Management of the primary sleep disorders

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Sleep is essential for health and wellbeing. Approximately one third of life is spent sleeping, during which the body is quiescent, motor activity and responsiveness to sensory stimuli are reduced, and there is a total lack of awareness to the outside world. The normal neurophysiology of sleep is highly complex, involving reciprocal interactions and feedback between multiple brain regions, genes, neurotransmitters and hormones. Furthermore, signalling pathways affecting sleep are not static and may be impaired or reinforced by neuroplastic changes in the central nervous system.[1-4] Consequently, sleep neurophysiology is extremely vulnerable to disruption.

There is a bidirectional relationship between poor health and disorders of sleep. Disrupted sleep is closely associated with increased susceptibility to a range of disorders, including depression, anxiety, chronic pain, metabolic abnormalities, obesity, immune impairment and increased risk of cancer. It also causes daytime somnolence, reduced vigilance and poor concentration, where reduced attentional capacity can change the nature of behaviour from goal-driven to model-free and habitual responses. This latter response may in part explain the significance of sleep disturbance in various neuropsychiatric disorders.[4-8]

Primary sleep disorders

The DSM-5 classification of sleep-wake disorders includes seven specified disorders or disorder groups **(Table 1)**. Individuals with these disorders present with dissatisfaction regarding the quality, timing or amount of sleep, with resultant complaints of daytime distress and impairment. Primary sleep impairment should not be secondary to any other identifiable cause, should occur at least 3 nights a week and be present for at least 3 months.[9]

Table 1. DSM-5 classification of sleep-wake disorders[9]

- Insomnia disorder
- Hypersomnolence disorder
  - Narcolepsy
- Breathing-related sleep disorders
  - Obstructive sleep apnoea hypopnea
  - Central sleep apnoea
  - Sleep-related hypoventilation
- Circadian rhythm sleep-wake disorders
- Parasomnias
  - Non-rapid eye movement (NREM) sleep arousal disorders (sleep walking, sleep terrors)
  - Nightmare disorder
  - Rapid eye movement (REM) sleep behaviour disorder (repeated episodes of arousal, often associated with vocalisations and/or complex motor behaviours arising from REM sleep)
  - Restless leg syndrome
  - Substance/medication-induced sleep disorder
- Other specified insomnia, hypersomnia and sleep-wake disorders (symptoms not meeting full criteria for other sleep-wake disorders)
- Unspecified insomnia, hypersomnolence and sleep-wake disorders

Sleep regulation

Sleep regulation may be divided into two inter-related processes. The circadian process, which is largely independent of previous sleep/wake episodes, schedules sleep and wakefulness to appropriate times of the 24 hour cycle. The homeostatic process regulates wakefulness and sleep, readiness to fall asleep while awake, and sleep intensity while asleep.[4]

1. Circadian sleep regulation

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by pinealocytes in the pineal gland, located behind the third ventricle in the brain. The pineal gland is directly influenced by changes in light detection by the retinal photoreceptors. The absence of light stimulates flow of information between retinal-hypothalamic pathways and the suprachiasmatic nucleus (SCN), which is the circadian pacemaker ('biological clock'), the main site controlling endogenous rhythm. From here signals travel via the paraventricular nucleus to the superior cervical ganglion (SCG). Noradrenergic fibers originating in the SCG terminate in the pineal gland, signalling conversion of tryptophan to serotonin, which is converted to N-acetylserotonin and finally to melatonin. Exposure of the retina to light rapidly inhibits activity in the SCG and consequently blocks synthesis of melatonin. Therefore, diurnal and seasonal exposure to light and dark and the resulting stimulation and inhibition of these pathways causes melatonin to be secreted into the blood with an individual and endogenous rhythm synchronised by the light-dark cycle.[10,11]

Melatonin receptors are widespread throughout mammalian tissues and modulate both autocrine and paracrine actions, including regulation of circadian rhythm and sleep, secretion of prolactin and growth hormone, modulation of adrenal activity and immune function. In the brain, melatonin receptors are found in the cortex, SCN and hypothalamic regions involved in thermoregulation.[3,10,11]

Administration of exogenous melatonin may be helpful to reset or re-establish the sleep-wake cycle where disruption of circadian rhythm (i.e. rapid change in environmental light/dark cues) leads to sleep problems, such as with travel across time zones, shift work and irregular bed-times. Timing of administration is important (e.g. one and a half hours before the desired bedtime at the new destination) and taking melatonin at the wrong time, such as before travel, can actually worsen symptoms.

