Sleep Disorders in Psychiatric Patients

A Practical Guide

Hugh Selsick
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To:
My parents Ica and Resa who made everything possible.

My wife Ella, without whom nothing would ever get done.

My children Joey, Miri and Leila who make everything worthwhile.

Acknowledgments

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Introduction

Sleep is ubiquitous and occupies a third of our lives. Whilst we still do not fully understand the functions of sleep, the fact that we spend so much time in this vulnerable state testifies to its importance. Furthermore, given how much time we devote to sleep itis not surprising that there is a lot that can go wrong with this vital biological function. Sleep has long fascinated people but the scientific study of sleep and its disorders is a very new endeavour. It is not an exaggeration to say that we are still only scraping the surface of this vast field.

One could make the same argument with regard to our understanding of the human mind and its disorders. The mind is surely the most individual and variable aspect of the human organism. This makes it incredibly difficult to find universal principles that apply to all minds and therefore all disorders of the mind.

Given the enormous variability of the human mind and psychiatric disorders and our still rudimentary understanding of sleep, the problem of applying sleep medicine research to patients with psychiatric disorders seems an impossible task. Indeed if one asks a specific question about the interactions between sleep and psychiatric disorders or how to treat a sleep disorder in a specific patient with a psychiatric condition one would be very fortunate to find research that specifically addresses that question.

This complexity makes the field of sleep and psychiatry challenging but it is also what makes it so fascinating. When approaching patients with co-morbid sleep and psychiatric disorders one can bring to bear three sources of knowledge. The first is the existing research. Incomplete as it is, there is still a wealth of useful information in the growing body of research. The second is the application of basic principles to specific clinical situations. Understanding the underlying science of sleep, the nature of sleep and psychiatric disorders, and the mechanisms of medication and other treatments allows one to make informed and decisions about how to treat each individual patient. Finally, as with all aspects of medicine, there is a wealth of knowledge in the accumulated clinical experience of those who work in the field.

The book is divided into three sections: *Foundations* contains a basic introduction to normal sleep, taking a sleep history, the classification of sleep disorders, the various sleep investigations and the impact of psychiatric drugs on sleep. *Insomnia* has a section of its own; it was felt that insomnia required a more detailed treatment as it is the sleep disorder most likely to present to psychiatric clinics and is often the disorder that sleep specialists feel the least confident in managing. The final section,

Other Sleep Disorders addresses the broad categories of sleep disorders with the exception of insomnia. Each chapter describes the aetiology, symptoms, assessment and treatment of these disorders. One can read the book all the way through but one can also refer to individual chapters as needed.

Sleep medicine is a truly multidisciplinary branch of medicine and one that is growing and evolving all the time. I sincerely hope that this book will be useful to all clinicians who encounter sleep disorders and psychiatric disorders. But ultimately, it is my greatest hope that this book will benefit the patients that we treat. Sleep is often thought of as the "Cinderella" of medicine. The importance of sleep is too often forgotten by medical professionals, but rarely forgotten by patients. My experience as a psychiatrist is that we often have a complex relationship with our patients. Unlike other branches of medicine where doctors and patients usually agree on the nature of the illness and the best treatment plan, in psychiatry we often have very different explanations for symptoms from our patients and there is not infrequently conflict about the treatment. But even when doctor and patient are unable to reach agreement on the nature of the patient's symptoms or the importance of their psychiatric treatment, they can find common ground on the importance of good sleep and can strengthen the therapeutic relationship by working together to help the patient to sleep well. The successful treatment of their sleep problems will be immensely satisfying to the clinician, and positively life changing for the patient.

Contents

Part 1

Foundations

Normal Sleep

1

Rexford Muza

1.1 Introduction—Definition of Sleep

The Oxford dictionary defines sleep as 'a condition of body and mind which typically recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed, and consciousness practically suspended'. Sleep is episodic and, unlike unconsciousness, is promptly reversible. Sleep is a brain state, a physiological process and a behavioural process. The familiar behavioural characteristics of sleep include recumbence, quiescence and eye closure. While asleep, there is reduced awareness and reduced responsiveness to external stimuli. In addition to the diminution of sensory awareness, an active initiating mechanism of sleep is also believed to be at play. Sleep is also associated with relative motor inhibition. The external observable behaviour of an asleep individual suggests relative inactivity; this masks the intense neurological and physiological activity which goes on in sleep. Sleep is also tightly controlled by a complex neuronal circuitry.

Sleep is universal and is a requirement which cannot be resisted. We spend a third of our lives sleeping. Sleep touches nearly every aspect of our physiology and psychology; the amount and quality of sleep we have impacts on our daytime functioning, yet the purpose of sleep is still something of a mystery. Some have found it useful to look at sleep as a drive state such as hunger or thirst. Although the real reason for sleep remains poorly defined, it is known that sleep deprivation has deleterious consequences (Banks and Dinger 2007; Cirelli and Tononi 2008; Durmer and Dinges 2005; Knutson et al. 2007; Oliver et al. 2009; Gangwisch et al. 2006; Thomas et al. 2003; Thorne et al. 1999; Welsh et al. 1998). It has been postulated that sleep is needed for restoration, conservation of energy and memory

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consolidation (Genzel et al. 2014; Maquet 2001; Sejnowski and Destexhe 2000; Siegel 2005). Whatever the functions of sleep are, it is quite clear that sleep is essential for all animals, particularly during periods of growth. A growing brain needs more sleep than an adult brain; daily sleep amount is highest during periods when the nervous system is developing. Some have indeed regarded sleep as being 'of the brain, by the brain and for the brain'.

1.2 Sleep Architecture

Sleep architecture describes the pattern or structure of sleep. Sleep is broadly divided into NREM sleep and REM sleep (Carskadon and Dement 1994). The first description of non-rapid-eye movement (NREM) sleep was by Loomis back in 1937 (Loomis et al. 1938). Aserinsky and Kleitman then went on to describe rapid-eye-movement (REM) sleep in the early 1950s (Aserinsky and Kleitman 1953; Dement and Kleitman 1957). This was followed in 1968 by the publication of the standards for sleep staging using electroencephalography (EEG), electromyography (EMG) and electro-oculography (EOG) by Rechtschaffen and Rales (Rechtschaffen and Kales 1968). This has evolved over the past few decades and has culminated in the current American Academy of Sleep Medicine (AASM) scoring manual (Iber et al. 2007).

