SPECIAL ISSUE 1: INVITED ARTICLE

Sleep Disorders

Preeti Devnani

Abstract

Sleep disorders are an increasingly important and relevant burden faced by society, impacting at the individual, community and global level. Varied presentations and lack of awareness can make accurate and timely diagnosis a challenge. Early recognition and appropriate intervention are a priority. The key characteristics, clinical presentations and management strategies of common sleep disorders such as circadian rhythm disorders, restless legs syndrome, REM behavior disorder, hypersomnia and insomnia are outlined in this review.

Keywords: Hypersomnia, Insomnia, REM behavior

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Introduction

Sleep disorders are becoming increasingly common in this modern era, resulting from several lifestyle changes. These complaints may present excessive daytime sleepiness, lack of sleep or impaired quality, sleep related breathing disorders, circadian rhythm disorder misalignment and abnormal sleep-related movement disorders.[1]

They are associated with impaired daytime functioning, increased risk of cardiovascular and cerebrovascular disease, poor glycemic control, risk of cognitive decline and impaired immunity impacting overall morbidity and mortality.

Diagnosis of sleep disorders is clinical in many scenarios, polysomnography is a gold standard for further evaluation of intrinsic sleep disorder such as obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD). Management and treatment choices include lifestyle modification, positive airway pressure (Pap) therapy, cognitive behavioral therapy (CBT), pharmacotherapy and phototherapy as well as targeted exercise regimens addressing myofunctional training. Dental and ENT approaches provide ancillary support and play a key role in individualizing optimum therapy. This review will address common sleep complaints encountered in sleep clinic beyond sleep-related breathing disorders.

> 33-year-old male, builder by profession, presents with difficulty falling asleep since the past 4 years. He reports a delayed sleep onset until 2.30 am. Most weekdays he awoke with an alarm at 8.30 am, but feels unrefreshed. On weekends he sleeps until 11 am. He also has a h/o anxiety, difficulty in concentrating and irritable mood. No c/o discomfort in legs at night, snoring or witnessed apneas. Past medical history significant for GERD and migraine headaches since age 18 that are aggravated with sleep deprivation.

Circadian rhythm sleep disorder (CRSDs) are a group of sleep/wake disorders in which there is a misalignment between the environment, i.e. work/school/social commitments and the endogenous circadian rhythm. This leads to impairment of an individual's ability to function optimally. Circadian rhythm disorders can present as difficulty with sleep onset as well as excessive daytime sleepiness. These sleep and wake disturbances characteristically have varying weekday and weekend wakeup times. The chronic sleep deprivation that results can cause significant impairment in mental, physical, social, occupational, academic outcomes.

Department of Neurology and Sleep Disorder, Cleveland Clinic, Abu Dhabi, United Arab Emirates

Corresponding Author: Preeti Devnani, Department of Neurology and Sleep Disorder, Cleveland Clinic, Abu Dhabi, United Arab Emirates, e-mail: drdevnani@gmail.com

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The following circadian rhythm sleep–wake disorders adapted from the ICSD-3:

- Delayed sleep–wake phase disorder
- Advanced sleep–wake phase disorder
- Irregular sleep–wake rhythm disorder
- Non-24-hour sleep–wake rhythm disorder
- Shift work disorder
- Jet lag disorder
- Circadian sleep–wake disorder not otherwise specified (NOS).

Delayed sleep phase disorder (DSPD) is a sleep/wake disorder presenting with delay in sleep onset accompanied by wake-up time that this typically later than desired and/or socially inacceptable. In the adolescent population, DSPD prevalence of 7%-16% can be observed.

In this susceptible age group the presentation of DSPD can be poor academic performance, increased school absenteeism, 'presenteeism', sleep onset insomnia, excessive daytime sleepiness. Mood dysfunction and seasonal affective depression have been linked to dengue shock syndrome (DSS). Physiologically, there is a delay in the peak of the core body temperature minimum as well as melatonin concentration.

Role of Genetics in DSS

Dominant coding of CRY1 is a familial trait. Mutation in gene CRY1 alters the circadian clock affecting the sleep/wake rhythmicity. The core molecular clock controlled by CLOCK and BMAL1 (ARNTZ- aryl hydrocarbon receptor nuclear translator) are in a negative feedback by PER/CRY family, this influences to 24 hours sleep/wake cycle.

Genes that are expressed in the hypothalamic suprachiasmatic nuclei such as Per1/2/3, CLOCK, Cry1/2, BMAL1, and casein kinase I epsilon (CK I ε) are associated with delayed sleep phase pattern in mice, suggestive of similar mutations in humans.[2]

Advanced sleep phase disorder (ASPD) clinically presents with early evening onset of sleep associated with early morning awakenings. In APSD, the core body temperature minimum and peak melatonin rhythm occur earlier in the morning than usual. The estimated prevalence of ASPD is 1% in middle-age adults.

Role of genetics in ASPD: Gene mutations identified include gene *hPer2* and the casein kinase 1 delta gene[3] .Families having ASPD show an autosomal dominant inheritance.

Irregular Sleep–Wake Rhythm Disorder

Patients that suffer from irregular sleep-wake rhythm disorder have non-aligned and disorganized sleep times with no clear sleep-wake routine. The irregularity may be caused by neurodegeneration in the SCN and a lack of effect of cues 'Zeitgeibers' such as light, social stimulation and physical activity.

