleep regulation: Process C (circadian). (Image supplied by Deepak Shrivastava)

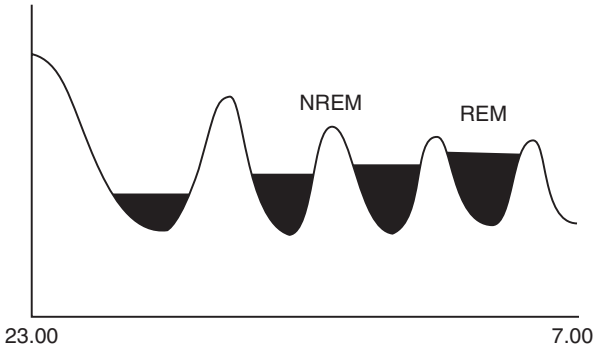

Fig. 2.3 Diagrammatic representation of the basic process of sleep regulation: Process U (ultradian). (Image supplied by Deepak Shrivastava)

The suprachiasmatic nucleus receives direct input from the retina [28], providing a mechanism by which entertainment to light-dark cycles occurs. Taken together, the studies so far suggest that the overall 24-h pattern of light and darkness to which humans are exposed plays a critical role in subsequent sensitivity to light exposure and thus in entertainment [29].

The circadian system of individuals who get little bright-light exposure may become more sensitive to moderate levels of light. Given that most studies show that modern humans get relatively little bright-light exposure and instead spend most of their waking day in light of indoor intensity, these findings may have very important practical relevance for most humans.

Process S is determined by the buildup rate and the saturation level of SWA within non-REM sleep episodes and also the sleep inertia (process W) [17, 30]. Not only the timing of sleep but also the time course of daytime vigilance can be accounted for by the interaction of homeostatic and circadian processes [17].

The posterior hypothalamus, tuberomammillary nucleus, and regions of the brain stem are all collectively involved in maintaining wakefulness with the release of excitatory neurotransmitters orexin, histamine, and acetylcholine, respectively, to specific cortical and subcortical sites. During wakefulness, adenosine, a nucleotide involved in intracellular energy transfer and storage, continues to build in the system and serves as a specific neurotransmitter to help transition into the sleep state. Adenosine represents the neurophysiologic marker of the homeostatic sleep drive. Therefore, like the process S, which increases with the duration of wakefulness, so too does the amount of adenosine along the neuraxis.

The two-process model of sleep, though first proposed nearly three decades ago, continues to be among the most applicable tools in understanding normal sleep regulation. Current understanding provides a model in which there is an interplay between the basic processes "S" for sleep homeostasis and "C" for circadian propensity for sleepiness and wakefulness.

2.4 Effect of Sleep on Organ Systems

2.4.1 Cardiovascular System

Cardiovascular changes are probably most important during normal sleep. During sleep, there is a decrease in blood pressure, a phenomenon referred to as "nocturnal dipping" defined as a 10% drop in blood pressure. This decrease is independent on the circadian influences and the postural effects during sleep. Dipping is also affected by the reduction of sympathetic tone at sleep onset. Normally, there is an increase in parasympathetic tone. Sleep state transitions are also accompanied by changes in the cardiovascular system. In the transition from the NREM to REM sleep, blood pressure and heart rate increase and become relatively unstable [31].

2.4.2 Respiratory System

Respiratory system responds to sleep by ventilatory and airflow changes and becomes irregular during REM sleep. The minute ventilation is reduced during sleep; several factors contribute to hypoventilation during NREM sleep, such as reduced pharyngeal muscle tone and lower tidal volumes. The partial pressure of carbon dioxide is increased and oxygen is decreased during sleep. During REM sleep, there is reduced rib cage movement and increased upper airway resistance due to the loss of tone in the intercostals and upper airway muscles seen by the respiratory inductance plethysmography (RIP) lead. The cough reflex and swallowing are suppressed during sleep. Hypoxic ventilatory response is lower in NREM sleep than during wakefulness and decreases further during REM sleep. Similarly, the arousal response to respiratory resistance is lowest in slow-wave sleep (N3) sleep.

2.4.3 Renal System

Renal system response to sleep indicates reduction in renal filtration, plasma flow, and the excretion of sodium, chloride, potassium, and calcium. These changes cause urine to be more concentrated during sleep. There is a sleep-related increase in plasma aldosterone, antidiuretic hormone levels, and prolactin secretion. There is increased parathyroid hormone release during sleep, which may affect calcium excretion.

2.4.4 Gastrointestinal System

Gastrointestinal system responds to sleep by a reduction of gastric acid secretion. In those with an active ulcer, gastric acid secretion is actually increased and swallowing occurs less frequently. Sleep is associated with increased gastric acid production, delayed gastric emptying, delayed esophageal clearance, and diminished upper esophageal sphincter pressure. Furthermore, unlike daytime esophageal acid exposure, nocturnal gastric acid production appears difficult to suppress pharmacologically. This can be due to paradoxical breathing during obstructive sleep apnea (OSA), pumping gastric acid up the esophagus into the oropharynx.

2.4.5 Thermoregulation

Thermoregulation is an important physiological function that is affected by sleep stages. The relationship between thermoregulation and sleep is reciprocal. Core temperature is lower during sleep or when sleep propensity is high. This is accompanied by a decrease in metabolic heat production and an increase in peripheral vasodilation. At sleep onset, there is a gradual decline in body temperature, a decrease in heat production, a reduction in body temperature rhythm, and an increase in heat loss, all of which promote sleep onset and maintenance, as well as EEG slow-wave activity. Awakening generally occurs during the rising phase of the temperature rhythm. These changes are likely induced by both circadian and sleep-related mechanisms.

2.5 Selected Clinical Sleep Disorders

Hypersomnolence is a recurrent state of excessive daytime sleepiness or prolonged nighttime sleep. This can occur at inappropriate times such as at work, conversation, or driving. Hypersomnia can be primary, which occurs with no other medical conditions present. The only symptom is excessive fatigue and sleepiness. Primary hypersomnia is due to abnormal control of sleep and waking function of the brain systems. On the other hand, secondary hypersomnia is due to conditions like insufficient sleep, sleep apnea, Parkinson's disease, kidney failure, and chronic fatigue syndrome. Secondary hypersomnia could also be a result of drug or alcohol use, low thyroid function, or head injury.

2.5.1 Obstructive Sleep Apnea (OSA)

OSA is a sleep disorder involving cessation of airflow or significant decrease in airflow, in the presence of breathing effort. OSA is the most common type of sleep-related breathing disorder (SRBD) and is manifested by recurrent episodes of upper

airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin saturation-desaturation and frequent arousals from sleep.

The nocturnal symptoms of OSA may include snoring, witnessed apneas, gasping or choking events during sleep, recurrent need to go to the bathroom at night, and restless sleep causing frequent nighttime arousals that result in non-refreshing sleep and tiredness in the morning.

The daytime symptoms of OSA include non-restorative sleep, morning headache, dry mouth or sore throat, and excessive daytime sleepiness. It is associated with daytime tiredness and cognitive impairment of short-term memory and ability to concentrate. If continued, it can cause personality and mood changes. In addition, it can affect sexual functioning and worsen gastroesophageal reflux, blood pressure, and blood glucose.

2.5.2 Obstructive Sleep Apnea-Related Hormonal Dysregulation

There are a number of hormones known to be secreted during the specific stage of sleep. During the first half of the night, N3 is dominant and there is a major peak of growth hormone secretion. In the second half of the night, REM sleep predominates, and secretion of the hypothalamic-pituitary-adrenal cortical (HPA) system is activated and secretes corticotropin (ACTH) and cortisol. Growth hormone secretion is reduced with aging when amounts of N3 are reduced and during the episodes of depression.

2.5.3 Growth Hormone Secretion in Obstructive Sleep Apnea

Deficiency in growth hormone (GH) could have a link with OSA, as it is associated with obesity and craniofacial and pharyngeal abnormalities. OSA patients have low GH levels without any specific causes of deficiency [32]. GH secretion occurs mostly during sleep, and 70% are associated with N3 sleep [33, 34]. In OSA patients, GH secretion is decreased not only due to obesity [35–37] but also due to sleep fragmentation resulting in decreased amount of N3 sleep [38]. The repetitive hypoxemia resulting from OSA may affect growth hormone secretion. GH deficiency in adults is associated with insulin resistance, endothelial dysfunction, impaired psychological well-being, increased visceral fat, accelerated aging, and increased cardiovascular mortality [39].

In theory, coexistence of GH deficiency and OSA could result in altered physiological functions, resulting in severe anatomical abnormalities. A primary GH deficiency could predispose a subject to OSA through short stature, deficiency of craniofacial growth, and low respiratory drive. OSA could further aggravate GH deficiency through sleep disturbance. A primary SRBD could aggravate itself by affecting craniofacial and upper airway soft tissue growth through induction of secondary growth hormone deficiency [40, 41].

2.6 Neurotransmitters for Wakefulness

2.6.1 Histamine

Histamine plays a key role in the maintenance of wakefulness. Histaminergic neurons originate from the posterior hypothalamus tuberomammillary nucleus (TMN) and project diffusely throughout the brain. In the cortex, histamine facilitates cortical arousal. Histaminergic neurons fire most rapidly during cortical activation in the wake state and turn off during REM sleep. Histamine receptors are found throughout the body and nervous system, where histamine (H1) receptor agonists induce wakefulness and administration of H1 antagonists causes sedation and drowsiness.

2.6.2 Acetylcholine

Acetylcholine (Ach) is found in the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) of the midbrain reticular formation and at the neuromuscular junction in skeletal muscle fibers where its action results in muscle contraction. These midbrain LDT and PPT areas contain two interspersed subsets of cholinergic neurons. One subset is responsible for the fast-frequency and low-voltage EEG pattern of "cortical activation," which appears in REM sleep and restful wakefulness. These are called wake/REM-on neurons. The second subset is responsible for generations of REM sleep called REM-on cells. The REM-on cholinergic neurons promote REM sleep by sending excitatory input to the pontine reticular formation (PRF). This causes the rapid firing of the PRF, which produces the three cardinal physiologic components of REM sleep (muscle atonia, rapid eye movements, EEG activation/desynchronization). The PRF is shut off during NREM sleep. Cholinergic neurons that project from the basal forebrain to the cerebral cortex and limbic areas are part of the vigilance-waking system.

2.6.3 Dopamine

Dopamine is a major neurotransmitter that regulates sleep and wakefulness and is produced in the substantia nigra, ventral tegmental area, and hypothalamus of the brain. The levels of dopamine are significantly higher during wakefulness than during N3 sleep [42]. It plays a vital role in reward and movement regulation in the brain. The role of dopamine dysfunction as a consequence of oxidative stress is involved in health and disease. The level of dopamine transmission increases in response to any type of reward and by a large number of strongly addictive drugs. Several pharmacologic studies have linked dopamine receptors to drug-induced arousal and spontaneous wakefulness [43].

2.6.4 Glutamate

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) and is associated with normal brain function during the waking state. Glutamate levels increase during wakefulness, and to a lesser degree during REM sleep, but decrease during NREM sleep.

2.6.5 Serotonin and Norepinephrine

Serotonergic neurons originate in the dorsal raphe nucleus and noradrenergic neurons originate in the locus coeruleus. Both sets of neurons act as suppressants of REM sleep (REM-off cells) by inhibiting REM-promoting cholinergic neurons and by sending inhibitory input to the PRF. Serotonin and norepinephrine neurons promote cortical activation during wakefulness by firing rapidly. During the NREM sleep period, at the beginning of the first sleep cycle, serotonergic and noradrenergic neurons significantly reduce their firing rate. This removes the inhibition from the REM-on cholinergic neurons, leading to the first REM sleep period approximately 90 min later.