NREM sleep is further divided into stage N1, stage N2 and stage N3. In a healthy adult, sleep is entered through NREM sleep. The normal sleep cycle in a healthy adult starts with stage N1 (drowsiness), followed by the intermediate stage N2 and then stage N3 which is also known as slow wave sleep or delta sleep. After a brief return to stage N2, the individual then enters stage R (REM sleep). The first episode of REM sleep occurs after about 60–90 min and thereafter alternates with NREM sleep approximately every 90 min or so (Fig. 1.1). NREM sleep predominates in the

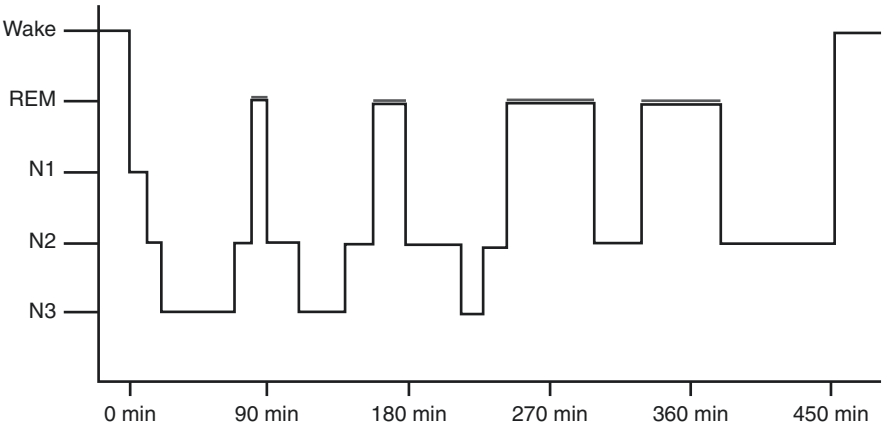

Fig. 1.1 Normal hypnogram: x axis = time in minutes from sleep onset. Y axis = sleep stages: Wake = wakefulness; Rem = Rapid Eye Movement Sleep; N1 = Non-REM Stage 1; N2 = Non REM Stage 2 and N3 = Non-REM Stage 3 (Slow wave sleep/Delta Sleep)

first third of the night. The amount of NREM sleep (delta power) decreases with the progression of the sleep period. REM sleep increases in frequency and length later during the sleep period. The first REM period of the night may be less than 10 min in duration, while the last may exceed 60 min. REM density (eye movements/time) is also greater in the second half of the night. Abnormal events (parasomnias) arising out of NREM sleep, such as sleep walking (somnambulism), are therefore more likely to occur in the first half of the night and events arising out of REM sleep, such as REM behaviour disorder, are more likely to occur in the second half of the night. In adults, the average sleep duration is about 8 h and 20 min; some individuals will need much less than this while others will need more to function optimally during the day.

Sleep in infants is quite different from sleep in the adult. Term infants enter sleep through REM sleep (active sleep). At that time, REM sleep comprises 50% of the total sleep time. Sleep cycles are 45–60 min in duration. Various EEG features emerge as the brain matures: sleep spindles appear at 2–3 months, K complexes appear at 4–6 months and slow wave activity appears at 4–5 months. By the time the infant is 6 months old, stage N1, N2 and N3 can be identified. Sleep across the lifespan is described in more detail below.

1.2.1 Stage Wake

The electrographic features of wakefulness were first described by Hans Berger in 1929. The electro-encephalogram (EEG) of stage wake with eyes open demonstrates low amplitude beta and alpha frequencies. Alpha rhythm activity (8–13 Hz) is usually demonstrated in the posterior regions of the head with eyes closed during relaxed wakefulness. A posterior dominant rhythm of less than 8 Hz is deemed pathological. It is important to be aware that the alpha rhythm of wakefulness is 1–2 Hz faster than the alpha rhythm which occurs during REM sleep. In addition to the EEG features of wakefulness, the electro-oculogram (EOG) may demonstrate rapid eye movements (REMs), blinks and reading eye movements. Slow eye movements (SEMs) may also be present. Chin electromyogram (EMG) activity could be normal or high. During wakefulness, respiratory activity is usually regular; but as with other physiological variables, it is also affected by external stimuli (Figs. 1.2 and 1.3).

1.2.2 Sleep Onset

The perception of sleepiness is all too familiar but the precise definition of sleep onset is still not so clear cut. Sleep onset is heralded by certain behavioural, EEG, EOG and electro-myographic (EMG) changes (Davis et al. 1938). As described above, stage wake is characterized by open eyes and low amplitude EEG activity (beta and alpha frequencies). REMs may be present. The EMG demonstrates muscle artefact and the chin EMG is usually relatively increased. As sleep onset

