Review Article

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Sleep, Sleep Disorders, and Sexual Dysfunction

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Good sleep is necessary for good health. Sleep health is increasingly recognized as important for physical and mental health by both the medical profession and the general public, and there is great interest in how to avoid and treat sleep disorders and problems. Recent research indicates that insufficient sleep, disrupted sleep, and sleep disorders affect many aspects of human health including sexual function. In fact, patients with urological disorders or erectile dysfunction (ED) may have a sleep disorder that contributes to their urological or sexual dysfunction. Obstructive sleep apnea, insomnia, shift work disorder, and restless legs syndrome are all common sleep disorders and are associated with ED and/or other urological disorders. Therefore, careful attention should be paid to the diagnosis and treatment of concomitant sleep disorders in patients with sexual dysfunction. In this review, we provide an overview of what sleep is and how it is assessed in the clinic or laboratory; our current understanding of the functions of sleep and sleep health; a description of common sleep disorders, as well as how they are diagnosed and treated; and how sleep and its disorders are associated with male sexual dysfunction. Sleep is considered to be a 'third pillar of health', along with diet and exercise. With an understanding of common sleep disorders and how they can impact male sexual function, the urologist can ensure that sleep disorders are considered as a contributor to sexual dysfunction in their patients in order to provide them with the optimal treatment for overall health.

Keywords: Erectile dysfunction; Sexual dysfunctions, psychological; Sleep; Sleep wake disorders; Testosterone

INTRODUCTION

As men age into midlife and beyond, they frequently experience changes in their sexual health, and those changes can lead to dysfunction. Most of the changes are due to diminished sex hormone levels, such as testosterone. Decreased testosterone can lead to erectile dysfunction (ED), decreased libido, loss of pubic and body hair, impaired orgasmic and ejaculatory function, etc. [1]. ED, due to the inability to achieve and maintain a sufficient penile erection in order to have satisfactory sexual intercourse [2], is the most recognized and distressing of these disorders, and often leads patients to seek treatment. ED is quite prevalent, especially among the middle-aged and older population, affecting more than half (52%) of men aged 40 to 70 years [3]. ED is typically assumed to be due to the natural aging process, but it may also occur secondary to other disorders, due to medical treatment, or to result from altered emotional states including fear, depression, or

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low self-esteem [4]. Regardless of origin, ED frequently has a strong negative effect on quality of life.

Good sleep is necessary for good health and well-being [5]. Recently, sleep medicine and sleep disorders have received more attention among physicians and the general public. Some of this attention is due to recent research that indicates clearly that insufficient sleep and sleep disorders affect many aspects of human health, and when untreated can cause serious illness. In the past, sleep disorders were not considered as risk factors for ED. However, sleep has been found to be disrupted in ED populations and the association between sleep disruption, sleep disorders, and ED has been increasingly studied.

In this review, we begin with a brief overview of what sleep is and how it is assessed in the clinic or laboratory, our current understanding of the functions of sleep, common sleep disorders, and how sleep and its disorders are associated with sexual dysfunction.

MAIN BODY

1. Sleep

Sleep is an essential biological process that is now appreciated as vital to both physical and mental health. Sleep is exhibited by all mammals, and sleep-like behavior is seen in birds, reptiles, amphibians, and even insects. Despite the fact that adults spend approximately one third of their life sleeping, for a long time sleep was ignored by physicians and scientists alike. Beginning in the 1980's, sleep disorders began to be systematically studied, understood, and more widely diagnosed, and sleep medicine became a medical specialty. More recently, as the quest for understanding the functions of sleep have been pursued by sleep scientists, we have begun to understand how important sufficient sleep quality and duration are to physical and mental health and quality of life.

Sleep consists of two different states, rapid eye movement (REM) sleep and non-REM sleep. For clinical purposes, sleep is divided into stages based on the polysomnogram (PSG), with each stage being characterized by particular electroencephalographic (EEG) waveforms as well as muscle tone (*via* electromyogram, EMG) and eye movements (*via* electrooculogram, EOG). Non-REM sleep is divided into three stages (called N1–N3), with N1 the 'lightest' and N3 the 'deepest' (Fig. 1A, 1B). N1 represents a transitional state between wake and sleep, N2 is the most abundant stage of sleep and is characterized by EEG waveforms called sleep spindles and K-complexes, and N3 is the deepest stage of sleep and is characterized by delta waves (also called slow waves, hence N3 is sometimes referred to as slow wave sleep). As the individual goes from N1 to N3, the EEG frequency slows and the amplitude becomes higher, respiratory rate and heart rate slow, and muscle tone relaxes. REM sleep is characterized by a fast frequency EEG, absent muscle tone, and REMs (Fig. 1C). In a typical night, non-REM and REM will alternate back and forth four to five times, with N3 sleep in the first 1–2 cycles and REM sleep duration becoming longer as the night progresses.