2.6.6 Hypocretins

Hypocretins (also called orexins) are two neuropeptides (hypocretin 1 and hypocretin 2) with key roles in regulation of arousal and metabolism. These peptides are produced by hypothalamic neurons that surround the fornix bilaterally and in the dorsolateral hypothalamus. These hypothalamic regions are implicated in control of nutritional balance, blood pressure, temperature regulation, endocrine secretion, and arousal. In accordance with circadian rhythm control of hypocretin levels (through SCN input), their concentration is highest during the waking period. Hypocretin levels also increase during a period of forced sleep deprivation. Hypocretin input to the brain stem REM-on cells controls the switch into REM by reducing the firing rate of the REM-on cells during the wake period. Most importantly, a reduction in the level of hypocretin is implicated in narcolepsy, a neurological disorder that manifests as excessive daytime sleepiness and sudden uncontrollable episodes of sleep that can last for a few seconds to several minutes. More recently, excessive amounts of hypocretin have been implicated in insomnia. Orexin also has an important effect on appetite. As levels increase, the craving for food and food intake also increases, possibly leading to weight gain and obesity, an important risk factor for OSA.

2.7 Neurotransmitters for Sleep

2.7.1 Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter in the brain. It has correlations with anxiety and stress regulation, circadian rhythm, sleep regulation, memory enhancement, mood, and even perception of pain [44, 45]. GABA acts by inhibiting the action of activating neurotransmitters, such as glutamate and NE, which promote wakefulness. Low levels or impaired GABA function is associated with the etiology and maintenance of acute and chronic stress, anxiety disorders, and sleep disturbances such as insomnia [46–48]. GABAergic neurons and neurotransmitters regulate the brain circuits in the (a) amygdala, to modulate stress and anxiety responses [49]; (b) cortico-medullary pathways, to modulate both REM and NREM, and N3 sleep [50]; and (c) suprachiasmatic nuclei (SCN), to modulate circadian rhythm [51]. GABA receptors allow inhibition of neurons in certain regions of the brain to be regulated with high accuracy, and these sites are targets for anxiolytic and hypnotic drugs to relieve anxiety and promote sedation and deep sleep [49, 52]. Therefore, pharmacological treatments for insomnia and anxiety disorders are usually benzodiazepine receptor agonists, which affect GABA adrenergic transmission [47, 52], and increase the binding of GABA to GABAa receptors to enhance inhibitory signals to cell groups regulating arousal. This results in reduced stress and anxiety, decreased sleep latency, and increased sleep continuity [47–49].

2.7.2 Adenosine

Adenosine is a neuromodulator regulating sleep [53–55]. It regulates the depth of sleep intensity and maintains sleep [56, 57]. Adenosine serves as a building block for adenosine triphosphate, and under increased energy demand when adenosine triphosphate (ATP) is used for energy production, the levels of adenosine increase as a result of ATP metabolism [55]. Adenosine is believed to be a homeostatic sleep factor that mediates the transition from prolonged wakefulness to NREM sleep. It mediates the transition by inhibiting arousal promoting neurons of the basal forebrain. Caffeine, which is present in coffee and tea, acts by blocking adenosine receptors, therefore stimulating wakefulness and reducing sleep.

2.8 Hormone Control of Sleep

Hormone secretion is controlled by the circadian clock and specific sleep stages. Sleep alters the timing of secretion for certain hormones. Concentrations of the hormones fluctuate throughout the day and night. Many hormones are affected by sleep and behavior. In normal physiology, the sleep-wake cycle and the endogenous circadian time systems are coupled and centralized.

2.8.1 Melatonin

Melatonin begins to increase during nighttime and decreases during daytime. Melatonin is synthesized by the pineal gland, known to control the body's sleep/wake cycles. It is often referred to as the sleep hormone due to its impact on the body's circadian rhythm. The pineal gland is inactive during the day when there is light and does not produce melatonin but becomes active and produces melatonin during darkness. The increase in melatonin levels causes the subjects to become less alert and sleepy. Due to frequent arousals during the night, OSA patients are exposed to more abnormal nocturnal light, which affects melatonin secretion. Melatonin acts as an antioxidant by reducing the formation of free radicals in bone cells and mesenchymal stem cells to become osteoblast precursors. Furthermore, treatment with melatonin in osteopenic postmenopausal women increased bone mass density (BMD) at the femoral neck in a dose-dependent manner. Studies with continuous positive airway pressure (CPAP) therapy have shown to normalize melatonin and leptin levels and possibly reverse bone destruction [58–60].

2.8.2 Ghrelin and Leptin

Ghrelin and leptin promote and suppress food intake, respectively. Ghrelin levels rise before decreasing after habitual mealtimes in individuals who are fasting. Normally, ghrelin levels increase in the early part of sleep and are blunted during sleep deprivation. Leptin levels increase with the onset of sleep, regardless of time of the day that sleep occurs.

Leptin, known as a satiety hormone, is also a powerful respiratory stimulant [41]. Hypercapnic patients with OSA have higher leptin levels. Leptin secretion can provide an adaptive mechanism to enhance ventilation in patients with severe respiratory impairment. Conversely, elevated levels of leptin suggest leptin resistance at the level of the CNS. Elevated leptin levels are likely to contribute to comorbidity of OSA as it is associated with coronary heart disease, insulin resistance, impaired fibrinolysis, development of obesity, and type 2 diabetes, which are all highly prevalent in patients with OSAS [61–66].

2.8.3 Follicle-Stimulating Hormone and Luteinizing Hormone

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are released during sleep. In fact, the sleep-dependent release of luteinizing hormone is considered to initiate puberty.

2.8.4 Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH) is released prior to sleep. Both sleep and circadian effects interact to produce the overall rhythmic pattern of the pituitary and pituitary-dependent hormones. Some of the 24-h hormonal rhythms depend on the circadian clock (ACTH, cortisol, and melatonin), or are sleep related (prolactin and TSH). GH secretion is influenced by the first slow-wave sleep at the beginning of the night.

2.8.5 Cortisol

Cortisol is a hormone that functions to promote wakefulness and alertness. Cortisol levels increase in the early morning hours to enhance wakefulness. It is released by the adrenal glands and is often associated with stress and may also be associated with depression and insomnia. Furthermore, children with sleep problems and adults who are sleep deprived also have greater cortisol reactivity to stress and lower stress reactivity seen with better sleep quality.

Both sleep-wake cycle and behavior activity like food intake and posture changes as well as environmental exposures contribute to the day-night rhythms and hormones. The internal circadian timing system has a robust effect on the number of hormones and contributes to their day-night rhythms. Obviously, dissociation of the behavior cycle in the circadian system has an adverse effect on many physiological processes leading to poor health [67, 68].

2.9 Diagnostic Process

2.9.1 Diagnosis

The diagnosis of OSA starts with a sleep history. High-risk patients include those who are obese and those with congestive heart failure, atrial fibrillation, stroke, nocturnal dysrhythmias, type 2 diabetes, pulmonary hypertension, treatment refractory hypertension, and high-risk driving populations (such as commercial truck drivers).

A comprehensive sleep history in a patient suspected of OSA should include an evaluation for snoring, witnessed apneas, gasping/choking episodes, and excessive daytime sleepiness not explained by other factors, including assessment of sleepiness severity by the Epworth sleepiness scale, total sleep time, nocturia, morning headaches, sleep fragmentation/sleep maintenance insomnia, and decreased concentration and memory.

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic systems. Particular attention should be paid to the presence of obesity, the signs of upper airway narrowing, or the presence of other disorders that can contribute to the development of OSA or to the consequences of OSA. Features to be evaluated that may suggest the presence of OSA include increased neck circumference (>17 in. in men, >16 in. in women), body mass index (BMI) $\geq$30 kg/m^2, modified Mallampati score of 3 or 4, the presence of retrognathia, lateral peritonsillar narrowing, macroglossia, tonsillar hypertrophy, elongated/enlarged uvula, high arched/narrow hard palate, nasal abnormalities (polyps, deviation, valve abnormalities, turbinate hypertrophy), and/or significant overjet.

2.9.2 Objective Testing

The severity of OSA must be established in order to make an appropriate treatment decision. Presently, no clinical model is recommended to predict severity of OSA; therefore, objective testing is required. The two accepted methods of objective testing are in-laboratory polysomnography (PSG) and home sleep testing with portable monitors (PMs). PMs may be used to diagnose OSA when utilized as part of a comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSA. PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, and congestive heart failure or those suspected of having a comorbid sleep disorder. High-risk patients with nocturnal symptoms of OSA should undergo sleep testing, including those who are obese, systolic or diastolic heart failure, coronary artery disease, congestive heart failure, history of stroke, transient ischemic attacks, and significant tachyarrhythmias or bradyarrhythmias [69].

2.9.3 Polysomnography

PSG for evaluating OSA requires recording the following physiologic signals: electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram (EMG), airflow, oxygen saturation, respiratory effort, and electrocardiogram (ECG) or heart rate. Other recommended parameters include body position and leg EMG. Anterior tibialis EMG is useful to assist in detecting movement arousals that have the added benefit of assessing periodic limb movements, which coexist with sleep-related breathing disorders in many patients. An attended study requires the constant presence of a trained individual who can monitor for technical adequacy, patient compliance, and relevant patient behavior.

Diagnosis for OSA is based on an apnea-hypopnea index (AHI) or respiratory disturbance index (RDI). AHI is composed of the number of apnea and hypopnea index per hour of sleep. The RDI is composed of the AHI and respiratory-related

Table 2.1 Definition of breathing events during sleep

	Definition
Hypopnea	Abnormal respiratory event with at least 30% reduction in thoracoabdominal movement or airflow as compared to baseline lasting 10 s and with 3–4% oxygen desaturation (Centers for Medicare and Medicaid Services (CMS) use 4% for their definition)
Obstructive sleep apnea	Cessation of airflow for at least 10 s. The effort to breathe is present
Central apnea	Cessation of airflow for at least 10 s. No effort to breathe is present
Mixed apnea	Cessation of airflow for at least 10 s. The event is considered mixed if apnea begins as central apnea, but toward the end, there is an effort to breathe without airflow
Respiratory effort-related arousal (RERA)	Sequence of breaths with increasing respiratory effort leading to an arousal from sleep, as shown by progressively more negative esophageal pressure for at least 10 s preceding arousal with a resumption of more normal pressure

arousals per hour. Some sleep physicians utilize the AHI or RDI for diagnostic purposes as reflected on the sleep study report. See Table 2.1 for definitions of sleep breathing events.

Full-night PSG is recommended for the diagnosis of a sleep-related breathing disorder, but a split-night study (initial diagnostic PSG followed by continuous positive airway pressure titration on the same night) is an alternative to a full-night diagnostic PSG. The split-night study may be performed if an AHI ≥40/h is documented during 2 h of a diagnostic study but may be considered for an AHI of 20–40/h based on clinical judgment [70].

The diagnosis of OSA is confirmed if the number of obstructive events (apneas, hypopneas + respiratory event-related arousals) on PSG is greater than 15 events/h or greater than 5 events/h in a patient who reports any of the following: unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue; insomnia; waking up breath holding, gasping, or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient's sleep. OSA severity is defined as mild for RDI ≥5 and <15, moderate for RDI ≥15 and ≤30, and severe for RDI >30/h [71].

2.9.3.1 Electroencephalography (EEG)

Brain electrical activity is recorded through surface electrodes placed on the head in accordance with an internationally accepted method. These electrical signals pass from the electrodes through amplifiers, where they are modified before being recorded. EEG is the primary source of documenting wakefulness, sleep stages, and arousals. It has several leads placed on top and around the head including the mastoids, to measure brain activity during different stages of sleep. During stage wake, alpha activity is seen on the EEG channels. Stage N2 sleep is indicated when sleep spindles and K-complexes are seen in the central vertex region channels. During stage N3 sleep, delta waves are seen as the patient is in deep restorative sleep. REM sleep is indicated when mixed frequencies are seen.