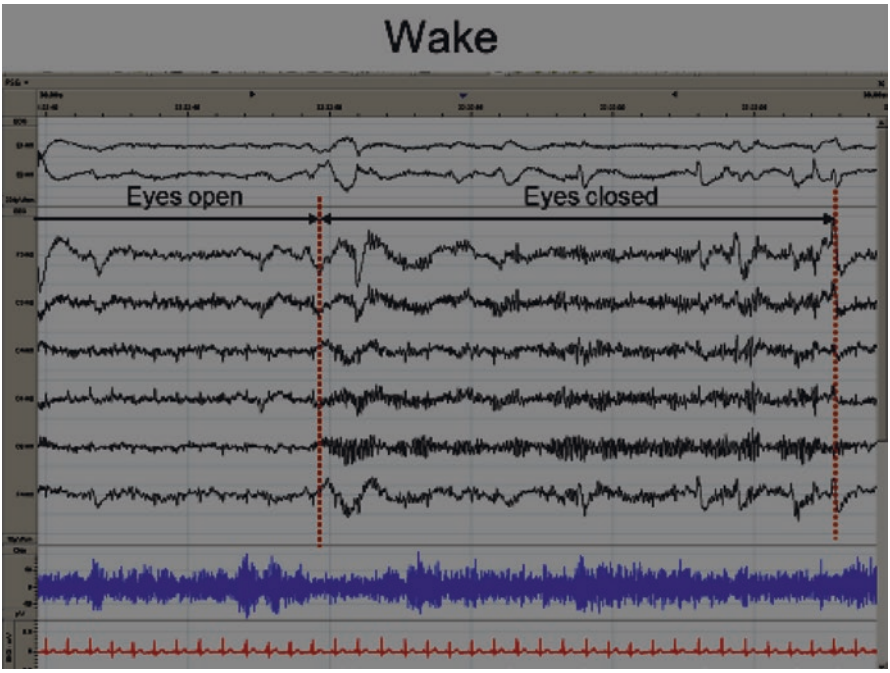

Fig. 1.2 Wakefulness

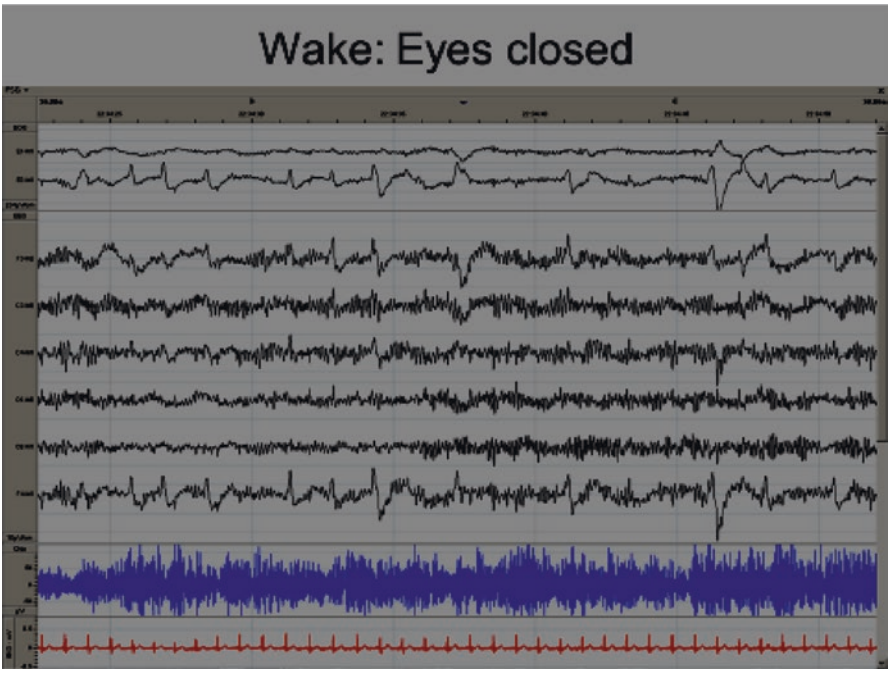

Fig. 1.3 Wakefulness with eyes closed

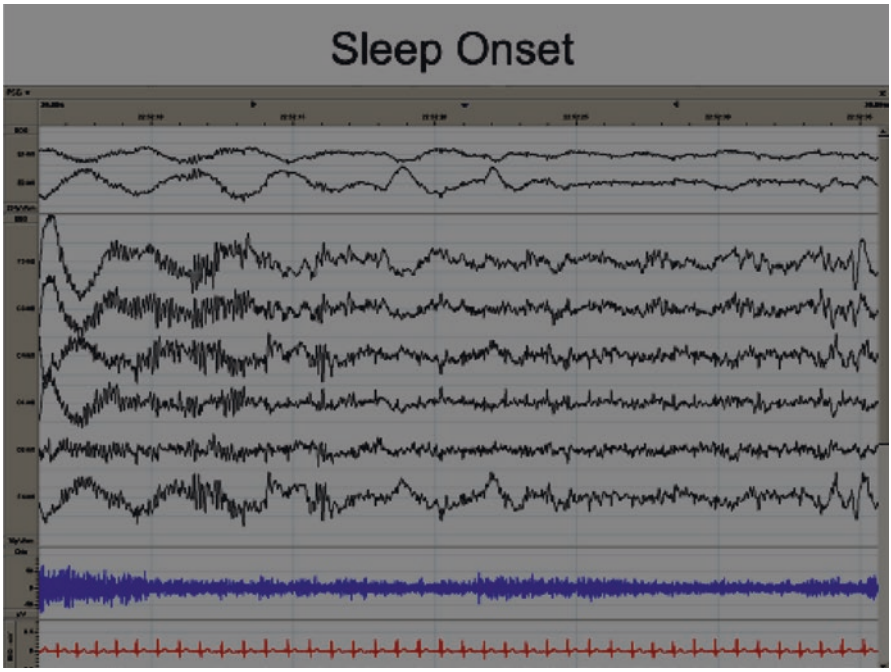

Fig. 1.4 Sleep onset

approaches, the EEG pattern of wakefulness is replaced by a low voltage mixed frequency pattern (Fig. 1.4). The EOG may show asynchronous eye movements and may also show SEMs. Generally, there is also a diminution in muscle tone on EMG. Behavioural features of sleep onset include eye closure and reduced attentiveness and responsiveness to external sensory input and stimuli; this could be visual, auditory, olfactory and indeed quite a number of other stimuli. Another curious but common phenomenon observed in healthy individuals at sleep onset is hypnic jerks (hypnic myoclonus) which are characterized by sudden muscle contractions. The hypnic jerks are not well understood but are non-pathological—although they tend to occur more frequently with stress, sleep deprivation and irregular sleep patterns.

1.2.3 Stage N1

Stage N1, the transitional stage, is characterized by a low-amplitude mixed-frequency (LAMF) EEG activity without sleep spindles and K-complexes (see below). The dominant EEG activity is in the 4–7 Hz range. Blinking stops and saccadic eye movements are absent. Vertex waves may be present but are not required to fulfil the criteria of stage N1. Chin EMG is of variable amplitude but is usually lower than in wake. Sudden muscle contractions (hypnic jerks) may occur and may

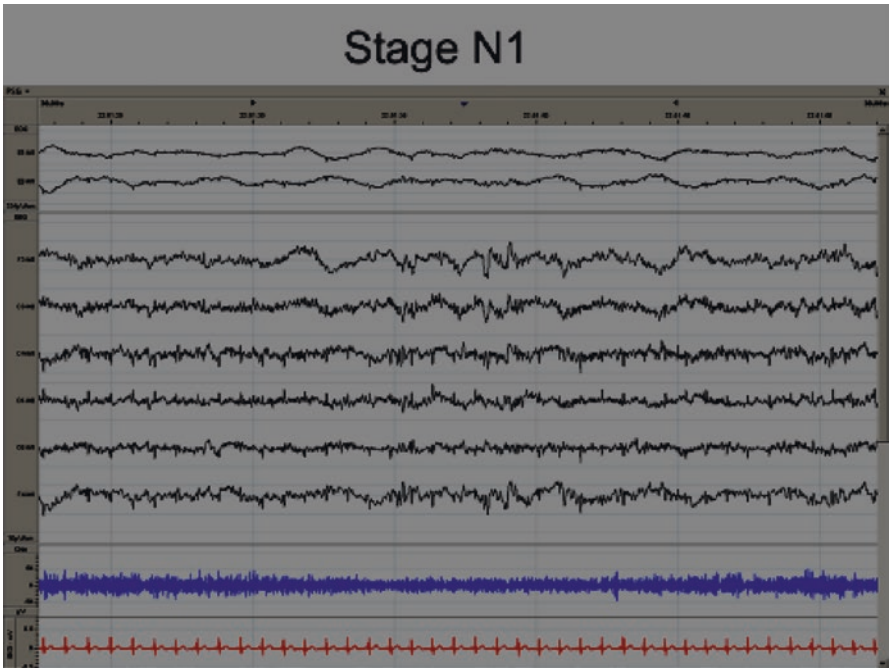

Fig. 1.5 Stage N1

jolt the individual awake. Individuals are easily woken up from stage N1 sleep as the arousal threshold is low. Stage N1 accounts for about 5% of total sleep time, but is increased in patients with a disturbed night's sleep. Such sleep is generally non-refreshing (Fig. 1.5).

1.2.4 Stage N2

Stage N2**,** the intermediate sleep stage, is characterized by the presence of K complexes which are not associated with arousals. These are brief (0.5 s) high voltage spikes on the EEG. Another hallmark of stage N2 is sleep spindles which are brief (0.5–1.5 s) bursts of high frequency (12–16 Hz) low amplitude waves which initially increase then decrease in amplitude. SEMs will have ended and usually no eye movements are seen on EOG. EMG demonstrates variable muscle tone which is usually lower than that of wakefulness. Stage N2 accounts for 50% of total sleep time (Fig. 1.6).