Human sleep and wakefulness is co-regulated by two

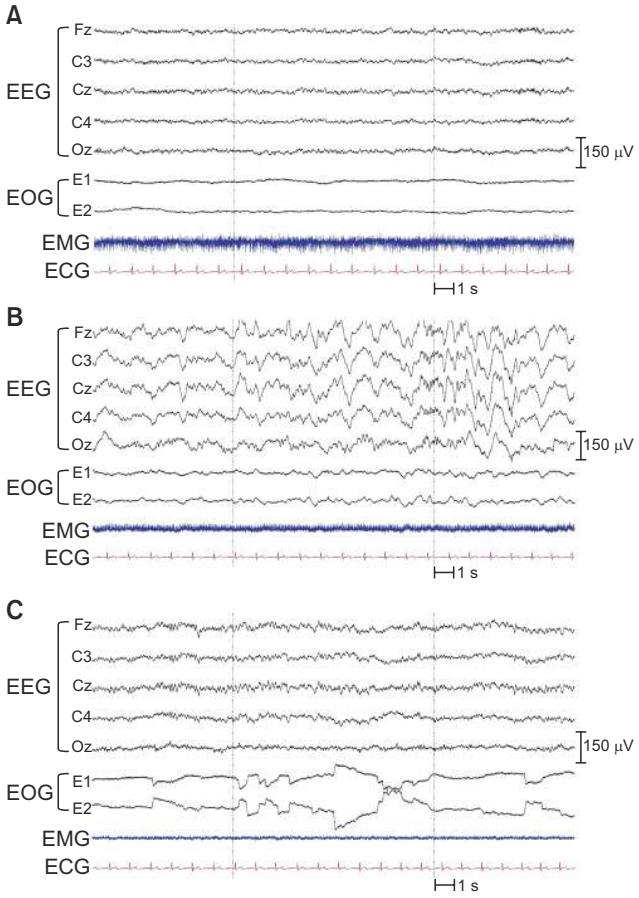

Fig. 1. Polysomnograms showing different sleep stages. (A) N1 non-rapid eye movement (REM) sleep is characterized by low amplitude mixed frequency electroencephalography (EEG) representing light sleep. (B) In contrast, high amplitude slow frequency EEG characterizes N3 non-REM sleep, the 'deepest' stage of sleep. Note that electromyography (EMG) tone is reduced compared with N1 sleep. (C) REM sleep is characterized by unique REMs on electrooculography (EOG) and low or absent EMG, with EEG showing low amplitude mixed frequency. ECG: electrocardiography.

interacting physiological processes, the circadian timing system (Process C) and a sleep-wake homeostatic process (Process S), first modeled by Borbély [6] more than 35 years ago as the 'two process model for sleep regulation'. The sleep-wake homeostatic process refers to a process by which the longer one is awake, the more sleep pressure they accumulate, and when they go to sleep that sleep pressure begins to dissipate. In the two-process model, the buildup of Process S is an exponential saturating function, while the dissipation is an exponential decaying function. If sleep is long enough and wake is not extended, dissipation of all sleep pressure is accomplished within the sleep episode, beginning each wake episode at the same (low) level. Process C in the original two-process model referred to a rhythmic drive for sleep from the circadian timing system. In this way, adult human sleep can be long and consolidated, and wake can be long and stable each day. Dijk and Czeisler [7] showed that the circadian rhythm of sleep-wake propensity is timed so that the strongest drive for wake occurs in the late evening, just before the usual sleep time, while the strongest drive for sleep occurs in the early morning, just before usual wake time. Thus, when sleep pressure has built up to a high level near the end of the wake episode, the circadian drive for wake is high, to oppose it and maintain wake, while near the end of the night when most of the sleep pressure has dissipated the circadian drive for sleep is high, allowing for an extended and consolidated sleep episode.

2. Sleep-related erection

Sleep-related erection (SRE) is a natural and involuntary phenomenon occurring typically during REM sleep in healthy males. SRE was called 'nocturnal penile tumescence' in work by Karacan [8], but current recommendation by the International Classification of Sleep Disorders is to use the term SRE [9].