2.9.3.2 Electrooculography (EOG)

The main reason to place one electrode above and below the outer canthus is to identify conjugate eye movements and to distinguish eye movements from artifacts. The main reason for recording the eye movements is to establish the presence of REM sleep. REM sleep cannot be diagnosed without the presence of REMs. The frequency of REMs per hour of REM sleep is designated as REM density and is a reflection of REM sleep intensity.

EOG measures eye movements with leads placed on the outer canthus (OC) of the eyes and are offset by 1cm above the left outer canthus (LOC) and below the right outer canthus (ROC). The cornea (front) has a positive polarity and the retina has a negative polarity. Electrooculography picks up the inherent voltage of the eye. During wakefulness when the eyes are open and blinking occurs, sharp deflections on the EOG tracing are seen. During stage 1 sleep (drowsiness), slow eye movements (SEMs) are seen as the eyes slowly roll from side to side. Brain wave activity (theta) starts to enter into the EOG tracing as an artifact. During REM sleep, rapid eye movement occurs while dreaming as eyelids are closed. The rapid eye movements appear as out-of-phase EOG channel deflections. Tracing shows movement in opposite directions (Fig. 2.4).

2.9.3.3 Chin Electromyography (EMG)

Submental EMG which records muscle tone is a mandatory recording parameter for staging sleep to distinguish REM sleep from NREM sleep. Muscle tone is high during wakefulness and NREM sleep and low during REM sleep. Yawning, swallowing, and bruxism may also increase muscle tone.

2.9.3.4 Masseter EMG

If bruxism is suspected, masseter EMGs are used to record the events.

2.9.3.5 Leg EMG

Periodic limb movements of sleep (PLMS) are often visually detectable during the sleep monitoring process. EMG leads placed bilaterally on the anterior tibialis muscles allow for the determination of the severity of the disorder by quantifying the rate of movements as well as the correlation with EEG arousal. Limb EMG of the upper extremities and masseters may also be recorded if clinically indicated.

2.9.3.6 Electrocardiogram (ECG)

ECG monitors the heart rhythm. ECG electrodes are placed on the right shoulder below the clavicle at the midclavicular line and the left shoulder below the clavicle at the anterior axillary line in the sixth or seventh intercostal space.

2.9.3.7 Respiratory Parameters

Upper airway sound recording: snore microphone or sound transducer is supplemental to help verify arousals. It is placed over the trachea to measure vibrations when snoring events occur.

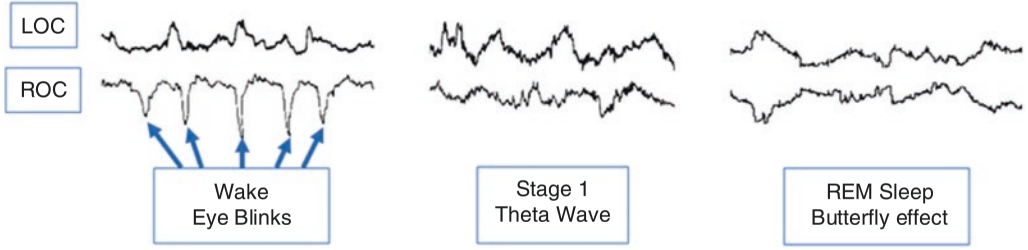

Fig. 2.4 EOG eye movements. *LOC* Left outer canthus, *ROC* right outer canthus

Thermistor, thermocouple, or device utilizes polyvinylidene fluoride film (PVDF) measures changes in oral and nasal airflow to differentiate between apnea and hypopnea [72].

Respiratory inductive plethysmography (RIP) and piezoelectrode (PE) belt measuring volume changes (movements) in the chest and abdomen as the belt stretches or contracts. The RIP or PE belt is used to distinguish between OSA from CSA [71, 73].

2.9.3.8 Blood Oxygenation (Oxygen Saturation: SpO_2)

The diagnosis of OSA during the standard PSG requires the continuous monitoring and display of blood oxygen saturation levels to provide crucial information about the severity of the SRBD. Pulse oximeters are used on the index finger of the non-dominant hand. If this proves to be uncomfortable for the patient or if perfusion is low, an ear probe can be applied to the lobe.

2.9.3.9 Capnography

Capnography is used to measure the patient's carbon dioxide (CO_2) level. There are two types of capnographs: end tidal and transcutaneous. End tidal capnography is commonly used in children and adults to measure PCO_2 using a nasal, nasal/oral cannula or a mask. End tidal measurement reflects the concentration of CO_2 in the lungs and in the blood at the end of expiration. Transcutaneous PCO_2 (TC PCO_2) recording measures the transpired PCO_2, which reflects tissue PCO_2. This is the preferred method for monitoring neonates in an intensive care setting [74].

2.9.4 Sleep Stages

Sleep staging is based on reviewing 30 s of the recording data.

2.9.4.1 Stage Wake

Stage wake is indicated when (1) over 50% of each epoch contains alpha activity, (2) slow rolling eye movements or eye blinks will be seen in the EOG channels, and (3) there is relatively high submental EMG muscle tone.

2.9.4.2 Non-REM Sleep

Stage N1 sleep is considered a transitional sleep stage. It is scored when more than 15 s of theta waves are seen replacing alpha waves. Stage N1 sleep is indicated when (1) $\geq$50% of the epoch contains theta activity (there may be alpha activity within <50% of the epoch), (2) there are slow rolling eye movements in the EOG channels, and (3) there is relatively high submental EMG tone. Stage 1 sleep lasts 15–20 min and comprises 2–5% of total sleep time (TST).

Stage N2 sleep makes up 45–50% of TST and is indicated when (1) when background EEG is theta waves, (2) K-complexes and sleep spindles occur episodically, (3) mirrored EEG is seen in the EOG leads, and (4) there is low tonic submental EMG. Excess sleep spindles may indicate the presence of some medications such as

benzodiazepines. If a K-complex or sleep spindle is not seen within 3 min of the previous K-complex or sleep spindle, the scoring will default to stage N1 sleep.

Stage N3 sleep comprises 20–25% of TST and is indicated when (1) 20% or more of the EEG is delta waves, (2) EOG leads only pick-up EEG activity, and (3) EMG may be slightly lower than that of stage N2 and no K-complexes.

2.9.4.3 REM Sleep

REM sleep (20–25% of TST) is indicated when (1) there is mixed frequency EEG where alpha may be seen slower than waking, (2) REMs are seen in the EOG leads, (3) there is low submental EMG, and (4) any two of the previous three criteria must be present to score REM sleep. K-complexes and/or spindles may occur while in stage REM. While in stage REM, there must be more than a 3-min separation period between K-complexes and spindles without REMs that the scoring will default to stage N2.

2.9.5 Sleep Cycles

Stage N3 sleep is predominant in the first half of the night. It decreases in the second half of the night. Stage R (REM) is short, usually lasting 10 min, in the first half of the night. Stage R duration progressively increases toward the latter part of the night. Stage R can last longer than 45 min toward morning (see Fig. 2.5).

2.9.6 Home Sleep Apnea Testing (HSAT)

Home sleep apnea monitoring is a common terminology used for out-of-sleep laboratory testing for sleep apnea and is known by many terms: portable sleep testing, home sleep testing, and portable monitoring. The most accurate term is "home sleep apnea testing" (HSAT). This term is precise and descriptive of what is actually being measured.

The types of sleep apnea monitoring devices available have been classified by the number and complexity of the signals they record:

Type 1: This is standard in-laboratory PSG.
Type 2: This is a miniature, portable, comprehensive PSG that can be performed outside of the sleep laboratory.
Type 3: These are devices that record cardiopulmonary signals; these are used for portable sleep apnea testing. They typically have a minimum of four signals (usually airflow, respiratory effort, heart rate, and oximetry).
Type 4: This is a continuous single or dual parameter testing, such as oximetry or several two-channel devices that measure oximetry and airflow.
Type 4 with three channels: This is a new addition to the accepted classification, because it was used in the CMS.

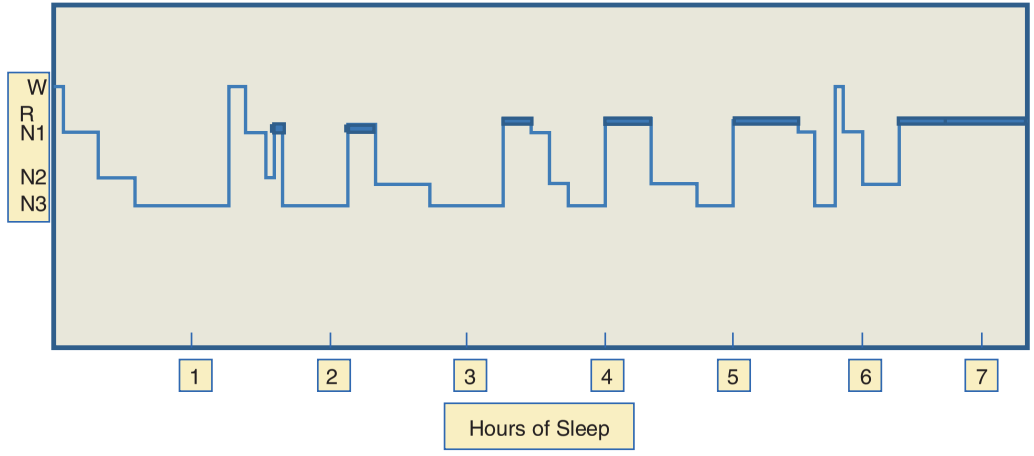

Fig. 2.5 Sleep cycle. Hypnogram showing wake (w); REM (R); N1, N2, and N3 sleep; and six progressively increasing REM cycles (thick lines). The sleep latency is the time from lights out to the sleep onset. Most adults enter sleep through N1. It quickly follows into N2 sleep and then N3 sleep. The first REM cycle occurs in 70–110 min after the sleep onset. N3 sleep is dominant in the first half of the night, while the REM sleep occupies most of the latter half of the night. (Figure supplied by Deepak Shrivastava)

HSAT records minimum airflow, respiratory effort, and blood oxygenation. HSAT may be used in the unattended setting as an alternative to PSG for the diagnosis of OSA. It is used in patients with a high pretest probability of moderate to severe OSA and no comorbid sleep disorder or major comorbid medical disorders when all of the previous parameters are met. The diagnosis of OSA is confirmed and severity determined using the same criteria as used for PSG.

The term AHI/RDI has been defined differently when used with HSAT than when used with PSG. HSAT AHI/RDI is the number of events/total recording time rather than total sleep time. As a result, HSATs are likely to underestimate the severity of events compared to PSG. Due to the known rate of false-negative HSAT tests, in-laboratory PSG should be performed in cases where HSAT is technically inadequate or fails to establish the diagnosis of OSA in patients with a high pretest probability [70, 75, 76].

2.10 Technical Aspects of Polysomnography

Biocalibration: Calibration is the documentation of the accuracy of the measurement of any polysomnography parameter. Machine calibration in digital systems is no longer needed as the software is incorporated into the amplifier circuitry and provides accurate information, although software provides for the several calibrations that could be used by the technologist.

With digital systems, there has been a revolution in techniques of data acquisition, display, and storage. Previously recorded data can be manipulated retrospectively, and changes can be applied to the filter settings, sensitivities, and monitor speeds. As a result, artifacts can often be minimized and eliminated, data can be analyzed in multiple ways, and areas of interest can be more easily pinpointed and logged for future reference. Computerized PSG recording is paperless, thus making it easy to store the data and conserve space.

See Figs. 2.6, 2.7, 2.8, 2.9, 2.10, and 2.11 for demonstrating the use of different channels during biocalibration. Figures 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, and 2.21 demonstrate the various sleep stages, and Figs. 2.22, 2.23, and 2.24 demonstrate various types of apneas.