1.2.5 Stage N3

Stage N3—deep sleep—is characterized by the presence of slow wave (delta) activity of 0.5–2 Hz which is equal to or greater than 20% of an epoch. SEMs and REMs

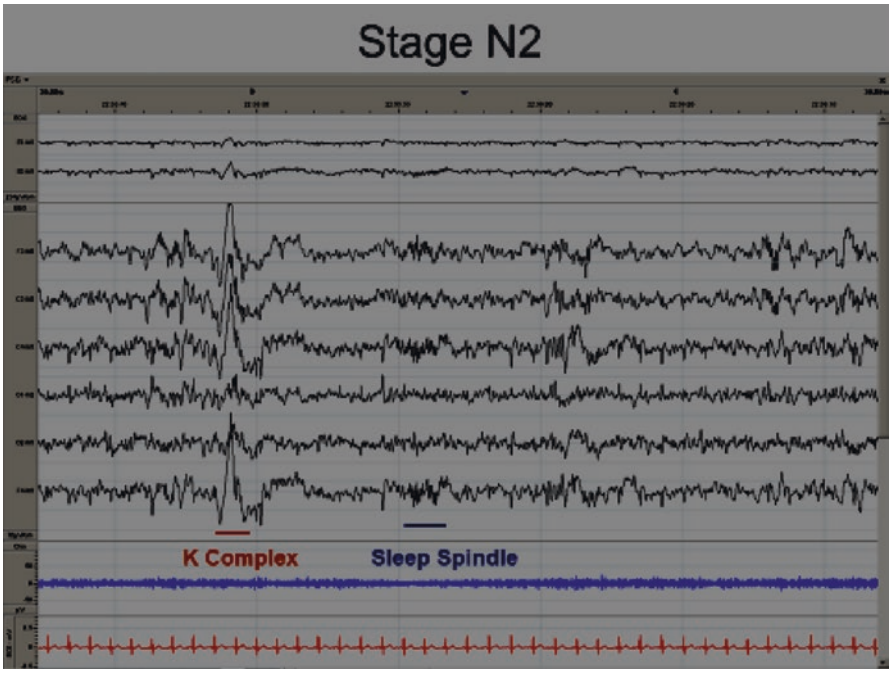

Fig. 1.6 Stage N2

are absent. The chin EMG is usually less than during wake. The arousal threshold is highest in stage N3; a larger stimulus is required to produce an arousal, hence the term deep sleep. This is the most restorative sleep stage. Most stage N3 sleep is during the first half of the night. Delta power decreases with each NREM cycle. Stage N3 accounts for 12.5–20% of total sleep time (Fig. 1.7).

1.2.6 Stage R

Stage R—REM sleep—is characterized by the presence of rapid eye movements (REMs), muscle atonia and EEG desynchronisation. The EEG background activity changes to a low voltage, mixed frequency activity not too dissimilar to that of wakefulness, but with alpha rhythm 1–2 Hz slower than the alpha rhythm of wakefulness. Saw tooth waves are frequently seen in stage R. The heart rate picks up and respiration becomes erratic. Blood brain flow increases as does brain metabolism. Penile tumescence occurs in males and vaginal engorgement in females. Muscle tone is lost (atonia) except for diaphragmatic activity that maintains respiration, the muscles controlling eye movements and the muscles of the middle ear. REM sleep has a baseline tonic component and intermittent phasic events (Table 1.1). This is the sleep stage associated with the most vivid and prolonged dreams. The purpose of REM atonia is presumably to stop the individual from acting out their dreams. Stage R

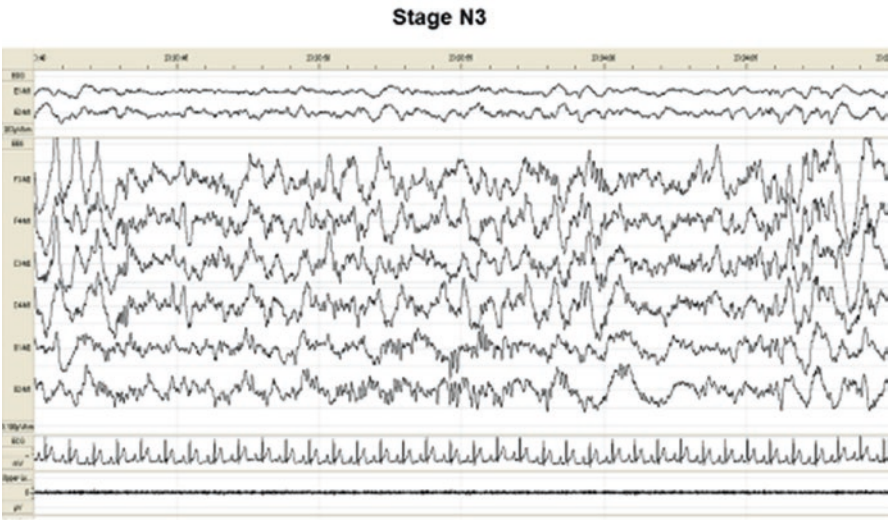

Fig. 1.7 Stage N3: Our sleep techs have offered the slide below as a better example of StageN3

Table 1.1 Physiological features of tonic and phasic REM sleep

Tonic features	Phasic features
1. Electro-encephalogram (EEG) desynchronization 2. Saw tooth wave on EEG 3. Muscle atonia 4. Absence of thermoregulation 5. Penile tumescence in males and vaginal engorgement in females 6. Pupil constriction	1. Ponto-geniculo-occipital (PGO) waves 2. Contraction of middle ear muscles 3. Irregular respiration and heart rate 4. Rapid eye movements (REMs)

typically follows epochs of N2. Stage R arising from stage N1 has recently been identified as a possible feature of narcolepsy (Drakatos et al. 2013). Muscle atonia is demonstrated by a low chin EMG tone. The arousal threshold in stage R is variable, but it is generally easier to wake someone from stage R than from stage N3. Episodes of REM sleep are longer in the second part of the night and REM density is also higher in the later episodes of REM sleep. Furthermore, arousals from stage R are usually complete and are not usually followed by post arousal confusion or disorientation. Stage R accounts for about 20–25% of sleep time (Figs. 1.8 and 1.9).