There is no clear theory about why and how SREs occur, but results from a study in rats in which lesions of the lateral preoptic area of the brain were made suggested that SREs are regulated by the hypothalamus [10]. It is known that SREs appear from infants to old age, and the magnitude and duration tends to decline with aging. SREs are considered to have a different mechanism from the erections that occur by sensory stimuli or fantasy [11]. Karacan [8] suggested that SRE testing is useful to differentiate psychogenic from organic ED, but other urologists demonstrated psychological factors can affect SREs, such as depression, anxiety, and fatigue [12,13]. Currently, it is believed that the overall quality of sleep is more important for SREs than whether they are caused by psychogenic or organic factors.

While at one point SRE testing was carried out in sleep laboratories along with polysomnography, this is no longer the case. There are no definite indications for SRE testing in the sleep laboratory due to the expense of overnight polysomnography, and because it is no longer considered useful in the diagnosis of ED or in attempting to determine whether the ED has an organic or psychogenic cause. Oral agents for ED are now available regardless of the origin of ED. Therefore, SRE testing could be considered only in very special situations, such as in individuals who are non-responders to medical therapy, those with abnormal SRE documented with a home screening device, or for legal cases requiring objective erectile evaluation [10].

3. Sleep disorders

1) Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by loud snoring and reduced or absent airflow due to partial or complete collapse of the upper airway. An apneic event is defined as a decrease of airflow of more than 90% for at least 10 seconds while respiratory effort continues (Fig. 2). A hypopnea is defined by a 30% to 90% decreased airflow accompanied by a 3% or greater oxygen desaturation [9]. As the partial or complete obstruction continues, oxygen saturation falls, and this ultimately triggers a brief arousal during which the patient gasps to reopen the airway. The arousals typically do not awaken the patient, who often is unaware of the occurrence of these events the next morning. The severity of OSA is measured by the number of events per hour of sleep (the apnea-hypopnea index, AHI), with stratification into normal ($AHI \leq 5$), mild ($5 < AHI < 15$), moderate ($15 \leq AHI < 30$), and severe ($AHI \geq 30$).

OSA causes sleep fragmentation (from the frequent arousals), hypoxemia, loud snoring, breathing interruptions, awakenings due to choking, and often (but not always) is accompanied by daytime sleepiness [14]. Epidemiologic studies have found that the prevalence of OSA is 4.0% to 32.8% in middle-aged men [15,16]. Data

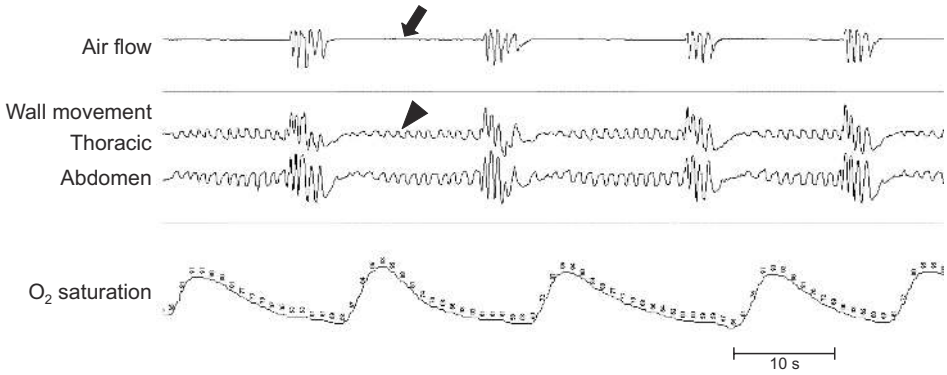

Fig. 2. Obstructive sleep apnea events on polysomnogram. A full diagnostic polysomnogram includes electroencephalography, electrooculography, and electromyography, along with a series of sensors to measure nasal airflow, thoracic and abdominal wall movement, and oxygen saturation. Complete cessations of airflow (arrow) with continued thoracic and abdominal wall movements representing respiratory efforts (arrowhead) are accompanied by falling oxygen saturation. This drop in oxygen saturation triggers a brief arousal during which the patient gasps and airflow is briefly re-established, but once he falls back asleep the obstruction reoccurs.

from a recent Korean questionnaire study found an OSA prevalence of 22.4% among people over 60 years of age [17]. While a large neck size, being overweight or obese, or having particular craniofacial features can lead to OSA, even those of normal weight and craniofacial structure can develop OSA, particularly as they get older. Even though the prevalence of OSA is high, it is estimated that at least 80% of moderate to severe OSA cases are still undiagnosed [18]. OSA is typically diagnosed with an all-night PSG that includes EEG, EOG, and EMG for sleep staging, electrocardiogram, a nasal pressure transducer to measure airflow, an oximeter, as well as thoracic and abdominal bands to measure respiratory effort. Left untreated, OSA can lead to serious medical conditions including hypertension, atrial fibrillation, congestive heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, type 2 diabetes, and depression [19].