There are two types of calibrations in digital PSG:

1. Machine calibration
2. Biocalibration

Both machine and biocalibrations should be done before lights off and after lights on.

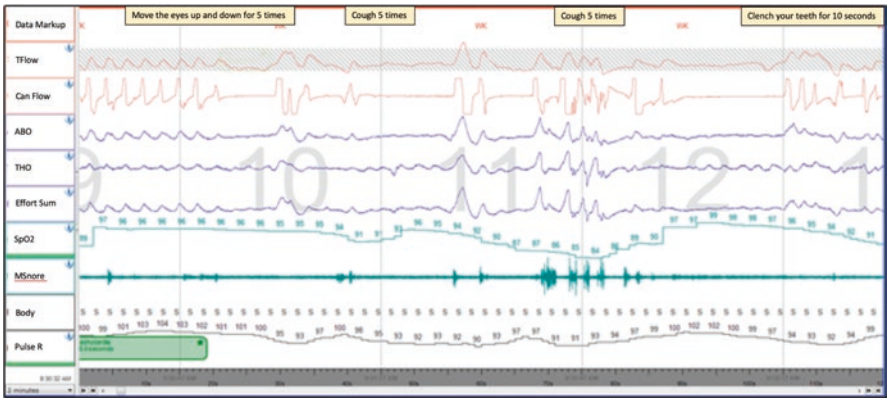

Fig. 2.6 Biocalibration command "Cough five times." With cough in snore channel (MSnore) shows activity which means snore channel is working well. Epoch duration: 2 min

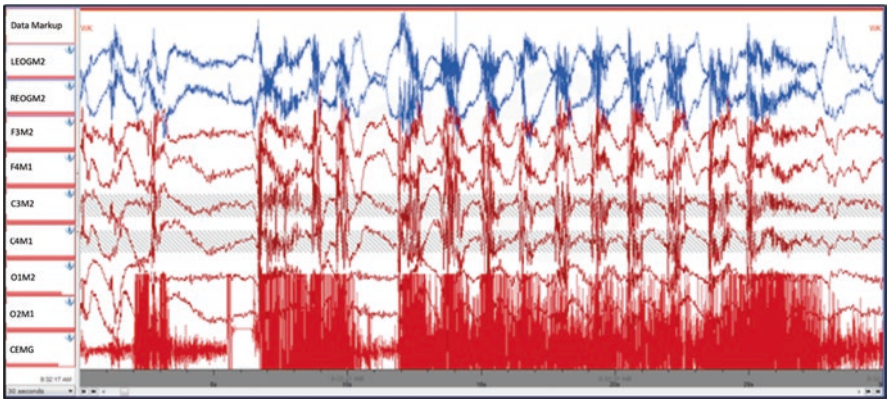

Fig. 2.7 Biocalibration command "Clench your teeth ten times." Activity in chin EMG (CEMG) channel increases which is reflected in EEG and EOG channels as well. Epoch duration: 30 s

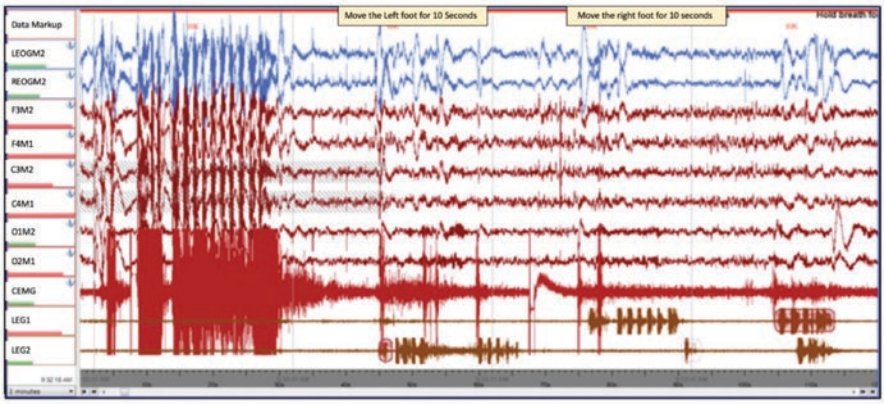

Fig. 2.8 Biocalibration command to move the left foot ten times and then to move the right foot for ten times. Leg 2 channel is indicating the sensor on the left leg and Leg 1 channel is indicating the sensor on the right leg

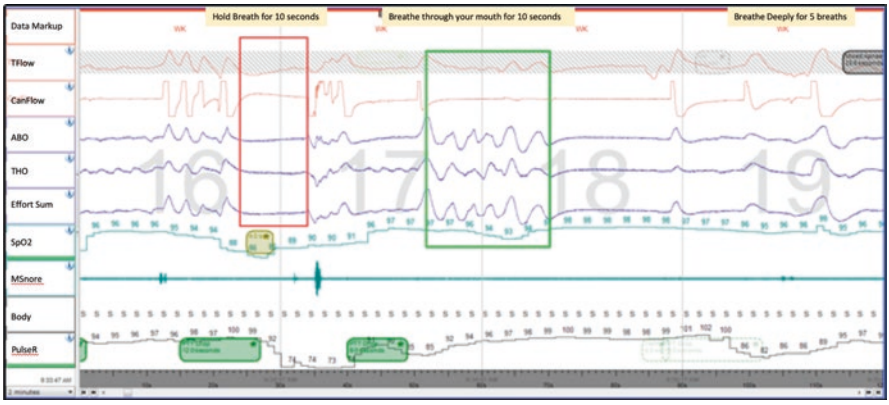

Fig. 2.9 Biocalibration command "Hold breath for 10 s" and "Breathe through your mouth for 10 s." The patient is using nasal cannula (CanFlow) and oronasal thermistor (TFlow). When a patient holds his breath, the following signals Tflow, CanFlow, ABD, and THO become flat mimicking central apnea (first box). When a patient breathes through his mouth, the signal in CANFlow becomes flat, but TFlow is recording airflow from the mouth and respiratory effort is present (second box). Epoch duration: 2 min

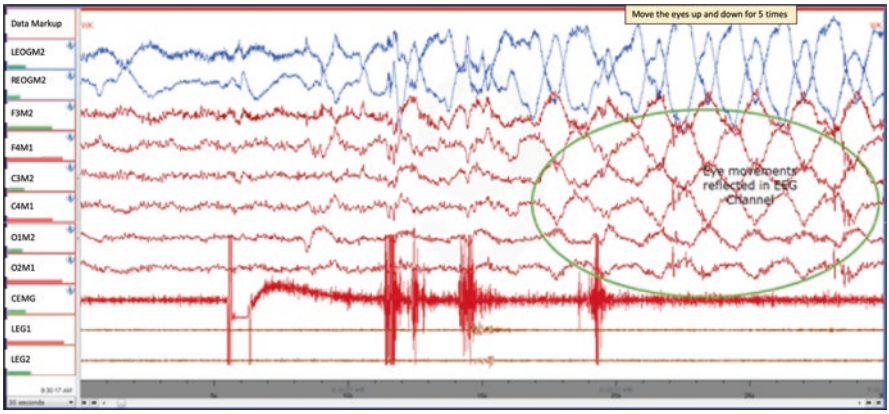

Fig. 2.10 Biocalibration command "Move the eyes up and down five times." LEOG and REOG channels show eye movements and eye movements are reflected in EEG channels as well (circle)

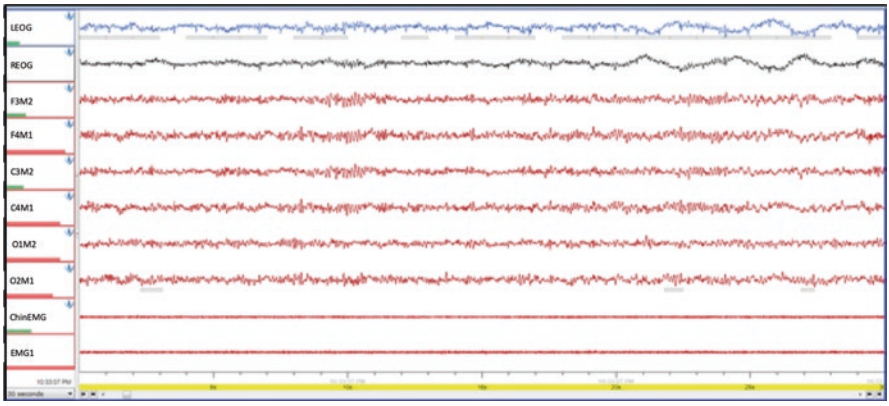

Fig. 2.11 Biocalibration command "Close your eyes for 30 s." Note the prominent alpha activity in all the EEG channels. Epoch duration: 30 s

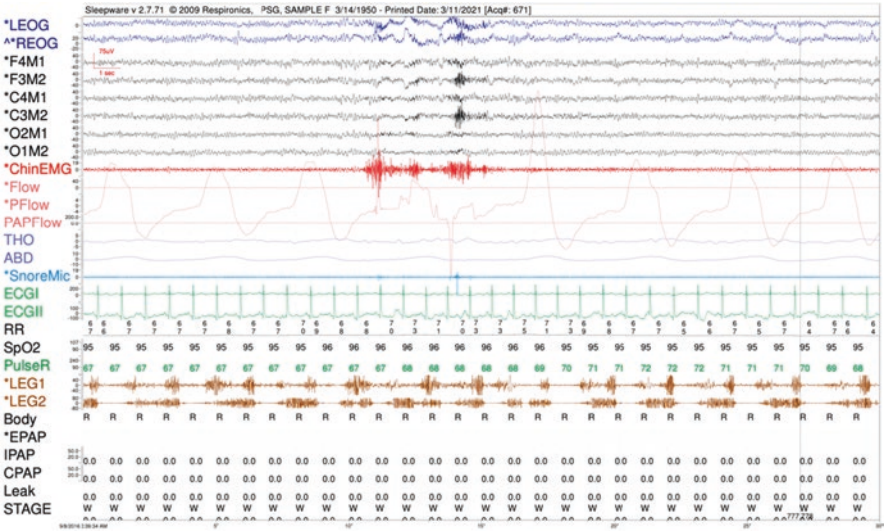

Fig. 2.12 Stage wake: Swallow seen in the middle of the epoch. Stage wake is indicated when (1) over 50% of each epoch contains alpha activity, (2) slow rolling eye movements or eye blinks will be seen in the EOG channels, and (3) there is relatively high submental EMG muscle tone