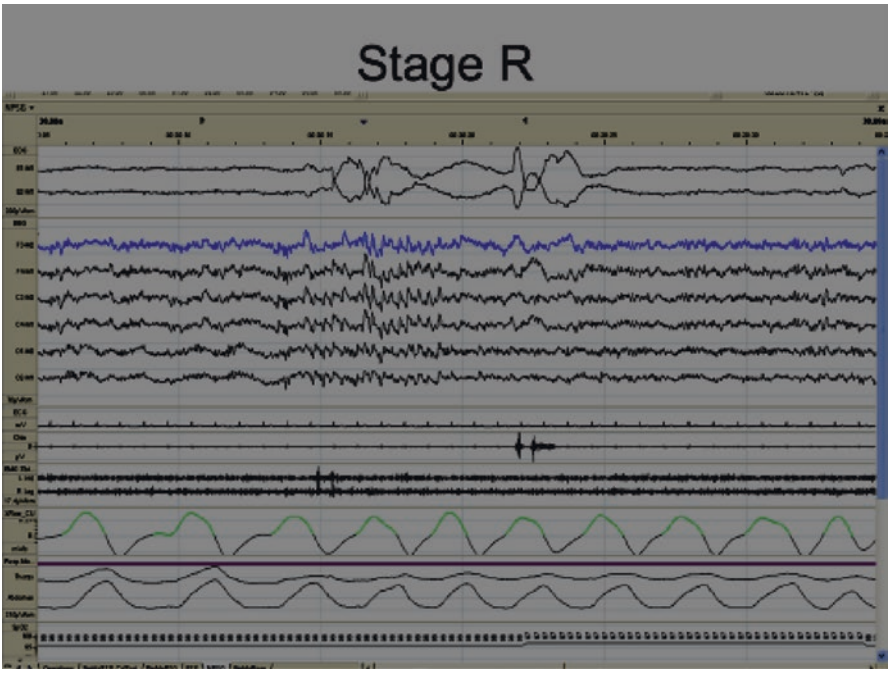

Fig. 1.8 Stage R: rapid eye movement sleep

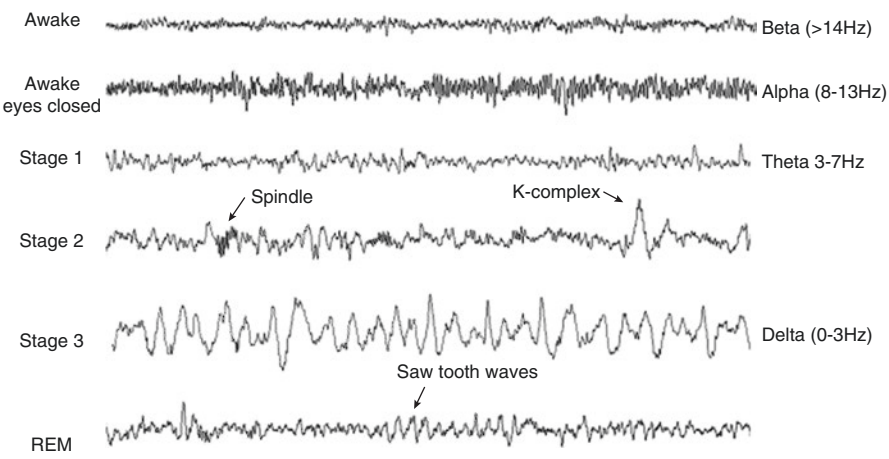

Fig. 1.9 Summary of the typical EEG features of the sleep stages

Most theories suggest a role for NREM sleep in energy conservation and in nervous system recuperation (Genzel et al. 2014; Chokroverty 1999; Scharf et al. 2008). The decreased metabolic rate in NREM sleep might help in the replenishment of glycogen stores. A role for NREM sleep in memory consolidation has also been suggested; the oscillating depolarizations and hyper-polarizations are presumed to consolidate sleep and remove redundant or excess synapses (Maquet 2001).

The functions of REM sleep and dreaming have been a subject of much debate since Sigmund Freud's publication of 'The Interpretation of Dreams'. It has been suggested that REM sleep, by its periodic brain activation, could have a role in localized recuperative processes and in emotional regulation (Hobson 2009; Horne 2000, 2013; Siegel 2011). However, deprivation of REM sleep, as occurs in patients on certain antidepressants, does not seem to have any significant adverse consequences (Espana and Scammell 2004). REM sleep might, so to speak, help expose the subject to situations and emotional experiences not commonly encountered; in other words, dreams might act as a rehearsal exercise. Others have suggested that REM sleep and dreams could be important in the processing and transfer of memories between the hippocampus and neocortex. On the other hand, Crick and Mitchison suggest that REM sleep serves as a way of degrading unhelpful neuronal activity during random cortical activation (Crick and Mitchison 1983). REM sleep might aid in the selection of brain networks that recover during NREM sleep and are ready for optimal functioning during the wake period. There has been some suggestion that REM sleep also plays a role in memory consolidation, but evidence supporting this is not strong. The periodic brain activation of REM sleep, which does not awaken the subject, allows sleep continuity.

1.3 The Two-Process Model of Sleep Regulation

In 1982 Alexander Borbély, a Swiss sleep researcher, proposed a two-process model of sleep regulation involving the homeostatic process (Process S) and the circadian process (Process C) (Achermann et al. 1993; Borbely 1982) (Fig. 1.10).

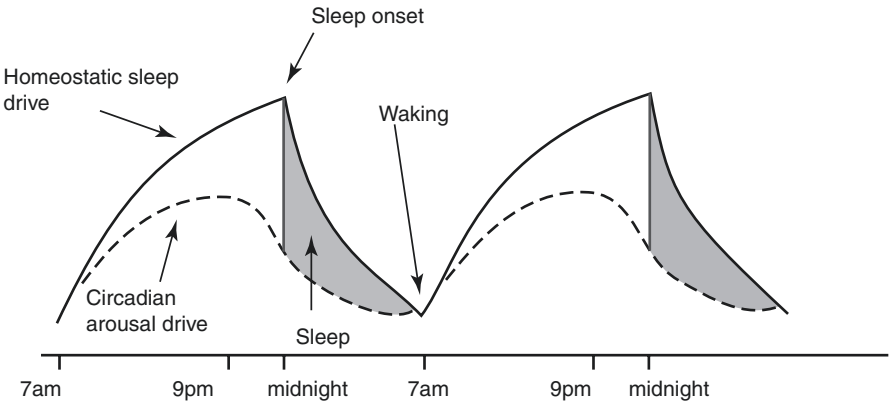

Fig. 1.10 Two-process model of sleep

1.3.1 The Homeostatic Process (Process S)

The propensity to sleep builds during the waking period and is dissipated during sleep, and so the longer an individual is awake, the higher is their propensity to sleep; conversely, the longer an individual is asleep, the lower their sleepiness (delta pressure on EEG is the surrogate of the sleep propensity) (Carskadon and Dement 1979). Adenosine has been identified as one of the possible somnogens responsible for the sleep propensity. The basal forebrain levels of adenosine progressively increase during wake periods. Adenosine is a breakdown product of adenosine triphosphate (ATP) which is the brain's metabolic substrate during wakefulness (adenosine inhibits the excitatory neurotransmitters acetylcholine and glutamate). In the basal forebrain, adenosine binds to A1 receptors thereby inhibiting the wakefulness signals which project to the cortex. In the ventrolateral preoptic area (VLPO), adenosine binds to A2 receptors to induce Fos expression and increase sleep. Caffeine, a non-specific adenosine receptor antagonist, is the most commonly used stimulant. There are most certainly other as-yet unidentified neurochemical pathways involved in homeostatic sleep regulation. The neuroanatomical and chemical basis of sleep will be described in greater detail later in the chapter.

The two-process model of sleep as proposed by Borbély considers the interaction of process S with the circadian drive (process C). As sleep pressure builds during the day, the circadian signal (see below) increases to help maintain alertness.