Several studies have shown a high incidence of ED among male OSA patients, ranging from 47.1% to 80.0% [20-24]. The severity of OSA is considered to be an important factor in the development of ED [25,26], however, this finding is not consistent [27]. A Korean study by Shin et al [28] showed that ED is associated with decreased minimum oxygen saturation, not with AHI. The underlying mechanism of interaction between OSA and ED remains unknown, although several theories have been proposed, including a hormonal effect of testosterone, peripheral neuropathy due to hypoxemia, or vascular endothelial dysfunction.

Many studies have found that male patients with OSA have lower serum testosterone, and there is a negative correlation between AHI, oxygen desaturation index, and testosterone level [21,25,29]. On the other hand, testosterone is believed to play a role in the pathogenesis of sleep apnea, and testosterone supplementation might worsen OSA. Schneider et al [30] demonstrated that treating hypogonadal patients with androgen significantly increased the number of apneas and hypopneas. Similarly, Cistulli et al [31] reported a 13-year-old boy with Marfan's syndrome showed a worsened OSA after testosterone injection. Therefore, the relationship between testosterone and OSA is complicated, and caution should be taken when considering treating a patient who has OSA with testosterone.

An altered bulbocavernous reflex among OSA patients, a widely accepted method to assess pudental neuropathies, is supportive evidence of the relationship between ED and peripheral nerve dysfunction [32]. In addition, the elevation of inflammatory markers such as high-sensitivity C-reactive protein, tumor necrosis factor α, interleukin (IL)-6, and IL-8 in patients with severe OSA with ED suggests that vascular endothelial dysfunction is involved in the pathogenesis of ED in OSA [33].

Continuous positive airway pressure (CPAP) is the first-line therapy for OSA. A number of studies have been performed to measure therapeutic effects of CPAP on ED in OSA patients. However, the results of those studies on the efficacy of CPAP in treating ED are inconsistent. Budweiser et al [34] reported beneficial long-term effects of CPAP on erectile and sexual function. Just one month of CPAP therapy elevated International Index of Erectile Function (IIEF-5) score

as well as serum levels of follicle stimulating hormone, luteinizing hormone, and testosterone, indicating improvement of sexual function [21]. Zhang et al [25] reported that 3 months of CPAP improved IIEF-5 scores of OSA patients significantly, despite no difference in their testosterone levels. Interestingly, in a study by Acar et al [35] which estimated sexual function by questionnaires, CPAP therapy improved not only the patients' IIEF scores, but also their female partner's sexual quality of life assessed by Female Sexual Function Index and Beck Depression Inventory. On the other hand, no meaningful changes of testosterone level or sexual function were observed in other studies following CPAP treatment, although daytime sleepiness and AHI were decreased effectively [36,37].

Another treatment modality for OSA, uvulopalatopharyngoplasty (UPPP), has shown promising results for ED [38], with better efficacy than CPAP or a mandible advancement device [39]. However, additional evidence from studies of surgical treatments are still required before UPPP is recommended for OSA with ED.

In addition to conventional OSA treatments for OSA patients with ED, direct management of ED may be helpful. Sildenafil has been demonstrated to produce better results in patients with OSA and ED than CPAP, leading to higher numbers of successful attempts and higher IIEF scores [40]. As noted above, testosterone supplementation might be considered as a therapeutic option given the association between OSA and low testosterone levels. However, a randomized placebo-control study of 67 obese men with OSA found that intramuscular injection of 1,000 mg testosterone increased sexual desire but had no effect on ED, frequency of sexual attempts, orgasmic ability, or quality of life [41].

Even though many studies demonstrate that OSA is associated with ED, the mechanisms underlying that relationship and the efficacy of treatments remain to be elucidated. This comorbidity may impair quality of life, not only for the patient but also for their partner. Due to this association and the under-diagnosis of OSA, a simple questionnaire at the andrology clinic would be helpful as a screening tool for detecting OSA and referring patients at high risk of OSA to a sleep specialist [42].

