Review Article

Raising awareness about sleep disorders

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ABSTRACT

Sleep disorders affect a substantial number of people worldwide and may be increasing in prevalence. Unfortunately, many of these disorders can go unrecognized and untreated in clinical practice. Although physicians understand that good sleep is essential to patient health, approaching the issue is often glossed over in the primary care setting. Importantly, recent data also suggest that sleep disorders are becoming increasingly recognized in developing nations. Here, we review the pertinent features and treatment of some of the major sleep disorders, including obstructive sleep apnea, central sleep apnea, insomnia, and others, that affect patient health. We aim to promote clinician and public awareness of various sleep disorders with the intent of increasing rates of recognition and treatment.

KEY WORDS: Central sleep apnea, obstructive sleep apnea, sleep disorders

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INTRODUCTION

Clinicians frequently recommend a good night's sleep for their patients but rarely focus on the issue when seeing them in the clinical setting. Sleep problems may also be increasing in developing nations as a recent study suggested that almost 17% of patients surveyed across eight countries in Asia and Africa reported trouble with sleep.[1] Literature over the past two decades has established a myriad of clinically important complications from various sleep disorders. Thus, a working knowledge of these disorders and their manifestations is imperative for optimal patient care. Here, we review some of the major sleep disorders with a goal of raising awareness about these conditions, eventually to stimulate further research and clinical focus in these areas.

SLEEP DEPRIVATION

Today's fast-paced lifestyle has led globally to an increase in sleep deprivation.[2-4] Although the recommended amount of sleep in a 24 h period is 7–8 h, recent data show that almost 30% of Americans are sleeping 6 h or less[5] and other countries are also reporting a decline in sleep duration.[6] The impact of this societal change is unclear, but some would argue that increasing sleep duration might have benefits for the population at large. Neurocognitive function decreases in a dose-dependent manner with chronic sleep deprivation,[7] which can impair productivity at work and in daily functioning. In addition, epidemiological studies consistently associate shortened sleep duration with weight gain, risk of myocardial infarction, hypertension, and diabetes when compared to individuals with normal sleep duration.[8-13] Of note, prolonged sleepers also have increased risk of mortality and cardiovascular complications when compared to 8 h per night sleepers although the mechanism remains unknown.[12,13] Experimental studies have also shown important effects of imposing reduced sleep duration on normal sleepers resulting in impaired glucose metabolism, altered satiety hormone regulation,

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and autonomic dysfunction.[14-18] The data currently fall short of providing rigorous evidence that extending sleep duration leads to important health benefits. Nonetheless, strong recommendations have been provided to educate the public regarding the health effects of sleep deprivation and the potential benefits of adequate sleep.[19] The methods to achieve adequate sleep duration in the 7–8 h range depend on the underlying cause but include a safe place to sleep, decreased noise and screen-time before bed, lifestyle modifications, sleep hygiene recommendations, and prioritizing sleep.

OBSTRUCTIVE SLEEP APNEA

Perhaps the most clinically important sleep disorder is obstructive sleep apnea (OSA), which is defined by interruptions in breathing during sleep. The pathophysiology of the disorder relates to intermittent, partial, and/or complete collapse of the upper airway during sleep. OSA patients often snore and report daytime sleepiness although their clinical characteristics vary considerably. Obesity is a major risk factor for OSA although 30–40% of OSA patients are lean. In the US, roughly 6% of women and 13% of men have clinically important OSA defined by an apnea–hypopnea index >15/h.[20] That is, individuals have a breathing problem during sleep at least once every 4 min. Worldwide, data are less abundant, but prevalence rates are similar, despite lower levels of obesity outside the US. For example, Heinzer *et al*. reported up to 50% of men in Switzerland had OSA with at least 15 breathing disturbances per hour of sleep.[21] In India, some prevalence figures are reported, which suggest that roughly 7–9% of the middle-aged population suffer from this condition.[22,23] Interestingly, although there are lower obesity rates reported in Asia than in the US, the prevalence of OSA is equivalent to that of Western nations,[24,25] suggesting that the prevalence of OSA is likely to be higher for a given body mass index in Asian populations. Furthermore, as the obesity pandemic spreads, OSA prevalence figures in developing countries are likely to increase over time.