1.3.2 Circadian Rhythm (Process C)

Alongside the homeostatic process is an altogether different rhythmic variation in sleep propensity that is controlled by a circadian oscillator (Dijk and Czeisler 1995; Fisher et al. 2013). This circadian oscillator, or pacemaker, is in the suprachaismatic nucleus (SCN) which is located in the anterior hypothalamus. The SCN sets the body clock at 24.2 h by rhythmic expression of clock genes. The SCN is entrained to conform to the daily 24 h cycle by light using specialized retinal cells containing melanopsin. From these melanopsin-containing photosensitive retinal ganglion cells, the light stimulus reaches the SCN via the retinohypothalamic tract. The SCN then signals the pineal gland to inhibit melatonin production. It is important to note that blue light has the most potent effect. Light is the most important external stimulus or *zeitgeber* ('time giver') which helps maintain the 24 h sleep-wake cycle. Other external stimuli include social activities, exercise and eating habits.

Wake-promoting signals from the SCN increase during the day; this counters the increasing homeostatic sleep drive. The SCN has projections to the sleep-wake centres (the VLPO and lateral hypothalamus). During the night, the reduced light signal helps promote sleep. In addition to the control of the sleep-wake propensity, the SCN also controls the rhythm of core body temperature as well as the secretion of hormones such as melatonin and cortisol.

Melatonin is secreted in the darkness by the pineal gland when the inhibiting signals from the SCN have been removed. Melatonin promotes sleep by binding

onto the SCN and inhibiting the alerting signal (the SCN and the pineal gland are mutually inhibitory.). In summary, light inhibits melatonin secretion and the absence of light (removal of this inhibition) allows secretion of melatonin.

Two important markers of the circadian phase are the dim light melatonin onset (DLMO) and the minimum of the core body temperature (CBTmin). As the ambient light falls, the melatonin begins to rise. The DLMO occurs about 2–3 h before the usual time of sleep onset. Salivary or plasma levels of melatonin are used in the measurement of DLMO. The CBTmin occurs at the peak of melatonin secretion which is about 2 h before the usual awakening time; usually around 4–5 am.

The interaction of the circadian rhythms and the homeostatic processes affect alertness. Human alertness is lowest around 4–6 am, after which it starts to increase. It decreases slightly around 2–4 pm and then rises again, peaking around 9 pm. During the first part of the day, the homeostatic drive is low due to prior sleep. During the second part of the day, the homeostatic drive is high and increasing due to prior wake, but the circadian alerting signal is also high. Once the circadian drive starts to drop in the late evening, the homeostatic drive to sleep becomes greater than the homeostatic drive to stay awake and the person falls asleep.

1.4 Sleep Across the Lifespan

It is not unusual to hear an older person yearning ‘to sleep like a baby’. Sleep quality and quantity do indeed change across the lifespan. Chronological as well as physiological/biological age has a bearing on the quality and quantity of sleep. Pathological neuro-degenerative processes can affect the integrity of the neurons and nuclei important in the regulation of sleep and wakefulness. On the other hand, psychiatric as well medical co-morbidities also affect sleep, as do various drugs. Polysomnographic studies have demonstrated changes in various sleep parameters across the life span. Different studies have sometimes yielded conflicting results. Notable gender differences in sleep architecture have been reported by some researchers (Latta et al. 2005). It must also be appreciated that in-laboratory studies might yield results different from ambulatory home studies. Generally, total sleep time, sleep efficiency and slow wave sleep tend to decrease with age. The amount of wake after sleep onset (WASO) tends to increase with age.

1.4.1 The Infant

Sleep in the infant is quite different from sleep in the adult individual. A healthy term infant normally spends about two-thirds of the time asleep i.e. 16–18 h. REM sleep constitutes about 50% of the total sleep time and NREM sleep 50%. Active sleep in an infant corresponds to REM sleep and quiet sleep corresponds to NREM. The term infant normally enters sleep via stage R (active sleep) whereas sleep onset REM in adults might have pathological connotations and has been associated with conditions such as narcolepsy. The sleep cycle periodicity in an infant is

45–50 min, which is much shorter than the adult cycle of about 90–100 min. Infant sleep is interrupted by the need to wake up for feeds every 3 h or so. The percentage of REM sleep starts to gradually decrease at about 3 months of age. Appearance of sleep spindles at the age of 2–3 months and appearance of K complexes at the age of 4–6 months are some of the notable EEG milestones of the growing infant. By the age of 6 months, stage N1, N2 and N3 can be identified polysomnographically. The amount of NREM sleep increases as the amount of REM sleep declines. The latency to REM sleep also gradually increases during the first year. As the infant adapts to the light-dark cycle and its associated social cues, the amount of day sleep decreases and sleep begins to consolidate into longer night time sleep, much to the delight of the parents.

1.4.2 The Child

By the time the child is 4–5 years of age, daytime napping is no longer common. Total sleep time (TST) progressively decreases as the child matures (Table 1.2) Sleep latency is usually 5–10 min and sleep efficiency is quite high at 95%. Stage N1 is short. Stage N2 progressively increases as stage N3 decreases. REM sleep decreases progressively as the child grows. When the child is about 2 years old, REM sleep constitutes about 30% of total sleep time; this decreases further to about 20–25% of total sleep time by the time the child is about 5 years of age. Between the ages 5 and 10, the sleep architecture gradually takes the shape of an adult with

Table 1.2 Total sleep duration by age in normal children

Age	Sleep duration (hr ± SD)
6 months	14.2 ± 1.9
1 year	13.9 =/− 1.2
2 years	13.2 ± 1.2
3 years	12.5 ± 1.1
4 years	11.8 ± 1.0
5 years	11.4 ± 0.9
6 years	11.0 ± 0.8
7 years	10.8 ± 0.7
8 years	10.4 ± 0.7
9 years	10.1 ± 0.6
10 years	9.8 ± 0,6
11 years	9.6 ± 0.6
12 years	9.3 ± 0.6
13 years	9.0 ± 0.7
14 years	8.7 ± 0.7
15 years	8.4 ± 0.7
16 years	8.1 ± 0.7

SD = standard deviation. From Iglowstein I, Jenni OG, Largo RH: Sleep duration from infancy to adolescence: reference values generational trends. Paediatrics 2003; 111: 302–307

more stage N3 in the first half of the night and more REM sleep in the second half of the night. The percentage of REM sleep will remain relatively stable until adulthood. Social circumstances, parental discipline, cultural habits (such as bed sharing) and the need to wake up early for school all have a bearing on sleep in children. In their meta-analysis, Ohayon and colleagues concluded that in children 5 years and older and in adolescents, the apparent decrease in TST with age might be related to environmental factors rather than to biologic changes (Ohayon et al. 2004). For instance, TST was not associated with age when studied on non-school days.