2) Insomnia, chronic sleep insufficiency

Insomnia is one of the most highly prevalent sleep disorders. While difficulty initiating sleep is a common insomnia symptom, other sleep problems that are considered symptoms of insomnia include difficulty maintaining sleep, awakening earlier than desired, resistance to going to bed on an appropriate schedule, and difficulty sleeping without parents (Table 1) [9]. According to previous epidemiologic studies, approximately 30% to 35% of the population has at least one of the insomnia symptoms occasionally, and 9% to 10% of the population meet the diagnostic criteria for insomnia disorder [43,44]. A Korean survey study also showed similar results, finding that 22.8% of the 5,000 people complained of insomnia, especially older people [45].

Sexual dysfunction is more common among older men, and insomnia has been found to be an independent risk factor related to sexual dysfunction, along with cardiovascular disease, diabetes, and depression [46]. The most likely explanation for the mechanism underlying the association between insomnia and sexual dysfunction is a decrease in the level of testosterone. Testosterone has a diurnal rhythm of production, starting to rise at sleep onset and reaching a peak during the first REM sleep bout [47]. Therefore, circulating testosterone levels are higher during sleep than during waking, and insomnia or insufficient sleep could adversely affect the level of testosterone *via* shortening sleep duration or altering the structure of sleep. In fact, it has been demonstrated that sleep loss during the second half of the night significantly reduces morning testosterone levels [48].

Chronic sleep restriction refers to an ongoing sleep duration shorter than normal, typically due to lifestyle choices made by the individual. In modern industrialized society with round-the-clock activities, the average sleep duration tends to shorten [49], and survey studies in the US and South Korea have found that 43.8% and 32.4% of the population reports sleeping less than 6 hours per night, respectively [50,51]. Chronic sleep restriction is associated with numerous medical problems, including type 2 diabetes, metabolic syndrome, obesity, depression, hypertension, and heart disease [52-58].

In addition to those health consequences of chronic insufficient sleep, numerous animal and human studies have demonstrated that insufficient sleep is related to a decreased of testosterone levels [59-61]. Leproult

Table 1. Diagnostic criteria for chronic insomnia disorder (from the International Classification of Sleep Disorders-3)

Criteria A–F must be met[a]	
A. Sleep disturbance/complaint (one or more)	1. Difficulty initiating sleep 2. Difficulty maintaining sleep 3. Waking up earlier than desired 4. Resistance to going to bed on appropriate schedule 5. Difficulty sleeping without parent or caregiver intervention
B. Associated consequence (one or more of the following related to the nighttime sleep difficulty)	1. Fatigue/malaise 2. Attention, concentration, or memory impairment 3. Impaired social, family, occupational, or academic performance 4. Mood disturbance, irritability 5. Daytime sleepiness 6. Behavioral problems (*e.g.*, hyperactivity, impulsivity, aggression) 7. Reduced motivation, energy, initiative 8. Proneness for errors, accidents 9. Concerns about or dissatisfaction with sleep
C. Frequency	Sleep difficulty and associated consequence occurs at least 3 nights per week.
D. Duration	Sleep difficulty and associated consequence is present for at least 3 months.
E. Adequate opportunity	Sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
F. Relationship to another condition	Sleep-wake problems are not better explained by another sleep disorder, a coexisting mental disorder, or coexisting medical condition and are not attributed to the physiologic effects of a substance.

[a]Data from American Academy of Sleep Medicine (AASM, 2014) [9].

and Van Cauter [62] demonstrated this in a highly controlled laboratory study. They studied a group of 10 healthy young men whose sleep was restricted to 5 hours per night for 8 nights and found that serum testosterone levels decreased markedly. Another study of 33 hours of acute sleep loss in 24 healthy young men found lowered salivary testosterone levels and reactive aggression but no change in cortisol concentrations [63]. In contrast to these studies showing significant results, another study with sleep restriction to 4 hours per night (4 am–8 am) for five nights found only a small trend towards decreasing testosterone [64]. The authors of the latter study attributed the inconsistency of their finding to methodological differences related to the duration and timing of sleep.

Testosterone plays an important role in sexual function, muscle mass, bone mineral density, and even mood. Chronic insomnia or chronic sleep restriction could therefore not only cause decreases in testosterone levels, but could also have marked implications for health and quality of life, including sexual function [65-67].