Melatonin will not be effective where endogenous melatonin levels and circadian rhythm are normal.

2. Homeostatic sleep regulation

Wakefulness

Wakefulness is a complex and dynamic state driven by homeostatic, affective, cognitive and motivational processes and the balance between wakefulness and sleep is under the influence of a large number of neurochemical systems across multiple areas of the brain **(Table 2)**. The neurotransmitters associated with these specific systems that promote arousal do so, not only through widespread, often excitatory effects on target neurones, but also by acting as neuromodulators to enhance other excitatory or inhibitory signals to these cells.

Therefore, arousal systems in the basal forebrain, hypothalamus and brainstem exert diffuse effects on cortical and many other target regions.

Different arousal systems promote different motor and affective behaviours appropriate to that moment based on detection of sensory and internal stimuli **(Table 3)**, and the neuromodulation can amplify neuronal signals over much of the brain to recruit as many of the arousal systems as required for the waking behaviour. Conversely, deficits in different arousal systems may not necessarily impair wakefulness, but may impair appropriate responses to specific circumstances and challenges.[2]

Table 2. Brain regions and selected neurotransmitters involved in promotion of wakefulness and/or sleep

Brain region	Neurotransmitters
Wakefulness/arousal	
Locus coeruleus	Noradrenaline
Dorsal and median raphe nuclei	Serotonin
Tuberomammillary nucleus	Histamine
Substantia nigra, ventral tegmental area, ventral periaqueductal gray	Dopamine
Basal forebrain	Acetylcholine GABA (inhibitory)
Pons: Laterodorsal and pedunculopontine tegmental nuclei	Acetylcholine
Hypothalamus	Orexin/hypocretin
Non-REM sleep	
Venterolateral and median preoptic areas	GABA and galanin
REM sleep	
Pons: Laterodorsal and pedunculopontine tegmental nuclei	Acetylcholine

Table 3. Motor and affective responses characteristic of different neurotransmitters related to wakefulness[2]

Brain region	Neurotransmitters
Arousal system	**Response**
Noradrenaline, histamine, acetylcholine	Enhanced attention, response to novel, stressful or salient stimuli
Dopamine	Arousal, especially when the individual is motivated or physically active
Orexin	Maintenance of sustained wakefulness, goal orientated behaviours, locomotion

Wakefulness is driven by activity of acetylcholine, the monoamines (noradrenaline, serotonin, dopamine and histamine) and the excitatory neuropeptides orexin-A and -B (hypocretin-1 and -2).

Orexin heavily innervates all of the other arousal regions and plays an essential role in sustaining and stabilising wakefulness. Levels are highest during wakefulness, whereas studies have demonstrated that narcolepsy with cataplexy and other disorders that cause sleepiness, such as Parkinson's disease, multiple system atrophy and traumatic brain injury, are associated with varying degrees of loss of orexin neurons, diminished levels of orexin in the cerebrospinal fluid, and loss of orexin signalling.

Sleep-promoting systems

Specific neurons, especially those in the ventrolateral and median preoptic areas (VLPO/MNPO), actively promote sleep. These neurons contain the inhibitory neurotransmitter gamma-amino butyric acid (GABA) and inhibitory neuropeptide, galanin. They innervate all of the arousal-promoting regions, such that coordinated inhibition of these arousal areas promotes sleep **(Table 2)**. A subpopulation of the neurones in the pons nuclei that contain wake-promoting cells are active in both wakefulness and REM sleep or are selectively active in REM sleep. Neurons in these nuclei may also help generate the cortical activation and atonia of REM sleep.

Transition between wakefulness and sleep (and between REM and non-REM sleep) occurs through a process of reciprocal inhibition/activation between arousal- and sleep-promoting neurons, preventing the occurrence of intermediate conscious states.[3]

Medications that affect sleep

Understanding the influence of the different neurotransmitters on sleep helps to explain the sleep effects of medications that modulate their activity **(Table 4)**.