1.4.3 The Adolescent

Biological and hormonal changes of puberty have an impact on the sleep of the adolescent. School schedules are usually out of sync with the natural tendency towards a phase delayed sleep pattern of the adolescent (Carskadon and Dement 1987; Carskadon et al. 1998). The intrinsic biological clock in adolescents dictates sleep onset times of around 11 pm to midnight, but they still have to get up before 7 am to prepare to go to school or college. This leads to chronic sleep deprivation with its associated daytime sleepiness. Sleep latency remains much the same and sleep efficiency also remains quite good and unchanged from childhood to adolescence. There is a significant decline in stage N3 with the onset of puberty. Stage N2 sleep may increase as Stage N3 declines. REM constitutes about 25% of total sleep time. Total sleep time averages between 7 and 8 h, but can be much reduced because of social and academic commitments. The sleep architecture gradually develops into the pattern seen in adults.

1.4.4 The Adult

As the adult ages, sleep efficiency becomes reduced and the number of arousals increase. Sleep latency, stage N1 and WASO all increase. Some studies have reported significant gender differences in adults. There is a greater association between declining sleep efficiency and ageing among women, though Redline and colleagues reported an increase in Stage N1 sleep with age in men but not in women (Redline et al. 2004). They also found stage N2 to increase with age in men but not in women. Stage N3 continues to decline as Stage N2 increases. In the meta-analysis by Ohayon and co-workers, the decrease of stage N3 with age was also noted; the effect size was greater in men than women (Ohayon et al. 2004). Redline and colleagues noted a decrease in stage N3 sleep in men only (Redline et al. 2004). Stage N3 is much more prominent in the first half of the night whereas stage R and stage N2 are more prevalent in the second half of the night. REM latency decreases with age. There is a decrease in Stage R as a percentage of TST in both men and women (Floyd et al. 1995, 2007). The decrease in stage R is more prominent after the age of 50. TST remains at about 7–8 h on average, but does tend to decrease with ageing. A greater association between declining TST and ageing is seen among women.

1.4.5 The Older Person

Sleep in older people is affected not only by the chronological age but also by the neuro-pathological processes and medical co-morbidities prevalent in that age group (Anderson et al. 2014; Carskadon et al. 1982). Use of medications, including sleeping pills, is also quite high in this age group. Sleep problems such as insomnia, intrusive early morning waking, restless leg syndrome and sleep disordered breathing are much more prevalent in the older person. In a meta-analysis of sleep parameters across the life span, Ohayon et al. concluded that sleep latency increases with age (Ohayon et al. 2004). The change with age is more apparent when young adults are compared to elderly individuals. The overall increase in sleep latency between ages 20 and 80 years was, however, not too impressive (less than 10 min).

1.4.6 Conclusion

In summary, all parameters of sleep change with ageing. Total sleep and sleep efficiency decrease with age. Sleep latency increases with age; this change is much more apparent in the older person. Wake after sleep onset (WASO) also increases quite significantly in adulthood and going into old age. Percentage of stage N1 increases with age across adulthood and more significantly going into old age. Stage N2 significantly increases with age in men with a corresponding decrease in stage N3. There is a modest decrease in the percentage of REM sleep and REM latency in adults.

1.5 Neuroanatomical and Neurochemical Basis for Sleep

Complex neurochemical circuitry is involved in the generation of wakefulness and sleep. Knowledge of this complex but exciting field is rapidly expanding and, with time, there will be a better understanding of the neurochemical basis of sleep. It is essential for a practising psychiatrist or sleep physician to have a basic knowledge of the neurobiology of sleep in order to understand the pathogenesis of sleep disorders and the mechanisms of action of various drugs.

Multiple excitatory and inhibitory neurotransmitters and neuromodulators are involved in sleep-wake regulation. Brain centres important in the promotion of wakefulness include the pons, midbrain and posterior hypothalamus. Wake-promoting neurotransmitters include acetylcholine, norepinephrine, dopamine, serotonin, histamine and orexin/hypocretin. The preoptic area in the anterior hypothalamus and the adjacent forebrain are important in the generation of NREM sleep. Gamma-aminobutyric acid (GABA) and galanin are the neurotransmitters which inhibit the arousal systems. On the other hand, pontine and adjacent midbrain structures are important in the generation of REM sleep with acetylcholine, glutamate and glycine being some of the important neurotransmitters in this process.

1.5.1 Historical Perspectives of the Neurobiology of Sleep

Our current understanding of neurobiology has evolved tremendously over the past century. The first insights into the neurobiology of sleep arose from the encephalitis lethargica epidemic of 1915–1920. Von Economo observed that patients with damage to the posterior hypothalamus had severe hypersomnolence, while those with damage to the anterior hypothalamus had insomnia (Von Economo 1930). He then hypothesized that the anterior hypothalamus contained sleep-promoting neurons whereas the posterior hypothalamus contained wake-promoting neurons. The first description of the ascending reticular activating system was by Mogoun and Moruzzi who demonstrated that stimulation of the reticular formation led to electrographic changes similar to those of arousal (Moruzzi and Magoun 1949). Kleitman and Aserinsky went on to describe REM sleep in the mid-1950s (Aserinsky and Kleitman 1953). Jouvet and others established that the REM sleep state is driven by circuitry in the pons (Jouvet 1962). A lot of work has gone on in the past few decades into elucidating the regions and circuitry important in the regulation of wakefulness, NREM sleep and REM sleep.

1.5.2 Hypothalamic Areas

The key hypothalamic areas in sleep neurobiology are the lateral hypothalamus, the ventrolateral preoptic (VLPO) nucleus and the tuberomammillary (TMN) nucleus.

1.5.2.1 The Lateral Hypothalamus

The neurons in the lateral and posterior hypothalamus secrete the wake-promoting peptides hypocretin 1 (also known as orexin A) and hypocretin 2 (orexin B). These excitatory hypocretin neurons project widely to areas that include the wake-promoting dorsal raphe nucleus (DRN), the locus coeruleus (LC) and the TMN. These three monoaminergic areas in turn send back inhibitory projections to the hypocretin areas. The DRN has receptors for both hypocretin 1 and hypocretin 2, whereas the LC nucleus exclusively expresses hypocretin 1 and the TMN exclusively expresses hypocretin 2. Hypocretin also has an excitatory influence on the basal forebrain cholinergic neurons leading to enhanced cortical arousal. Hypocretin stabilizes wake-sleep transitions. Deficiency of hypocretin results in loss of sleep-wake control with resultant unstable transitions between wake, NREM and REM sleep. Hypocretin neurons discharge during active waking but are relatively inactive during quiet waking. They are silent during NREM sleep and tonic REM but have some activity during phasic REM.

Clinical and Pharmacological Correlates

Loss of the hypocretin-secreting neurons leads to narcolepsy (Siegal et al. 2001). In patients with narcolepsy with cataplexy, cerebrospinal fluid hypocretin is either very low or undetectable. Research into pharmacotherapy using hypocretin receptor agonists and antagonists to treat narcolepsy/hypersomnolence and insomnia respectively has gathered pace in the last two decades. Almorexant, a hypocretin antagonist, has been shown to promote sleep and exacerbate cataplexy in a murine model of narcolepsy.