3) Circadian rhythm sleep disorders

Circadian rhythm sleep disorders are problems with sleep characterized by an inability to sleep at the desired time, rather than a dysfunction with the underlying mechanisms generating sleep [68-72]. These sleep-timing disorders result in a mismatch between the clock hour at which sleep is attempted and the underlying biological time at which sleep is promoted by the circadian timing system. Circadian rhythm sleep disorders can be due to transient, self-correcting factors, such as what happens when traveling rapidly to a new time zone ('Time Zone Change Syndrome', 'Jet Lag') or when attempting to stay up at night for work and sleep during the daytime hours ('Shift Work Disorder'). While jet lag is self-correcting, it affects millions of travelers annually and can have a high cost in terms of productivity. For shift workers, the impacts continue for as long as the work schedule includes overnight work or early shift start times.

Shift work is prevalent all over the world, comprising more than 15% of the workforce [73]. The proportion of shift workers in some professions can reach as high as 50%, including police, firefighters, manufacturing employees, transportation, and hospital workers. Many industries that formerly had few or no shift workers now do so given our 24/7 culture, including retail, customer support, and food-service [74]. Working at night or on a rotating schedule results in frequent shifting of the timing of sleep-wakefulness, feeding-fasting, and

rest-activity with respect to the solar day and with respect to the underlying biological clock timing. This poses a serious threat to the shift worker's physical, mental, and psychosocial health [73,75-77]. In fact, the disruption caused by shift work is recognized as a circadian rhythm sleep disorder in both the International Classification of Sleep Disorders and the Diagnostic and Statistical Manual of Mental Disorders-fourth edition. Even those workers who choose to work at night because of higher pay or to accommodate childcare or other demands report that working at night can negatively influence their health and safety [78,79]. Adverse consequences of shift work include gastrointestinal disorders [70,80-82], increased risk of accidents while at work and while commuting home [70,79,83-85], greater likelihood of depression, increased risk of myocardial infarction and cardiovascular disease [86-88], greater risk for developing certain cancers, metabolic syndrome [89-91], and more sleep complaints [72,73,75,92-96]. While female workers who experience frequent transmeridian travel or night work are reported to experience higher rates of menstrual irregularities, miscarriages, and difficulty becoming pregnant compared with day workers [97-99], sexual dysfunction in male shift workers has received much less attention.

Given the research results showing that testosterone secretion starts to rise at sleep onset and reach the highest point at the first REM sleep cycle, it can be inferred that sleep disruption by shift work should influence testosterone secretion. A small study with 4 healthy shift workers demonstrated a significant increase of melatonin and decrease of testosterone compared to a control group [100]. Another experimental study in the lab showed that fragmented sleep resulted in a decrease of REM sleep and a corresponding loss of the testosterone surge [47]. Recently, Pastuszak et al [101] found that nonstandard shift workers with poor sleep quality had a greater risk for sexual dysfunction and hypogonadal symptoms. Interestingly, there was no association between sleep quality and levels of sexual hormone including testosterone, estrogen, follicle-stimulating hormone, and luteinizing hormone in that study. That result suggested that the poor sleep quality of nonstandard shift workers may have a negative impact on hypogonadal symptoms regardless of testosterone levels.

Three other circadian rhythm sleep disorders can result from an intrinsic origin, causing a chronic mismatch between the time when sleep is attempted and the patient's ability to sleep. Advanced and Delayed Sleep Phase Disorders result when sleep regularly occurs at times that are earlier or later than desired. Advanced sleep phase disorder (ASPD) occurs when sleep is earlier than desired, and occurs most often in the elderly [68]. Delayed sleep phase disorder (DSPD) is characterized by late sleep-wake times, and sleep onset insomnia and/or an inability to arise at the desired time [68,69], often resulting in negative occupational, educational, and social consequences as a result of the inability to wake at a socially-acceptable time in the morning. Patients with DSPD, when allowed to sleep at their desired times, are able to fall asleep and have normal sleep structure, but when attempting to sleep and wake at earlier (conventional) hours will have abnormally long sleep latencies. Due to the negative consequences associated with the absenteeism and tardiness of DSPD (resulting from the lack of ability to wake up on time), more complaints of DSPD than ASPD are seen clinically [68]. DSPD has been hypothesized to be due in some patients to a circadian period that is significantly longer than 24 hours, and to represent an extreme beyond the normal spectrum of morningness-eveningness. Unlike ASPD and DSPD, non-24-hour sleep-wake disorder is characterized by sleep times that progressively delay to a later hour from one day to the next [68]. Non-24-hour sleep-wake disorder occurs in about half of all totally blind individuals [102,103] due to a lack of photic input to the circadian system. In sighted patients, non-24-hour sleep-wake disorder has been hypothesized to develop in some DSPD patients [104,105] as the patient's sleep times move later and later, such that they eventually lose their ability to remain entrained to the 24-hour day, and can result in them becoming unable to function at regular jobs or in school [68]. No studies to date have examined the relationship between these circadian rhythm sleep disorders and sexual dysfunction. Only one study of young healthy university students reported that high testosterone levels are associated with a stronger evening-orientation [106].