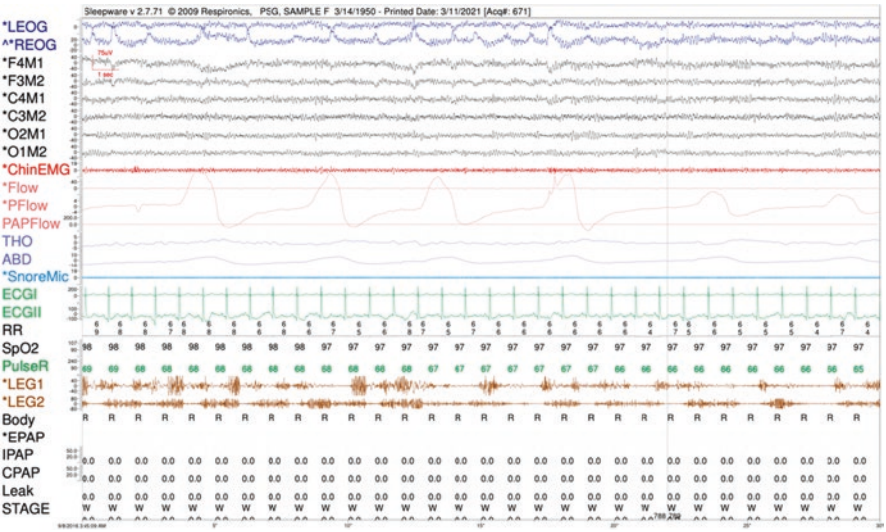

Fig. 2.13 Awake: Eye movements and leg movements

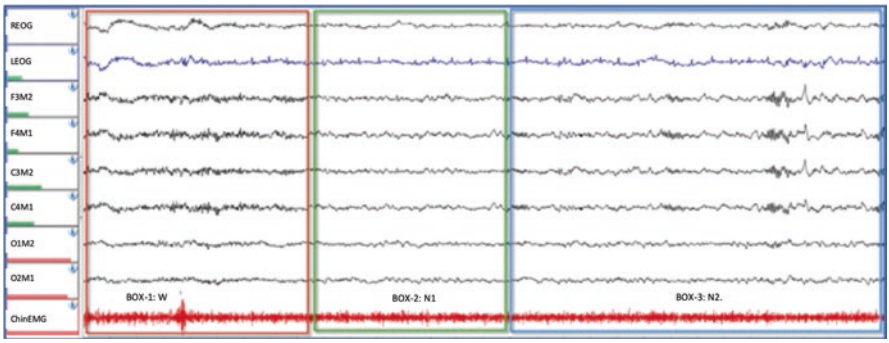

Fig. 2.14 Sleep onset: Previous epoch was stage W; this shows a change in EEG activity. Therefore, a change in sleep stage has occurred. This 30 s epoch shows three stages in one epoch: stage W (Box-1), stage N1 (Box-2), and stage N2 (Box-3). Stage W is present for 8.5 s, stage N1 is present for 7.5 s, and stage N2 is present for 14 s. First step: 21.5 s is sleep, so overall, this epoch should be scored as sleep. Second step: Stage N2 occupies 14 sec and stage N1 occupies 7.5 s; therefore, this epoch should be scored as N2

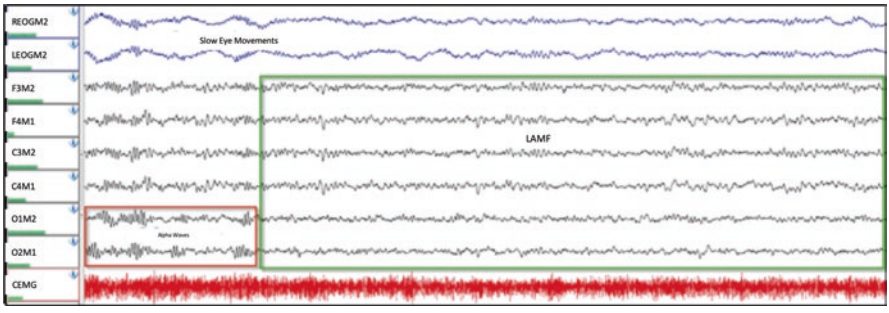

Fig. 2.15 Non-REM stage 1 sleep: Stage 1 sleep is considered a transitional sleep stage. It is scored when more than 15 s of theta waves are seen replacing alpha waves [low-amplitude mixed frequency (LAMF)]. Stage 1 sleep is indicated when (1) ≥50% of the epoch contains theta activity (there may be alpha activity within <50% of the epoch), (2) there are slow rolling eye movements in the EOG channels, and (3) there is relatively high submental EMG tone. Stage 1 sleep lasts 15–20 min and comprises 2–5% of total sleep time (TST)

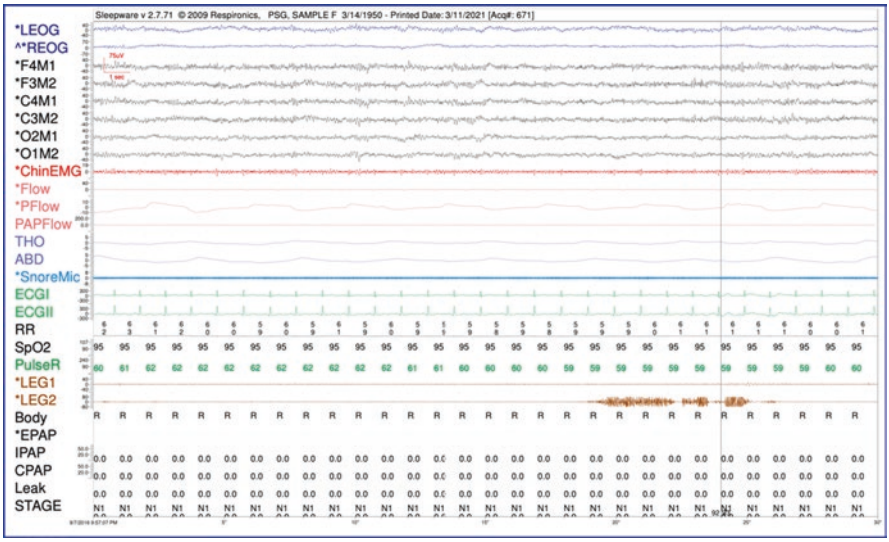

Fig. 2.16 N1 sleep: Stage N1, 30 s epoch. In order to score this epoch as N1, the previous epoch had to be stage W. Changes seen on the channels are as follows: EOG: It shows slow eye movements (SEMs). EEG: Alpha activity is replaced with LAMF for 24 s. EMG: Chin EMG tone is high and has not decreased compared to stage W. This epoch is scored as stage N1 because alpha activity is replaced with LAMF for >15 s without sleep spindle or K-complex and no REM is present in EOG

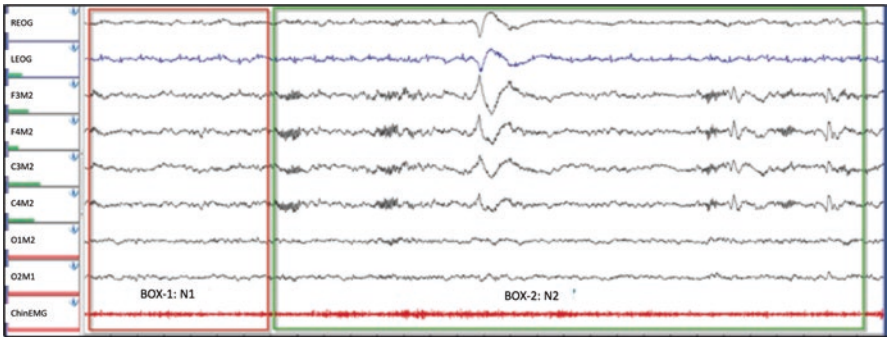

Fig. 2.17 Stage 2 sleep: Stage N2, 30 s epoch. In order to score this epoch as N2, the previous epoch had to be N1, to show EOG, EEG, and EMG activity changes. Changes seen for stage N2 are as follows: EOG: No eye movements are present. EEG: First 8 s show LAMF continuing from previous epoch of stage N1, and appearance of spindle at 8 s marks the beginning of stage N2. EMG: Chin EMG has further decreased as compared to stage N1. This epoch is scored as stage N2 because N2 is present for 22 s and N1 is present for only 8 s. Therefore, we assign the stage which occupies the majority of the epoch

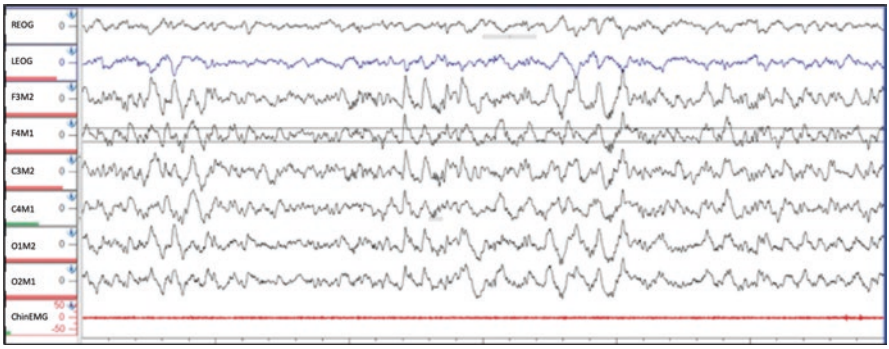

Fig. 2.18 Stage 3 sleep: Stage N3, 30 s epoch. In order to score this epoch as N3, the previous epoch had to be N2. This epoch is scored as stage N3 because there are >6 s of slow waves in this epoch. (Reference lines have been drawn at F4A1 channel. Any wave touching both the reference lines will have an amplitude of 75 mV.) This is a 30 s epoch. All EEG leads show slow waves. EOG does not show any eye movements. EEG waveforms are reflected in EOG

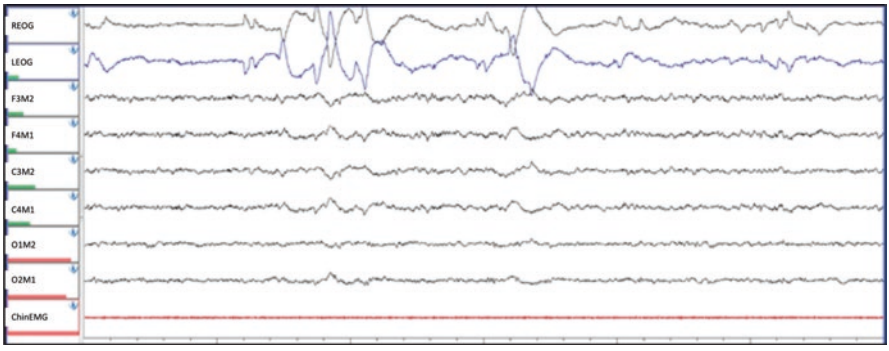

Fig. 2.19 REM sleep: REM, 30 s epoch. Previous epoch was stage N1. Appearance of REM sleep marks termination of stage N1

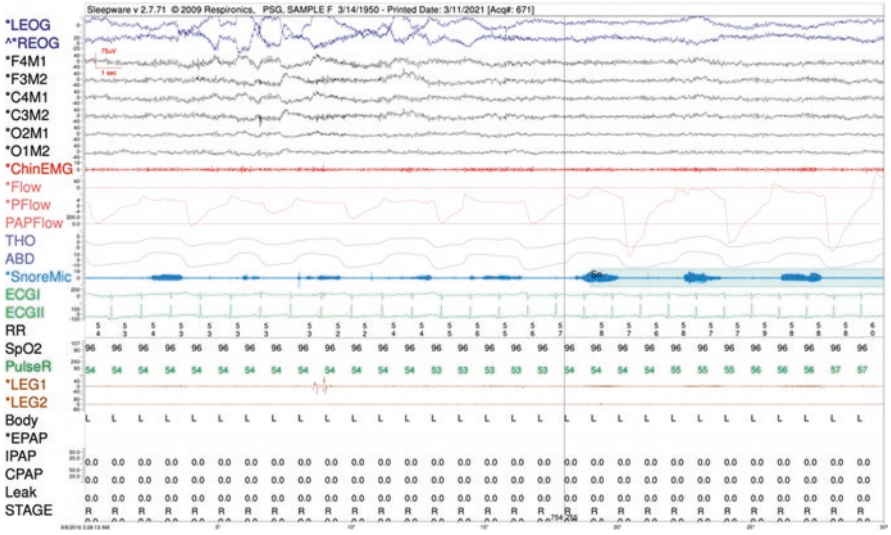

Fig. 2.20 Stage REM phasic: Rapid eye movements, and some muscle twitching is seen in stage R sleep