1.5.2.2 The Ventrolateral Preoptic Nucleus (VLPO)

The VLPO nucleus neurons are active during both NREM and REM sleep, but are silent during wakefulness. These neurons contain the neurotransmitters GABA and galanin and are activated by sleep-inducing factors such as adenosine and prostaglandin D2. A group of VLPO neurons, called the VLPO cluster, has an inhibitory projection to the TMN. Another group of neurons, called the extended VLPO neurons, has inhibitory projections to the DRN and the LC. The DRN, LC and TMN, in turn, have inhibitory projections on the VLPO. There is thus reciprocal inhibition. The median preoptic nucleus neurons are also sleep active and discharge during both NREM and REM sleep. They also discharge during prolonged wakefulness, thereby contributing to sleep pressure.

Clinical and Pharmacological Correlates

Lesions in the VLPO area result in sleep impairment. Benzodiazepines exert their anxiolytic effect by binding to a specific site on the GABA-receptor, thus potentiating the effect of the inhibitory neurotransmitter GABA.

1.5.2.3 The Tuberomammillary Nucleus (TMN)

The TMN is found in the posterior hypothalamus and contains excitatory histaminergic neurons. The neuronal projections are quite wide and include projections to the cerebral cortex, amygdala, substantia nigra, DRN, LC and nucleus of the solitary tract. The TMN receives stimulatory input from the hypocretin neuronal projections from the lateral hypothalamus. The TMN is the sole source of brain histamine. The histaminergic neurons are wake-active, less active during NREM sleep and silent in REM sleep. Although silent in REM sleep, interestingly, the firing rate is high during attacks of cataplexy (REM intrusion into wakefulness). Cerebrospinal fluid levels of histamine are low in patients with narcolepsy.

Clinical and Pharmacological Correlates

Drugs that reduce histaminergic signalling, such as the H_1 receptor antagonists like diphenhydramine and low dose doxepin, increase NREM and REM sleep. Cerebrospinal fluid histamine levels are low in narcoleptics with and without cataplexy and in patients with idiopathic hypersomnolence. H_3 receptors are autoinhibitory; H_3 receptor agonists therefore cause sleepiness by decreasing histamine release whereas H_3 receptors antagonists will do the opposite and promote wakefulness. Pitolasant is a selective histamine H_3 receptor inverse agonist and shows promise as an additional wake-promoting agent in the management of narcolepsy.

1.5.3 Brainstem Regions

The main sleep-relevant brain dopaminergic areas are the substantia nigra and the ventral tegmental area. Their firing rates do not seem to be that sleep-stage dependant, but the dopaminergic neurons in the ventral periaqueductal grey are wake-active.

1.5.3.1 Clinical and Pharmacological Correlates

In Parkinson's disease, where there is nigrostriatal degeneration leading to the loss of dopaminergic neurons, sleepiness is a common problem. Amphetamines increase wakefulness by increasing dopamine signalling. Dopamine antagonists such as Chlorpromazine and Haloperidol induce sleepiness whereas dopamine agonists, such as Ropinirole and Pramepexole also induce sleepiness by reducing dopamine signalling through activation of auto-inhibitory D_2/D_3 receptors.

1.5.4 Reticular Formation

The ascending reticular activating system plays a major role in the maintenance of wakefulness. It has two main pathways: the dorsal reticular activating system and the ventral reticular activating system. Although the reticular activating system is a useful anatomical way of localizing the arousal system, recent research has shown that there are a number of neural groupings that act in concert to promote arousal.

The dorsal reticular activating system is made up of lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) cholinergic neurons. Some of these neurons discharge during wake and REM (Wake/REM-on) whereas others discharge during REM only (REM-on). They are inactive during NREM sleep. Neurons from these two areas have axonal projections to the subcortical centres including the thalamus, hypothalamus and the midbrain, which in turn project to the cortex leading to the characteristic EEG features of wakefulness and REM.

The ventral reticular activating system ascends through the lateral hypothalamus and the forebrain. It terminates in the substantia innominata, medial septum, magnocellular preoptic nucleus and diagonal band of Broca. These neuronal regions in turn project to the cortex leading to cortical arousal. The ventral reticular activating system receives neuronal projections from the DRN and the LC.

1.5.5 Dorsal Raphe Nucleus (DRN)

Neurons in the DRN produce serotonin. These neurons project to the preoptic area, the basal forebrain hypothalamus and thalamus. They promote wakefulness and suppress REM sleep. The firing rates of these serotonergic neurons are highest during wakefulness, lower in NREM sleep and lowest in REM sleep. The actions of serotonin are complex as there are at least 15 different types of serotonin receptors with varied effects.

1.5.5.1 Clinical and Pharmacological Correlates

Some serotonin receptor agonists increase wakefulness and, in clinical practice, selective serotonin reuptake inhibitors such as fluoxetine and citalopram similarly increase wakefulness and reduce REM sleep. Drugs such as Agomelatine which block serotonin ($5\text{-}HT_2$) receptors may induce NREM sleep and might therefore be helpful in managing insomnia.

1.5.6 Locus Coeruleus (LC)

The LC is the main brain source of noradrenaline, although noradrenaline is produced by many other nuclei. These noradrenergic neurons project widely in the brain with mostly stimulatory effects. The firing rates are highest during wake, lower in NREM sleep and absent in REM sleep. The LC activity is inhibited by noradrenaline acting on the alpha 2 receptors.

1.5.6.1 Clinical and Pharmacological Correlates

Excessive noradrenergic tone can cause agitation, anxiety and insomnia. The alpha 1 antagonist Prazosin can reduce the noradrenergic tone and has found some use in the management of post-traumatic stress disorder (PSTD) nightmares. Alpha 2 antagonists like clonidine induce sleepiness by inactivating the LC neuronal discharge.

1.5.7 Basal Forebrain

The basal forebrain has both cholinergic and GABAergic neurons. Basal forebrain cholinergic neurons project to the cortex to promote arousal. The GABAergic neurons disinhibit cortical neurons and thus augment arousal.

1.5.8 Control of NREM Sleep

During wakefulness, there are high neuronal firing rates from the wake-promoting cholinergic (basal forebrain) and monoaminergic nuclei (TMN, the DRN and the LC) and hypocretin neurons (lateral hypothalamus). During NREM sleep, the VLPO neurons are active and release GABA which inhibits the neuronal discharge from these arousal systems. The GABAergic neurons of the VLPO are themselves inhibited by the cholinergic and monoaminergic systems. This mutual inhibition operating in a 'flip-flop' manner facilitates a stable transition between wake and NREM sleep (Espana and Scammell 2004; Brown et al. 2012; Saper et al. 2001; Schwartz and Roth 2008; Sigel 2009; Super et al. 2001).

1.5.9 Control of REM Sleep

As previously discussed, the hallmarks of REM sleep are EEG desynchronization, ocular saccades, muscular atonia and dreaming (Table 1.1). The noradrenergic (LC), serotonergic (DRN), and histaminergic (TMN) neurons are active during wake, less active during NREM sleep and much less active or completely inactive during REM sleep. For some time, the understanding has been that cholinergic and monoaminergic systems interact to produce REM sleep. It is now known that the neurotransmitters of the REM-on neurons include acetylcholine, glutamate, GABA