4) Restless legs syndrome

Restless legs syndrome (RLS) is a movement disorder characterized by peculiar sensory symptoms of the legs, including unpleasant discomfort and an irresistible urge to move the legs to relieve the sensations. These

symptoms are typically worse at rest when lying or sitting, and appear at night or in the evening [107]. The pathophysiology remains elusive, but dysfunction of the dopamine and iron systems in the brain are considered to play a key role [108]. The prevalence of RLS is lower in men, affecting approximately 4.1% to 7.6% of men [109,110]. Interestingly, the prevalence in men was directly proportional to increasing age in one study [110], whereas another study showed an inverse trend [111]. RLS is frequently found in anemia, pregnancy, iron deficiency, and uremia, especially in hemodialysis patients [19,108].

Although there are only a few studies about RLS and ED, it is thought that RLS is associated with ED [109]. The mechanism of interaction has not been clarified yet, but it may be because RLS and ED have similar biological processes, including autonomic dysfunction and dopamine deficiency. A 6-year prospective study found that RLS was a risk factor for developing ED with a relative risk of 1.33, and the frequency of RLS symptoms had a linear relationship with the magnitude of the that risk [112]. In a recent case-control study with 50 subjects each, Kurt [113] reported that not only ED but also premature ejaculation is more common in men with RLS than in controls. Among hemodialysis patients, the presence of RLS symptoms was related with sexual dysfunction [114], and in a study of Swedish RLS patients, those with RLS had significantly reduced libido more often than controls [115]. These findings are in agreement with previous studies.

Generally, dopaminergic agents such as pramipexole and ropinorole are used for the treatment of RLS [116]. Gabapentin and pregabalin are also available. There has been no study about the efficacy of treatment of RLS on ED or sexual dysfunction yet. However, an interesting case study of a patient with RLS and ED was reported [117]. The 65-year-old RLS patient was treated with tadafinil, a long-acting phosphodiesterase type 5 inhibitor, for his ED. After the first intake of tadafinil, his RLS symptoms completely disappeared and his ED recovered as well. More studies testing treatments for patients with comorbid ED and RLS are needed.

5) Periodic limb movements during sleep

Periodic limb movements during sleep (PLMS) is a type of movement disorder consisting of repetitive limb movements most often impacting the lower limbs, especially as extension of the toes, flexion of the ankles and knees and sometimes even the hips, during sleep (Fig. 3). These movements consist of bursts of muscle activity throughout sleep, and can cause both EEG arousals as well as autonomic arousals. Usually, RLS patients tend to have PLMS once they fall asleep [118]. PLMS is a relatively common sleep disorder with a prevalence ranging between 3% to 26% of the general population. The prevalence of PLMS has been known to be higher among ED patients, affecting 54% to 60%, especially men aged greater than 70 years [119,120].

Some RLS studies have shown that dopaminergic treatment also reduced the PLMS indices of RLS/PLMS patients. Clonazepam showed significant improvement of subjective sleep quality but not PLMS index. Anticonvulsants and gamma-aminobutyric acid agonists are used to treat the symptoms of PLMS as well. However, treatment is often only considered if the patient has frequent arousals or persistent excessive daytime sleepiness [108]. There is insufficient evidence for pharmacologic treatments for PLMS in patients without RLS [116].

6) Narcolepsy

Narcolepsy is a rare chronic sleep disorder with a prevalence of 0.02% to 0.06%, affecting both sexes equally [121]. The main symptom is excessive daytime sleepiness or unexpected sleep attacks. Some narcolepsy patients may have cataplexy (a sudden loss of muscle tone provoked by emotion), sleep paralysis, or sleep hallucinations at sleep onset or upon awakening. Narcolepsy is caused by loss of hypocretin (also known as orexin), a neuropeptide involved in regulating vigilance [122].