OSA has important consequences. With stoppages in breathing, individuals frequently have to wake up from sleep to breathe again, and thus sleep becomes very fragmented. This fragmentation leads to excessive daytime sleepiness, reduced quality of life, impaired neurocognitive function, increased risk of road traffic accidents, and other complications.[26-29] In addition, with each breathing stoppage, gas exchange is disturbed due to pharyngeal collapse, and consequently, hypoxemia and hypercapnia can occur with associated catecholamine surges from arousal from sleep. These factors, along with others, likely underlie the substantial cardiovascular sequelae of OSA, which include increased risk of coronary artery disease, stroke, congestive heart failure (HF), and cardiac arrhythmias. In addition, OSA is well established as a risk factor for hypertension, based on animal models, human epidemiological studies, and rigorous randomized controlled trials.[30-33] Further details regarding the association of OSA and cardiovascular disease have been reviewed extensively elsewhere.[34-36] Ongoing studies are examining the impact of intervention on OSA, but treatment of OSA is felt to improve cardiovascular risk although the extent of the improvement is still debated.

The diagnosis of OSA starts with a history and physical examination in those where clinical suspicion exists. In general, OSA diagnosis requires objective testing, with home sleep testing (HST) now emerging as a reasonable approach for the vast majority of patients.[37] In-laboratory polysomnography (PSG) is historically the gold standard diagnostic test but is expensive and cumbersome and yields similar outcomes to simpler and cheaper tests. HST equipment varies in its complexity, but in general, simple devices (e.g., pulse oximeter, respiratory belt, and nasal pressure sensor) provide satisfactory diagnostic information to yield a diagnosis. In some cases, a repeat HST or in-laboratory testing may be required if a diagnosis remains elusive.

For therapy, continuous positive airway pressure (CPAP) remains the treatment of choice. Rigorous, randomized trials have shown that CPAP improves daytime symptoms and blood pressure.[38-40] CPAP also likely reduces the risk of road traffic accidents and cardiovascular events although these data are still evolving. CPAP works well in those who tolerate it, but in those who are intolerant, further education and support are often required. CPAP adherence is likely improved with patient education, addressing nasal patency, optimizing the interface, and regular feedback/interactions. In those who truly cannot tolerate CPAP, alternative positive airway pressure (PAP) devices (e.g., bi-level PAP) may have value although the data are not compelling in clinical trials. Alternative therapies such as oral appliances and upper airway surgery have variable efficacy and have risk/expense associated with them. However, In their recent 2015 practice guidelines update, the American Academy of Sleep Medicine (AASM) recommends that treatment with custom oral appliance in patients who are intolerant of CPAP or who prefer alternate therapy as treatment with an oral appliance is preferred to no therapy.[41] Conservative measures include weight loss[42] through diet and exercise, the avoidance of alcohol,[43,44] goal of 7–8 h of sleep at night, and maintenance of nasal patency. Positional therapy (e.g., avoidance of the supine posture) may have some value although, in general, it is hard to implement and monitor in the patient's home. Despite considerable progress in OSA, the majority of patients remains undiagnosed and untreated, speaking to the need for increased awareness and clinician suspicion for patients to receive optimal management.

CENTRAL SLEEP APNEA

Breathing centers in the medulla drive motor output to all of the various respiratory muscles including the diaphragm, muscles in the chest wall, and to the upper airways/tongue.

These breathing centers respond to blood PCO_2 and PO_2 levels, as well as other information from the periphery to regulate the rate and depth of inspiration. Affected individuals have inappropriate or absent responses to breathing stimuli, which leads to unstable ventilatory patterns during sleep. Clinically, central sleep apnea (CSA) is defined as cessation of airflow for at least 10 s in the absence of any inspiratory effort. The consequences and pathophysiology of CSA overlap to some degree with those of OSA, including increased sympathetic nervous system activation and arrhythmogenesis.[45,46] In general, CSA can be divided into hypercapnic and nonhypercapnic types.

Hypercapnic CSA can present in patients with strokes and brain lesions where direct neuronal injury occurs in the brain's chemoreceptive or respiratory rhythm generator regions. Patients with neuromuscular disorders such as myasthenia gravis or amyotrophic lateral sclerosis also fit into this category although the cause of their disease originates from neuromuscular dysfunction in ventilatory muscles in the periphery and not the central nervous system. Narcotic-induced CSA[47,48] occurs in a dose-dependent response to central respiratory depression facilitated by actions on opioid receptors in the brainstem;[49] patients receiving morphine equivalent daily dose of 200 mg or greater may have increased risk.[50] A recent study showed that 46% of patients on long-term opioid therapy demonstrated severe sleep disordered breathing with AHI >30/h and had a high risk of central apneas.[47] Obesity hypoventilation syndrome (OHS), another form of hypercapnic CSA, is also clinically important given the global obesity epidemic although the exact pathophysiology of the disorder requires further elucidation. OHS occurs in a subset of obese patients; in general, elevated HCO_3-/$PaCO_2$ levels on laboratory work-up along with continued nocturnal desaturations despite CPAP therapy help in establishing the diagnosis. These patients usually require nighttime CPAP for treatment although bi-level PAP and new therapies such as intelligent volume-assured pressure support/averaged volume-assured pressure support are now commonly used.