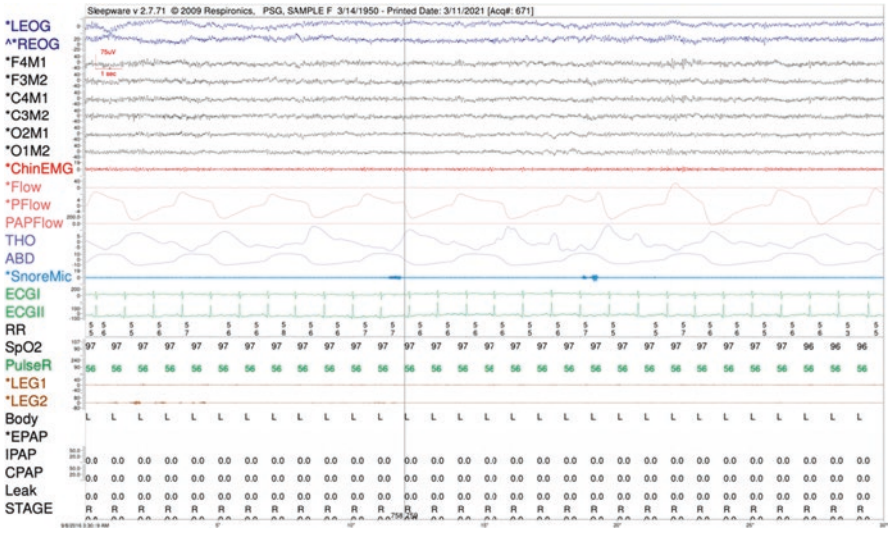

Fig. 2.21 Stage REM tonic: No eye movements or muscle tone is noted in stage R sleep

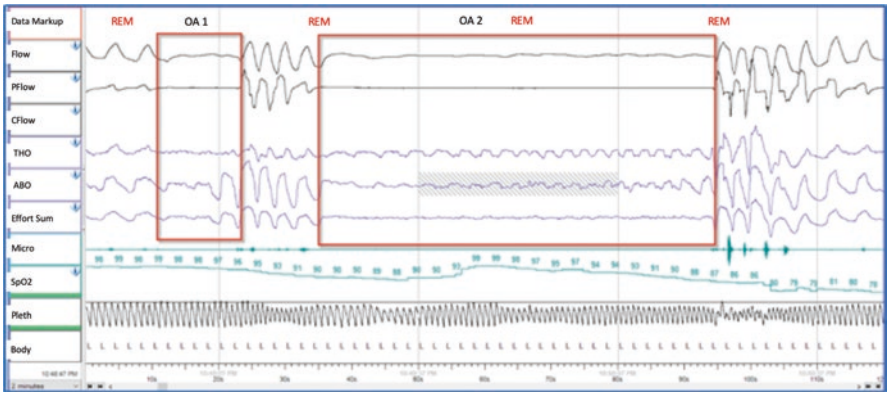

Fig. 2.22 Obstructive sleep apnea (OSA): Obstructive apnea (OA) in level 1 or 2 diagnostic study. A 2 min window. This figure shows two OA (OA 1 and OA 2). Airflow amplitude has decreased by 90% on oronasal thermal sensor (flow) and duration is 13 s for OA 1 and 1 min for OA 2, and respiratory effort (THO and ABD channels) is present throughout the duration of both apneas

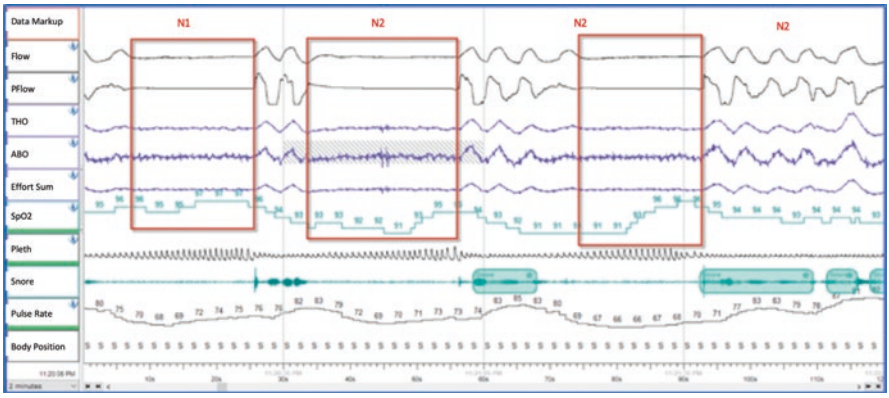

Fig. 2.23 Central sleep apnea: Central apnea (CA) in level 1 and 2 diagnostic sleep study. A 2 min window. Oronasal thermal sensor records three CA (inside box). Airflow amplitude has decreased by 90% on oronasal thermal sensor (flow) and duration is 19 s for first CA, 24 s for second CA, and 18 s for third CA, and respiratory effort (THO and ABD channels) is absent throughout the duration of apnea in all three apneas

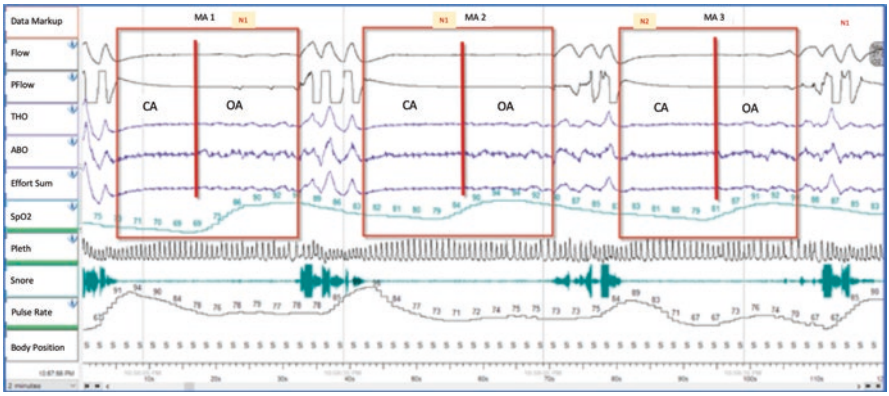

Fig. 2.24 Mixed sleep apnea: Mixed apnea (MA) in level 1 and 2 diagnostic sleep study. A 2 min window. In this figure, the oronasal thermal sensor (flow) shows 3 MA (MA1, MA2, MA3 (inside box)). Airflow amplitude has decreased by 90% on an oronasal thermal sensor (flow), and duration is 25 s for MA1, 30 s for MA2, and 28 s for MA3. Respiratory effort (THO and ABD channels) is absent during the first portion of the apnea (CA) and resumes during the second portion of the apnea (OA)

2.10.1 Machine Calibration

- It is done by inputting a known voltage, typically 50 μV, to all channels.
- It confirms amplifier function and amplifier control response for each channel.
- Machine calibration is performed by sending a signal of known voltage (50 μV) through all the amplifiers, with each channel set to its recommended values for low-frequency filter (LFF), high-frequency filter (HFF), gain, or sensitivity.
- The signal that is generated on giving the calibration command is evaluated for consistent amplitude, morphology, and time constant.
- In digital PSG, this is sometimes referred to as montage calibration.

2.10.2 Biocalibration

- Biocalibrations serve two general purposes.
- Biocalibrations allow for immediate determination of any problems in the recording.
- Calibration tracing is invaluable for scoring the record as it shows how a certain signal displays in a particular individual.

2.11 Understanding Findings of a Polysomnography Report

Sleep study reports are typically arranged into sections containing patients' information, which includes their sleep-related symptoms, the technical details, quantitative data regarding distribution of different stages of sleep called sleep architecture, and sleep staging.

Technical details document the number of channels to record electroencephalogram (EEG), electrooculogram, chin and leg electromyogram, electrocardiogram, and airflow at the nose and mouth. The chest and abdominal wall movements are recorded by plethysmographic strain belts. The oxygen saturation is sampled by continuous pulse oximetry, and the snoring microphone is used for recording the snoring and its intensity. Multiple simultaneous parameters are recorded using an arrangement of wires and belts called a montage.

The indications for the study are recorded in the context of patients' complaints, family history, medical history, and psychosocial- and sleep-related problems as well as their medications. Each of these elements has a significant impact on the recording of the data and the interpretation and final impression drawn after review of the sleep study [77].

2.11.1 Definitions of PSG Report

The next section of the report generally includes sleep architecture, including total recording time and/or time in bed along with total sleep time.

2.11.1.1 Total Recording Time

Total recording time is the total amount of time during which the patient is in bed with recording equipment activated. The amount of time actually spent in bed is an important limiting factor for the total sleep time and sleep stages. A patient who spends only 3–4 h in bed cannot reasonably accumulate normal amounts of sleep and may not go to all normal stages and cycles of sleep. Therefore, a low total time in bed may be of clinical significance and may support a diagnosis of insufficient sleep.

2.11.1.2 Sleep Latency

Sleep latency is one of the most important parameters in a sleep study. The duration of time between when the lights are turned off (lights out) as the patient tries to fall asleep, until the time the patient actually falls asleep, as evidenced by the specific changes in EEG and behavioral parameters consistent with onset of sleep, is reported as sleep latency. Sleep latency is the time in minutes from "lights out" that marks the starting of total recording time to the first epoch scored as sleep. Sleep latency also indicates if reasonable attention was paid to the patient's sleep diary and the "lights out" time was close to the patient's routine bedtime at home. Clearly, if the lights are turned out earlier than the patient's usual bedtime, sleep latency would be spuriously long, and the patient may not fall asleep until his/her usual sleep time is reached. Similarly, if the "lights out" time is later than the patient's usual bedtime,

the patient will be sleepy, and a spuriously short sleep latency will be recorded. It is important that the patient's usual habitual sleep time is incorporated into the patient's sleep study design and "lights out" time is approximated.

2.11.1.3 Total Sleep Time

Total sleep time is the total amount of sleep time scored during the total recording time. This includes time from sleep onset to sleep offset and is distributed throughout the sleep time as minutes of stage N1, stage N2, stage N3, and REM sleep. All these times are described in minutes.

A low total sleep time may indicate that the patient slept for an insufficient period of time due to nonmedical/nonphysiological reasons, certain medical or sleep disorders, or as a result of the effect of medications.

A long total sleep time may suggest prior sleep deprivation, medical conditions, or effects of medications.

2.11.1.4 Sleep Fragmentation

High levels of sleep fragmentation, as defined by recurrent awakenings and/or stage shifts, may result in complaints of non-restorative sleep even when an apparently normal total sleep time is present.

2.11.1.5 Sleep Efficiency

Sleep efficiency is another important parameter that refers to the percentage of total time in bed actually spent in sleep. It is calculated as the sum of stage N1, stage N2, stage N3, and REM sleep, divided by the total time in bed and multiplied by 100.

Sleep efficiency gives an overall sense of how well the patient slept, but it does not distinguish frequent, brief episodes of wakefulness.

A low sleep efficiency percentage could result from long sleep latency and long sleep offset to lights on time with otherwise normal quantity and quality of sleep in between. Many laboratories report total wake time, that is, the amount of wake time during the total recording time in minutes after the sleep onset. The total amount gives a general estimation for overall quality of sleep. Total wake time is the reciprocal of total sleep time. A high total sleep time percent is always associated with low total wake time percent and vice versa.

2.11.1.6 WASO and WASF

Wake after sleep onset, also known as "WASO," is an important parameter. This refers to periods of wakefulness occurring after the sleep onset. This parameter measures wakefulness, excluding the wakefulness occurring before sleep onset. WASO time is a better reflection of sleep fragmentation.

Wake time after sleep offset is known as "WASF" and refers to wakefulness that occurs after sleep offset. Long periods of wakefulness following an atypically early morning awakening could be consistent with one of the classic diagnostic signs of depression. This can be found in elderly patients who have no difficulty in falling asleep but wake up after 3–4 h of sleep and are unable to return to sleep. This pattern may be seen in patients who suffer with depression or anxiety and possibly an effect of medications.