To date, just a few studies about narcolepsy and

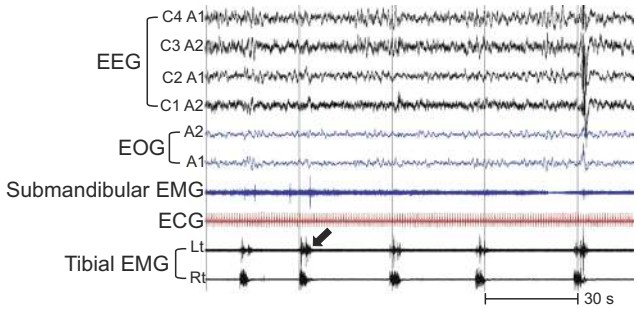

Fig. 3. Polysomnogram from a patient with periodic limb movements during sleep. The bursts of tibial EMG (electromyogram, arrow) occur periodically in both legs. EEG: electroencephalogram, EOG: electrooculogram, ECG: electrocardiogram, Lt: left, Rt: right.

sexual dysfunction have been carried out. In his study measuring SRE of 28 narcolepsy patients, Karacan [123] found that all the medicated patients had a shorter duration of SREs by 20%, and none of them had full SREs. This finding suggested a connection between ED and the medications such as stimulants and antidepressants used to treat narcolepsy. In addition, although just two of five untreated patients demonstrated impaired SREs, all five patients complained of their potency, indicating subjective belief seemed to underestimate their erectile function.

7) Nocturia

The definition of nocturia is the need to wake up one or more times to void urine during sleep [124]. Nocturia is a common complaint in middle-aged and older patients. While young adults rarely report symptoms of nocturia, urological surveys find that approximately half of adults age 60 or older report nocturia, and the prevalence increases with advancing age [125-127]. Sleep surveys also find a high prevalence of nocturia among middle-aged and older individuals, and it is a major cause of sleep disruption. In fact, a majority of older adults with sleep disruption cite the need to void as the cause of their awakening. Therefore, frequent nocturia could produce fragmented sleep and consequentially decrease the level of testosterone [128]. In spite of a lack of evidence, recent studies suggested that low testosterone might be related with nocturia [129,130]. A study of type 2 diabetes patients also found nocturia was associated with ED, and patients with lower levels of testosterone had a higher prevalence of nocturia [131]. It is currently considered that nocturia and testosterone have a negative feedback relationship, in which nocturia produces a decrease of testosterone, and a testosterone decline contributes to the development of nocturia in hypogonadal men with nocturia [46]. Hence, nocturia treatment could increase testosterone levels [132], and testosterone replacement therapy could decrease the frequency of nocturia in reverse [133].

While nocturia is typically thought to be a urological disorder resulting from either an excess production of urine at night or a diminished nocturnal bladder capacity, there is evidence that sleep may play a more causal role in some cases of nocturia. First, there is extensive evidence that sleep apnea can lead to nocturia [134-138] and some studies find that the association between sleep apnea and nocturia is stronger in younger adults [139] and in women [140]. The mechanism by which sleep apnea leads to nocturia is *via* an increase in the circulating levels of the hormone atrial natriuretic peptide ([136]), which in turn leads to suppression of arginine vasopressin. However, even healthy older adults without clinical sleep disorders have lighter and more fragmented sleep than younger adults [141-143], which could lead them to be awakened more easily by internal (bladder stretch signal) or external (noise) stimuli [144]. Once awake, they may then decide to void. In fact, sleep disruption has been suggested as a cause of decreased nocturnal bladder capacity and nocturia [145-147].

Thus, any middle-aged or older patient with nocturia not attributable to a urological cause should be referred for evaluation to a sleep specialist to rule out sleep apnea as the underlying cause [138]. In fact, some have advocated for differential treatments for nocturia subtypes depending on the underlying cause of their disorder [148], and CPAP treatment of sleep apnea has been shown to significantly reduce nighttime voids and other associated symptoms of nocturia [149,150].

CONCLUSIONS

The relationship between sexual dysfunction and sleep disorders is a highly relevant topic for research and for the clinician. While additional research is needed to elucidate the mechanisms by which sleep disorders cause sexual dysfunction, there is evidence that ED can be a consequence of several sleep disorders. We suggest that andrologists, urologists, and other physicians at clinic consider sleep disorders when they see patients with sexual dysfunction, especially given the fact that many sleep disorders are underdiagnosed. There are brief questionnaires that can help determine whether the patient is likely to have one of the common sleep disorders, and these can help in the diagnosis. If the patient is presumed to have a sleep disorder, referral to sleep medicine specialists should be considered to improve modifiable risk factors of ED.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contribution

Cho JW and Duffy JF each contributed to the conceptualization of the paper, as well as the original draft preparation, review, and editing. Both reviewed and approved the final version of the paper.

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