Treatment options for insomnia

Basic principles for treatment of insomnia include the following:

- Associated conditions that might affect sleep (i.e., causes of secondary sleep disorders), including prescribed and over-the-counter medications and supplements, should be identified and managed accordingly.
- Nonpharmacological approaches are recommended for first line management of primary sleep disorders. Cognitive behavioural therapy aimed at improving sleep-related behaviours can be very effective for patients suffering from insomnia **(Table 5)**, and unlike drug therapy the beneficial effects last beyond the active treatment phase.[12]

Pharmacological management of insomnia

Both antihistamines and benzodiazepines/benzodiazepine receptor agonists may be helpful for patients where nonpharmacological techniques are not effective. Benzodiazepines suppress stages 3 and 4 sleep and cause a slight decrease in REM sleep. In contrast, the benzodiazepine receptor agonists shorten stage 1 of sleep and prolong stage 2, but have little effect on stages 3, 4 and REM sleep and are the drugs of first choice.

The pharmacology of the various benzodiazepines and benzodiazepine receptor agonists varies, especially in terms of half-life and this must be considered when choosing medication appropriate for the individual. Although there are often concerns that the benzodiazepines and benzodiazepine-like drugs may be addictive, if used correctly in the appropriate patient, the risk of addiction is very low. Nevertheless, they may be associated with tolerance and withdrawal symptoms, including rebound insomnia, if stopped abruptly.[12,13] Risks and benefits of therapy should be carefully discussed with all patients before prescribing.

Table 4. Effects of medications on sleep and waking[2]

Drug type	Examples	Pharmacological effect	Clinical effect
Selective serotonin reuptake inhibitors	Fluoxetine Fluvoxamine Citalopram	Increase extracellular levels of serotonin	Increase wakefulness and decrease REM sleep
Tricyclic antidepressants	Amitriptyline Nortriptyline Clomipramine Desipramine	Increase extracellular levels of serotonin and noradrenalin	Decrease REM sleep
Traditional amphetamine-like stimulants	Amphetamine Dextroamphetamine Methylphenidate	Increase extracellular levels of dopamine and noradrenalin	Increase wakefulness
Wake-promoting, non-traditional stimulants	Modafinil Armodafinil	Increase extracellular levels of dopamine	Increase wakefulness
Cholinergic agonists	Pilocarpine	Desynchronise cortical activity	Increase wakefulness
Benzodiazepines	Diazepam Clonazepam Lorazepam Triazolam	Enhance GABA signalling via $GABA_A$ receptors	Increase sleep
Benzodiazepine-like sedative hypnotics (benzodiazepine receptor agonists)	Zolpidem Zaleplon Zopiclone	Enhance GABA signalling via $GABA_A$ receptors	Increase sleep
Classic antihistamines	Diphenhydramine Triprolidine	Block histamine H_1 receptors	Increase sleep
Typical antipsychotics	Haloperidol Chlorpromazine	Block dopamine receptors	Increase sleep

Table 5. Cognitive behavioural therapy for insomnia[13]

Focuses on changing false beliefs and attitudes about sleep (e.g. everyone needs at least 8 hours of sleep for good health)

Sleep hygiene education

- No pets in the bedroom
- No caffeine consumption after 4 pm
- Keep bedroom cool and conducive to sleep
- No watching the bedroom clock
- No nicotine use, especially in the evening
- No exercising within 2 to 3 hours before bedtime

Sleep restriction

- Time in bed can be reduced by estimating the actual total time that the patient is sleeping (e.g. if the patient is in bed for 8 hours but sleeps for 5.5 hours, time in bed could be reduced to 5.5 hours); time in bed usually should not be reduced to less than 5 hours
- After sleep efficiency (ratio of time sleeping to time in bed) reaches 90%, the time in bed can be increased by 15 minutes every week

Stimulus control

- Go to bed only when sleepy
- Use the bedroom only for sleep and sex
- Go to another room if unable to fall asleep within 15 to 20 minutes
- Read or engage in other quiet activities and return to bed only when sleepy

Conclusions

Sleep disorders are complex and are not an innocuous medical complaint. They are responsible for considerable impairment, comorbidity and reduced quality of life. However, with proper assessment and a carefully considered management approach that includes timeous follow-up, almost all patients can be successfully managed, with potential for complete recovery in the vast majority.

References available on request.