2.11.1.7 Rapid Eye Movement Latency

Rapid eye movement latency also known as REM latency is another crucial reported parameter. Rapid eye movement latency is the time from the sleep onset to the first epoch of REM sleep; therefore, it depends on the patient's sleep latency.

The REM sleep cycles every 90–120 min intervals throughout the night. The changes in REM sleep latency are considered potential biological markers for a number of sleep-related disorders. REM sleep is very sensitive to the effects of medication, sleep deprivation, and circadian rhythm disorders. The knowledge of patients' current medications and the quality of sleep the night before the sleep study therefore is extremely important to review.

A short REM latency time may result from withdrawal from tricyclic antidepressants (TCAs) or monoamine oxidase inhibitor (MAOI) medications. Withdrawal from amphetamines, barbiturates, and alcohol can also cause a shortened REM latency period. Patients with a history of narcolepsy, sleep apnea, and depression may have short REM latency.

A long REM latency may result from the use of REM-suppressing medications, including TCAs, MAOIs, amphetamine, barbiturates, and alcohol. Sleep apnea and periodic limb movement of sleep can also lead to long REM sleep latency.

2.12 Stages of Sleep

A sleep study report describes the percentages of various sleep stages. The normal percentage of each stage is reported with the number of total REM stage sleep cycles recorded overnight. In adults, approximately 5% of the total sleep time is stage N1 sleep; 50% is stage N2 sleep; and 20% is stage N3 sleep. The remaining 25% is REM stage sleep [78, 79].

2.12.1 Non-rapid Eye Movement Sleep

Sleep staging is described in a separate section of the report.

Stage N1 sleep is associated with the transition from wakefulness to sleep and is considered a direct measure of daytime alertness and the subjective refreshing quality of sleep. The quantity and the percentage of stage N1 sleep is an estimate of the degree of sleep fragmentation. A high percentage of the stage N1 sleep is generally a result of frequent arousals caused by sleep disorders, like sleep apnea, periodic movement of sleep, or snoring. Other causes of sleep disruption, including environmental disturbances, may also lead to increased amounts of stage N1 sleep.

Stage N2 sleep predominates the sleep stages with 50% of the total sleep time. It follows the stage N1 sleep and continues to recur throughout the night. A low percentage of stage N2 sleep may be a result of sleep fragmentation, increased REM, stage N3, or a result of obstructive sleep apnea-related arousals. An increased

amount of stage N2 sleep may also be noted in age-related changes in sleeping pattern and may be a result of medication effect.

Stage N3 is considered as "deep sleep." It is sometimes referred to as slow-wave sleep. The stage N3 sleep generally cycles frequently in the first third of the night and begins to reduce toward the second half of the night. A high amount of stage N3 sleep is noted during rebound sleep (such as recovery sleep after sleep deprivation, initiation of nocturnal CPAP treatment, or treatment of periodic limb movement syndrome). Less stage N3 sleep is noted as a side effect of certain medications, including benzodiazepines, TCAs, and barbiturates. Episodes of night terror, sleep walking, sleep talking, and confusional arousals also occur during stage N3 sleep. Stage N3 is also known to suppress the occurrence of sleep-disordered breathing [80, 81].

2.12.2 Rapid Eye Movement Sleep

The exact function of the REM is uncertain. However, it occupies approximately 25% of the total sleep time. REM sleep cycles occur every 90–120 min throughout the night with progressively increasing periods of time. REM sleep is associated with more frequent and longer duration apneas, hypopneas, and severe hypoxemia. REM sleep suppresses periodic leg movements. Certain medications suppress the REM sleep including amphetamines, barbiturates, TCAs, MAOIs, anticholinergics, and alcohol. Certain sleep disorders, including sleep apnea, REM behavior sleep disorder, and nightmares occur in REM sleep. A higher amount of REM sleep is notable during recovery sleep after selective deprivation of REM sleep. REM sleep "rebound" occurs after discontinuation of REM sleep-suppressing medications, alcohol, and initiation of CPAP therapy [82].

2.12.3 Practice Implications

An overall review of the sleep study report provides an excellent account of what was recorded over 6–8 h of sleep. It is important for the referring physician to review the sleep study report and correlate patient's presenting sleep complaints to the results. Patients may also report their posttreatment residual problems and complications to their healthcare provider. Multiple recommendations can be made based on the observations made in the sleep study report. The clinical management decisions regarding normalizing the long sleep latency may be made by practicing good sleep hygiene, thus avoiding over-the-counter sleep aids and prescription hypnotics. Improvement in sleep efficiency can be accomplished with an increase in total sleep time in relation to total time in bed, as well as exploring potential causes of poor sleep efficiency. A good example of this is when adequate pain management is applied in chronic pain syndrome, resulting in improved sleep quality.

An understanding of the effect of medications on sleep architecture and staging helps the primary care physician manage sleep disorders, as well as the primary disorder for which these medications were started in the first place. In general, REM sleep is suppressed by MAO inhibitors and tricyclic antidepressant, amphetamines, barbiturates, and alcohol. Withdrawals from these medications cause rebound and excessive REM sleep. Benzodiazepines increase the amount of stage N2 sleep and reduce stage N3 sleep.

Sleep reports are concluded with recommendations regarding the management plan including the use of CPAP therapy, consideration of other treatment modalities like dental sleep appliances, and surgical intervention. If the patient is a candidate for CPAP, management plans include recommendations for the type and the size of the mask and whether a warm or cold humidifier is recommended for patient comfort and to prevent drying of secretions. "Ramp time," a gradual increase in CPAP pressure over many minutes as the patient tries to fall asleep, is recommended for patients who may not tolerate high CPAP pressures. If a mouth air leak is noted while using a nasal mask, a chinstrap is recommended to keep the jaw from falling open.

Multiple variables affect the sleep pattern including the "first-night effect" when the patient cannot sleep well in the sleep laboratory and has a different sleeping pattern than usual [83]. First-night effect can increase both stage N1 sleep and REM latency recorded in the sleep study. The "reverse first-night effect" is when the patients sleep better in the sleep laboratory compared to their home, as in case of psychophysiologic insomnia and frequently observed "night-to-night variability" in sleep [84]. It is therefore important to realize that in a patient with high pretest probability of sleep-disordered breathing, a negative sleep study may not rule out the condition [85].

2.12.4 Insomnia

Insomnia is one of the common manifestations among sleep disorders. It has been estimated that about a third of the population of industrialized nations have occasional episodes of insomnia and more than one out of every ten individuals report chronic difficulties that impact daytime activities.

ICSD-3 consolidates these types and groups them into categories of chronic and short-term insomnia. Within the chronic insomnia grouping, several characteristic types of insomnia are described. The four main categories of insomnia include the following entities:

- Chronic insomnia disorder
- Short-term insomnia disorder
- Other insomnia disorders
- Isolated symptoms and normal variants

Difficulties in initiating sleep, difficulties in maintaining sleep, and waking up too early have been reported in all age groups. However, resistance in going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker due to significant level of functional impairment (e.g., those with dementia).

Often, patients with chronic insomnia may show recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years and yet not meet the 3-month duration criterion for any single such episode. It is prudent to assign these patients a diagnosis of chronic insomnia disorder, given the persistence of their intermittent sleep difficulties over time.

Primary insomnia is hypothesized to result from factors that are amenable to cognitive and behavioral treatment approaches. These factors include poor sleep hygiene (SH), somatic arousal, cognitive arousal, and excessive worry regarding the ability to achieve sufficient sleep.

Primary insomnia is defined as a complaint of difficulty in initiating or maintaining sleep for at least a month, associated with daytime fatigue or impaired performance and no evidence of another sleep, medical, psychiatric, or substance abuse problem. Many times, the complaint of insomnia will be associated with another primary sleep disorder (sleep apnea, restless legs syndrome, circadian rhythm disorders, poor sleep hygiene, or sleep).

The differential diagnosis in any case of insomnia would include medical conditions, medication/substance use, psychiatric conditions, and other sleep disorders (insufficient sleep, circadian rhythm sleep-wake disorders, restless legs syndrome, periodic limb movement disorder, and sleep-disordered breathing).

A thorough comprehensive and systematic evaluation can help in identifying the core condition among heterogeneous and complex sleep disorders like insomnia. This can include medical disorders (pain, allergies, respiratory disease), neurologic conditions (parkinsonism, dementia, degenerative disorders), or psychiatric disorders (mood disorders, anxiety disorder, alcoholism).

There is a close relationship between insomnia and depression. Insomnia appears before depression in approximately 40% of patients, and patients with insomnia may later develop depression. In contrast, treatment protocols for patients with secondary insomnia recommend targeting the primary medical or psychiatric condition for treatment, with perhaps adjunctive pharmacologic treatments.

The underlying assumption is that insomnia will remit with successful resolution of the primary condition. Often patients with insomnia due to depression, anxiety, or other primary disorder continue to report disturbed sleep after the primary condition has resolved.

Factors contributing to insomnia can be categorized as predisposing, precipitating, or perpetuating. In this generally accepted model, it is easy to see how insomnia begins with the introduction of a primary medical or psychiatric disorder (precipitating factor) but then continues because of changes in adaptive behavior.

For example, when an individual is sleeping well, he/she is much less likely to eat during the night, leave the TV in the bedroom on, stay in bed late into the morning, take an afternoon nap, self-medicate with alcohol at bedtime, spend time during the day worrying about getting sufficient sleep, etc. These are precisely the types of behaviors that people adopt when sleeping poorly, often as a misguided attempt to improve their sleep or compensate for the lack of sleep.

2.12.5 Parasomnias

Parasomnias are unpleasant or undesirable behavioral or experiential phenomena that occur during the sleep period. These spells may be extremely undesirable to some but may be of no concern to others. They occur exclusively and may be augmented by the sleep state.

There are 24 distinct parasomnias listed in the International Classification of Sleep Disorders. They are sometimes dismissed in clinical practice as "bumps in the night." They are related to a change in brain organization across sleep states and are particularly apt to occur during the transition from one sleep state to another.

2.12.6 Confusional Arousals

These are often seen in children and are characterized by movements in bed, occasionally thrashing about or inconsolable crying. Sleep drunkenness is probably a variation on this theme. The prevalence of confusional arousals in adults is approximately 4% [86].

2.12.7 Sleepwalking (Somnambulism)

Sleepwalking is a series of complex behaviors that are initiated during SWS that result in walking during sleep. Sleepwalking is prevalent in childhood (1–17%), peaking at 11–12 years of age, and is far more common in adults (nearly 4%), than generally acknowledged [86].

Sleepwalkers may be either calm or agitated, with varying degrees of complexity and duration. Communication with the patient is often difficult. The main concern with this parasomnia is the risk of injury. Patients may engage in activities that may produce cuts and bruises from bumping into objects or falling. Sleepwalking often lasts 1–5 min, but rarely if behavioral spells are complex, episodes may last more than an hour.

2.12.8 Sleep-Related Eating Disorders

Sleep-related eating disorders are characterized by frequent episodes of nocturnal eating, generally without full conscious awareness, usually not associated with waking eating disorders, and likely represent a specialized form of disorder of arousal.

Formal sleep studies are indicated because sleep-related eating may be the manifestation of other sleep disorders, such as restless legs syndrome, periodic limb movements of sleep, and obstructive sleep apnea, all of which predispose to arousal. Sleep-related eating has been associated with zolpidem administration [87].

2.12.9 Sleep Terrors ("Pavor Nocturnus" Incubus)

Sleep terrors are the most dramatic disorder of arousals. It is frequently initiated by a loud blood-curdling scream associated with extreme panic, followed by prominent motor activity such as hitting the wall, running around, and out of the bedroom or even the house. This can result in bodily injury or property damage. A universal feature is inconsolability. Complete amnesia for the activity is typical.