The most clinically relevant type of CSA is nonhypercapnic and presents in the context of HF patients with reduced ejection fraction, with an estimated 30–50% of patients affected.[46,51] These patients develop a distinct, crescendo-decrescendo pattern of breathing termed Cheyne–Stokes respiration. Patients may have an exaggerated ventilatory response (hyperventilatory) to PCO_2 to the point where they lower the PCO_2 below the chemical apnea threshold, thereby causing apnea. Previous studies have examined the utility of CPAP therapy in HF patients with CSA, and although it may improve some outcomes in HF such as nocturnal oxygenation and 6-min walk time, it does not appear to improve mortality.[52,53] Recently, a considerable amount of interest has arisen in the potential of adaptive (or auto) servo ventilation (ASV) in treating CSA in HF patients. ASV uses a noninvasive ventilator to measure patient ventilation and subsequently adapt expiratory PAP and pressure support levels to eliminate apneas and hypopneas. Some studies have shown short-term benefits with ASV,[54,55] but a recent trial of 1325 HF patients treated with ASV versus medical therapy showed a significant increase in cardiovascular and all-cause mortality at 12 months in the ASV group. The reasons for this increase in morality are unclear and are under investigation.[56] Accordingly, the most recent AASM practice guidelines recommend that physicians stop prescribing ASV to treat CSA in patients with symptomatic HF and left ejection fraction <45%. Further studies are needed to determine the utility of ASV for short-term use and other outcome measures. In the meantime, the optimal therapy for Cheyne–Stokes respiration remains optimization of HF therapy, which can also reduce CSA severity.

INSOMNIA

Insomnia remains one of the most common sleep complaints in the primary care clinic although the prevalence varies depending on the definition used and the population studied. Importantly, insomnia differs from sleep deprivation in that there is adequate time and opportunity to obtain sleep, but sleep is impaired and has negative consequences for the patient during the daytime.

In the United States, the estimated prevalence of chronic insomnia ranges from 9% to 19%.[57] Women report higher rates than men,[58] and minority[59] and elderly populations are also at an increased risk, with the latter reporting rates of approximately 50%.[60,61] The International Classification of Sleep Disorders, Third Edition defines insomnia as difficulty with sleep initiation, sleep maintenance, or early sleep termination, a minimum of three nights per week for 3 months, with patients also reporting impaired daytime functioning.[62] In general, most insomnia patients fall into the category of secondary insomnia, meaning that medication, a comorbid illness, exogenous substances (e.g., caffeine, nicotine, alcohol), another sleep disorder, or poor sleep environment are the root cause of symptoms. In contrast, primary insomnia occurs in the absence of these other factors and affects approximately 25% of patients suffering from chronic insomnia and, in approximately, 5–10% of the US population in general.[58,63]

Insomnia reduces the quality of life[64,65] and is also heavily associated with depression and anxiety although the directionality or causality of this relationship is not fully understood.[66,67] A recent study examining the rates of accidents in over 5,000 patients with insomnia in 10 countries showed that insomnia increased the number of motor vehicle and occupational accidents,[68] which potentially places the lives of others at risk.

Treatment for insomnia has frequently involved the use of pharmacologic interventions including benzodiazepines and nonbenzodiazepine sedative-hypnotic agents such as zolpidem, eszopiclone, and zaleplon. These interventions may have short-term efficacy, but long-term use is not

recommended due to issues with dependence, tolerance, as well as medication side effects.[69-71] Interestingly, cognitive behavioral therapy (CBT) has been shown to improve sleep quality, as measured by sleep efficiency, time spent in slow-wave sleep, and total sleep time, when compared to pharmacologic intervention or placebo in older adults[72] as well as younger patients.[73] CBT including measures of sleep hygiene, sleep restriction, cognitive therapy, and relaxation may be one of the most effective treatments for insomnia.[72] Internet-based behavioral therapies are now being used and are potentially "scalable" even in under-resourced areas.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENTS

The prevalence of restless legs syndrome (RLS) varies depending on geographic location, but individuals in Asia experience lower rates of the disorder than individuals in North America and Europe, where disease rates have been reported as high as 30% in the latter two continents.[74-76] RLS patients usually describe an uncomfortable sensation in the lower extremities, sometimes described as itching, tingling, or crawling, which leads to an irresistible urge to move that temporarily relieves the sensation. Symptoms are typically worse at rest compared to during activity and worse at night compared to daytime. The diagnosis requires exclusion of various mimics such as arthritis, vascular insufficiency, akathisia, and peripheral neuropathy. Patients can have milder disease, with symptoms occurring episodically with little to no sleep interruption or they may suffer from more severe disease, where episodes occur 3 or more times per week with severe interruption of nighttime sleep and presence of daytime symptoms. RLS can lead to insomnia due to an inability to fall asleep as patients often complain that their leg movements keep them awake.