As with sleepwalking, sleep terrors are much more prevalent in adults than generally acknowledged (4–5%) [88]. Although usually benign, these behaviors may be violent, resulting in considerable injury to the victim and others or damage to the environment, occasionally with forensic implications [89].

2.13 Basics of Sleep Hygiene

1. Sleep as much as needed to feel refreshed and healthy during the following day, but not more. Curtailing time in bed a bit seems to solidify sleep; excessively long times in bed seem related to fragmented and shallow sleep.
2. A regular arousal time in the morning seems to strengthen circadian cycling and to, finally, lead to regular times of sleep onset.
3. A steady amount of daily exercise probably deepens sleep over the long run, but occasional one-time exercise does not directly influence sleep during the following night.
4. Occasional loud noises (e.g., traffic noise) disturb sleep even in people who do not awaken because of the noises, and individuals cannot remember them in the morning. Sound attenuating in the bedroom might be advisable for people who must sleep close to excessive noise.
5. Although an excessively warm room disturbs sleep, there is no evidence that an excessively cold room solidifies sleep, as has been claimed.

6. Hunger may disturb sleep. A light bedtime snack (especially warm milk or similar drink) seems to help many individuals sleep.
7. An occasional sleeping pill may be of some benefit, but the chronic use of hypnotics is ineffective, at most, and detrimental in some insomniacs.
8. Caffeine in the evening disturbs sleep, even in persons who do not feel it does.
9. Alcohol helps tense people to fall asleep fast, but the ensuing sleep is then fragmented.
10. Rather than trying harder and harder to fall asleep during a poor night, switching on the light and doing something else may help the individual who feels angry, frustrated, or tense about being unable to sleep.

2.14 Sleep-Related Medications and Their Effect on Sleep

This section is based on Refs. [90–94].

Complex neurobiologic processes oscillate in opposite directions to promote sleep and wakefulness. Similar oscillation is noted between NREM and REM sleep. These processes are mediated by the neurotransmitter systems.

As discussed earlier, many neurotransmitter systems, including noradrenergic, serotonergic, cholinergic, adenosinergic, and histaminergic, and more recently, the hypocretin/orexin and dopamine systems have been well studied.

The chemical substances influence the neurotransmitter systems and make desired and sometimes undesired changes. Amphetamine-like stimulants are known to increase wakefulness by blocking dopamine reuptake, by stimulating dopamine release, or by both mechanisms. Modafinil may increase wakefulness through activation of noradrenergic and dopaminergic systems, possibly through interaction with the hypocretin/orexin system. Caffeine inhibits adenosinergic receptors, which in turn can produce activation via interaction with GABAergic and dopaminergic neurotransmission. Nicotine enhances acetylcholine neurotransmission in the basal forebrain and dopamine release.

Brain stem has specific areas that serve as a locus of certain types of neurotransmitter and neuromodulator systems. The substantia nigra (dopamine), gigantocellular nucleus of reticular formation (acetylcholine), locus coeruleus (norepinephrine), and nuclei of the raphe (serotonin) are a few examples of such areas.

Wakefulness is mediated in the basal forebrain (acetylcholine), tuberomammillary nucleus (histamine), suprachiasmatic nucleus (SCN) [projection to ventral tegmental area (VTA)], reticular formation (dopamine), raphe nuclei (serotonin), pedunculopontine nucleus (PPT), and lateral dorsal tegmentum (LDT) (acetylcholine).

NREM sleep is controlled by ventrolateral preoptic (VLPO) area, gamma-amino butyric acid (GABA), tuberomammillary nucleus (histamine), suprachiasmatic nucleus projection to VTA, raphe nuclei (serotonin), locus coeruleus, and PPT and LDT nuclei.

REM sleep is induced by cholinergic nuclei at PPT and LDT (acetylcholine).

2.14.1 Benzodiazepines and Barbiturates

The $GABA_A$ receptor is perhaps one of the important receptor complexes that serves GABA, benzodiazepine (BZD) and barbiturate subunits. The combination of GABA and benzodiazepine agonists causes profound sleepiness due to the larger opening of the chloride channel on the GABA receptor complex. Both BZDs and barbiturates increase total sleep time and stage N2 sleep. Both decrease sleep latency, slow-wave stage N3 sleep, and REM sleep. Barbiturates are a potent suppressor of REM sleep compared to BZD. The withdrawal from barbiturates may cause severe adverse events and overdose liability is high. The withdrawal from BZDs leads to rebound insomnia and its overdose liability is low. Other drugs which manifest their effects through the GABA receptors include non-benzodiazepine hypnotics, alcohol, chloral hydrate, and steroids.

Adenosine is delivered to the preoptic area and anterior hypothalamus to induce NREM sleep. In the basal forebrain (BF), adenosine levels rise during prolonged wakefulness. These levels decline during the recovery sleep. BZD decreases adenosine uptake but caffeine does not alter BDZ receptor action. Caffeine is an adenosine antagonist. In addition, theobromine and theophylline increase wakefulness and reduce sleep efficiency. Adenosine agonists increase sedation and slow-wave sleep.

2.14.2 Gamma-Hydroxybutyrate (GHB)

GHB is structurally similar to GABA and its agonism is mediated through $GABA_B$ receptors. GHB may induce G-protein-mediated decrease in acetylcholine and decreased dopamine release under normal circumstances and is partially reversible by naloxone. GHB does not bind to mu, delta, or kappa receptors. The sleep and endocrine response of GHB is well studied. It decreases sleep latency, decreases wake after sleep onset time, and increases sleep efficiency and slow-wave sleep. GHB increases the levels of growth hormone, prolactin, and cortisol.

2.14.3 Neuroleptics

Traditional neuroleptics like chlorpromazine, thorazine, haloperidol, haldol, thioridazine, and mellaril are D_2 and D_3 receptor antagonists and cause increased sedation, sleep efficiency, and slow-wave stage N3 sleep and aggravate periodic limb movement of sleep and produce restless legs syndrome-like effects. They also decrease REM sleep based on anti-acetylcholinergic properties.

Newer non-D_2 receptor neuroleptic drugs like clozapine, clozaril, olanzapine, zyprexa, risperidone, and risperidone cause variable amounts of increase in sedation and decrease in slow-wave N3 sleep. These newer compounds also tend to worsen restless leg syndrome and periodic limb movement disorder.

2.14.4 Dopamine

Dopamine has a significant effect on sleep-wake physiology. L-dopa, a precursor of dopamine at high doses, can cause insomnia. Apomorphine, a dopamine agonist, increases wakefulness. The D_2 receptor agonist, bromocriptine, decreases both the REM sleep and the REM rebound. Cocaine is a dopamine reuptake blocker and causes increase in wakefulness and an increase in REM sleep. The two dopamine antagonists, pimozide and neuroleptic group of drugs, are sedatives.

Some of the clinically used and recreational drugs cause stimulation by affecting dopamine and norepinephrine, increasing the wakefulness, sleep latency, number of awakenings, and REM latency. Obviously, the total sleep time, REM sleep percentage, and slow-wave sleep are reduced. These drugs include pemoline, mazindol, selegiline, amphetamines, methylphenidate, cocaine, and ecstasy.

2.14.5 Adrenergic Drugs

Adrenergic drugs exert their actions on sleep and wake via alpha and beta adrenergic receptors. Phenylephrine and clonidine are $alpha_1$ receptor agonists and reduce the amount of REM sleep. Prazosin, an $alpha_1$ receptor antagonist, possibly increases REM sleep. Yohimbine and mirtazapine are both $alpha_2$ receptor antagonists but have opposite effects on sleep with increased wake and increased sleep, respectively. Propranolol, a beta adrenergic receptor blocker, increases wakefulness, insomnia, and nightmares and reduces REM percentage.

2.14.6 Recreational Drugs

Recreational drugs affect sleep acutely, chronically, and upon withdrawal of the drug. The effects of alcohol are dose dependent and include decreased sleep latency, increased amount of N3 early in the night, and decreased REM sleep early in the night and rebound in the second half of the night. Nicotine disturbs the sleep by fragmentation and its withdrawal disturbs sleep. On the other hand, THC (marijuana) acutely causes reduced REM and REM density and increased REM on withdrawal. Chronically, THC does not cause any consistent alteration in sleep. LSD-25 increases early REM sleep, increased arousals and movements, and REM intrusion into the slow-wave N3 sleep. Opioids are known to cause sedation, increasing stage N1 sleep, stage REM, and N3 sleep during withdrawal. Recently, opioids are also known to cause central sleep apnea.

2.14.7 Antidepressants

Atypical antidepressant drugs like bupropion increase REM sleep and are less sedating, whereas venlafaxine and trazodone decrease REM and are very sedating. Nefazodone, on the other hand, increases REM and is nonsedating.

Serotonin selective receptor inhibitors (SSRI) in general decrease N3 sleep and REM sleep and are less sedating. Fluoxetine, paroxetine, and sertraline are few popular SSRI antidepressants used in clinical practice.

Another group of antidepressants is tricyclic antidepressants (TCAs). These drugs differ from one another depending on what their effect is on sleep. In general, they tend to increase N3 sleep, reduce REM sleep, and have variable degree of sedation. The exceptions are trimipramine that has no effect on REM and clomipramine which is most REM suppressing but is least sedating. Amitriptyline, trimipramine, and doxepin are most sleep inducing due to their high affinity for histamine$_1$ receptor blockage.

Monoamine oxidase (MAO) inhibitors like phenelzine strongly decrease REM sleep, increase REM sleep latency, and cause REM rebound when discontinued. MAO inhibitors do not change N3 sleep.

2.14.8 Antihistamines

Antihistamines exert their variable effects on sleep through histamine receptor antagonism. Cimetidine increases N3 sleep. Diphenhydramine is sedating, and triprolidine and brompheniramine reduce REM sleep. Astemizole and terfenadine are histamine$_2$ receptor antagonists and are nonsedating as they do not cross the blood-brain barrier.

2.14.9 Melatonin

Melatonin provides the human brain a signal for darkness. Exogenous melatonin can promote sleep-wake cycles in the blind humans. If taken 30–90 min before bedtime, it advances the sleep phase. Melatonin can cause drowsiness. When taken several hours before bedtime, the dosage should be small to avoid sleepiness. Exogenous melatonin has acute sleep-inducing and temperature-lowering effects during biological daytime (wake hours), and when suitably timed (it is most effective around dusk and dawn), it will shift the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times.

2.14.10 Modafinil

Modafinil, a wake-promoting drug, seems to selectively reduce GABA in sleep promoting regions. Modafinil increases histaminergic activity in the posterior hypothalamus (wakefulness-generating neurons) in the tuberomammillary nucleus. Modafinil inhibits ventrolateral preoptic area (sleep-generating neurons) activity in the anterior hypothalamus.

Caffeine, an adenosine antagonist, decreases total sleep time, slow-wave sleep, and REM sleep. It increases sleep latency and wake after sleep onset time. Caffeine increases dopamine levels in the same way that amphetamines do. The half-life of caffeine is about 6 h.

Neural mechanisms that control sleep and arousal have been discovered in the last many years. The level of arousal is controlled by an intricate interplay between wakefulness and sleep-promoting nuclei located in the hypothalamus and brain stem. Currently available drugs exert their therapeutic effects in the three major classes of sleep disorder (insomnia, hypersomnia, and parasomnia) by modifying neurotransmission at distinct sites within the arousal-controlling neuronal network. This enables classification of therapeutic drugs for sleep disorders on the basis of their modes of action: drugs that interact with the GABA sleep-promoting system, drugs that interact with different wakefulness-promoting systems, and drugs that modulate the level of arousal.

The routinely prescribed drugs and over-the-counter medications have significant effects on sleep and wakefulness. These effects are predictable as they alter the neurotransmitter systems. Understanding the basics of sleep pharmacology is crucial in diagnosis and treatment of sleep disorders.

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