Periodic limb movement (PLM) disorder involves repetitive episodes of stereotyped limb movements – usually, in the lower extremities occurring during sleep, and frequently occurs in conjunction with RLS; approximately 80–90% of RLS patients exhibit PLMs.[77] PLMs are usually assessed during in-laboratory testing based on measurement of the anterior tibialis electromyogram. With the move toward HST, PLMs are becoming harder to assess and quantify. PLMs are frequently inconsequential but occasionally lead to sleep fragmentation.

The treatment of isolated PLMs is controversial, with minimal data showing improvement in important outcomes with therapy. On the other hand, RLS can respond to treatment with rigorous randomized controlled trials showing important outcomes.[77] When treating patients with RLS, it is important to think about underlying causes, such as end-stage renal disease,[78,79] low ferritin levels,[80,81] and pregnancy.[82] Patients with RLS related to low iron levels can respond to treatment with iron repletion in those with ferritin <50 mcg/L.[83] In cases where pharmacotherapy is required, pramipexole or ropinirole can be helpful although hypnotic agents, gabapentin, and physical massaging devices may all have value.[77]

NARCOLEPSY

Our understanding of the neurobiology of sleep has progressed substantially over the last several decades, due largely in part to animal models that allow deeper understanding of the brain's complexities in relationship to sleep. Animal models of narcolepsy show that certain hypothalamic lesions lead to a loss of muscle tone in response to emotional stimuli (cataplexy).[84,85] Neurons in the posterior lateral hypothalamus secrete hypocretin (orexin), which is key in sustaining normal wakefulness and in preventing rapid eye movement (REM) activity from occurring at inappropriate times.[86,87] Human and animal studies have implicated a loss of these neurons with reduced orexin secretion in narcolepsy.[86,88] The classic tetrad for narcolepsy includes excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnogogic hallucinations. People with narcolepsy often experience very fragmented sleep such that narcolepsy is often described as sleep encroaching on wakefulness and wakefulness encroaching on sleep. People with narcolepsy often go undiagnosed, and thus a high index of suspicion is required by clinicians to make the diagnosis. The diagnosis of narcolepsy is usually made by PSG with multiple sleep latency testing. The overnight sleep test is primarily to exclude other sleep disorders such as sleep apnea, PLMs. The daytime naps occur at 2-h intervals and are used to quantify sleep onset latency as well as propensity for REM sleep. People with objective evidence of sleepiness will have reduced sleep onset latency. People with multiple sleep onset REM episodes frequently have narcolepsy although occasional false positives can occur (e.g., depression, severe sleep apnea, and circadian misalignment). In patients where the diagnosis remains unclear, a lumbar puncture can occasionally be helpful to document low levels of hypocretin (orexin) in patients with narcolepsy plus cataplexy. In narcolepsy without cataplexy, cerebrospinal fluid orexin is typically normal, making lumbar puncture less helpful in these cases. The treatment of narcolepsy involves stimulants; modafinil is commonly used in the US although methylphenidate, dextroamphetamine, and other agents have utility.[89] Nap therapy can also be helpful in some cases since people with narcolepsy frequently wake up feeling refreshed. Cataplexy on the other hand does not always require specific treatment depending on severity. Stimulus control can be helpful if certain emotional stimuli known to trigger cataplexy can be anticipated. If pharmacotherapy is required, certain antidepressant medications such as selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors (SNRIs) can help suppress REM sleep and prevent cataplexy attacks; of note, antidepressant therapy is not currently recommended for treatment in narcolepsy alone.[90] Sodium oxybate also has

a role as it helps consolidate sleep, can eliminate cataplexy, and improve daytime sleepiness; the combination of modafinil and sodium oxybate can be highly effective for afflicted individuals.[91]

CONCLUSIONS

Our knowledge of the mechanisms and consequences of sleep disorders have become increasingly compelling over the last several decades and has now reached a point where we know that ignoring issues regarding sleep lead to poor clinical outcomes. Progress is being made in increasing awareness of sleep disorders, but further efforts are required to improve the situation, particularly in developing countries. The spread of Western culture, including technology, sleeping, and activity habits, as well as diet, suggest that sleep issues may only continue to increase in other countries. Only with further efforts in advocacy, research, and education will major progress continue. It is also important that clinicians utilize their knowledge and current research regarding sleep disorders to recognize these problems in the clinic and treat their patients accordingly.

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Conflicts of interest

There are no conflicts of interest.

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