Free-running (Non-entrained to 24-hour Period) Circadian Sleep Disorder

Free-running type occurs primarily in visually impaired persons, as there is a lack of the entraining effects of light. It is rare in sighted patients and occurs in environments with low light levels and those working unusual schedules.

Jet Lag

Jet lag syndrome is caused by transmeridian travel across time zones, it is caused by a desynchronization of the biological clock and the day-night rhythm of the location. Association of this malalignment has been associated with menstrual disturbances, cognitive defects, carcinogenic risk, cardiovascular disease and poor glycemic control.

Anticipation of jet lag and planned manipulation of circadian rhythm before departure can be helpful. Limited sunlight exposure, timed naps, short duration sleep aids can help limit jet lag.

Shift Work Disorder

Shift work disorder (SWD) is a matter of public health and a growing epidemic. Our society is now working a 24-hour schedule, several professions such as health care, aviation, technical support. The sleep-wake cycle of individuals becomes irregular and delayed secondary to later sleep onset and wake times resulting in rhythm desynchronization. This leads to reduced total sleep time on a nightly basis resulting in an accumulation of chronic sleep debt.

Due to its impact on sleep-wake cycles, it affects the gastro-intestinal function and the neuropsychiatric health. Hormonal and reproductive symptoms have also been reported.

Assessment of CRSD: A detailed sleep history supported by detailed sleep wake dairy for at least 7–14 consecutive days along actigraphy are helpful. A polysomnography may be requested to evaluate for any other intrinsic sleep disorder.

Treatment pillars of CRDS: It includes cognitive behavior therapy for insomnia CBT(I), pharmacotherapy and phototherapy.

Sleep restriction therapy (SRT): Time in bed is restricted in an effort to increase sleep efficiency and increase the homeostatic sleep drive for the next sleep period.. This is done by eliminating naps and reducing time in bed.

Sleep chronotherapy: Manipulation of the sleep-wake cycle, the patient may be asked to delay his sleep onset or advance the wake up time in a graduated manner, until he/she can manipulate the sleep schedule around the clock to a more socially acceptable "time. It is imperative that there is consistency during the weekday/weekend schedules.

Pharmacotherapy: Melatonin, hormone produced naturally by the pineal gland, concentration has a circadian variation, higher during the hours of sleep, and lower during wakefulness. Melatonin administration has hypnotic and chronobiotic effect aiding in advancing the circadian rhythm. Zolpidem, short-acting non-benzodiazepine agonists are also used.

Phototherapy/light therapy: It has phase-shifting effect on human circadian rhythm and provides a safe treatment option. It can improve mood and sleep quality in 7–18% subjects (n = 1154 meta-analysis of 13 interventional studies).[4]

Administration of 2 hours of bright light exposure in the morning in addition with light restriction in the evening in patients with DSPS successfully advances circadian rhythm. Evening melatonin administration in addition to morning light treatment for circadian phase advance has an additive effect."

Circadian Rhythm Disorder

Physiological and behavioral changes in the body occur on a 24-hour cycle in synchronization with the body clock i.e. 'suprachiasmatic nucleus'

- Light is an effective 'Zeitgeber 'that entrains this rhythm
- Patients can present with either insomnia or excessive sleepine
- CRSWDs, such as DSPD, may be comorbid conditions making the diagnosis and treatment even more challenging
- For effective management, manipulation of factors such as light along with temperature, food and other social cues that help control the circadian rhythms are essential

Sleep-related Movement Disorders

Sleep-related movement disorders are characterized by relatively simple, benign, self-limiting, stereotypical, non-purposeful movements that occur in or around sleep, primarily occurring during sleep–wake transitions. This can be associated sleep disruption of the patient and their families/caregivers as well as result in physical/bodily injury. Clinical criteria are established to diagnose Restless legs syndrome; however video PSG may be required for other entities in this group including periodic limb movement disorders, sleep related rhythmic disorder, benign sleep myoclonus of infancy. Bruxism is characterized by the presence of teeth grinding sounds occurring during sleep associated with abnormal dental decay and/or jaw pain.

Restless Legs Syndrome

68 years old women presents with a long-standing h/o "restlessness" in the evenings and at bedtime. She notes that she had difficulty with sleep onset. She has noticed occasional leg jerks in sleep. Symptoms were intermittent initially, now increasing in intensity and frequency. Serum ferritin levels 35 mg/dL, she was taking vitamin D supplements. Past medical history significant for hypertension, transient ischemic attack, recurrent atrial fibrillation.

Restless legs syndrome (RLS) as well as Willis-Ekbom disease (WED) can be either primary or secondary in conditions such as iron deficiency, pregnancy, renal failure or polyneuropathy.

Essential RLS diagnostic criteria also known as the 'URGE' criteria describes RLS as an urge to move the legs typically associated with an uncomfortable and unpleasant sensation, aggravated with rest and has a circadian variation with improvement either partial or total with movement.

The severity of which can be rated using the RLS rating scale which is self-assessed based on the symptoms that occurred in the past 2 weeks.

Pathophysiology

Iron, dopamine, adenosine and glutamenergic states have been proposed in the activation of arousal systems associated with RLS. The resultant dysfunction of the corticospinal–thalamic circuit contributes to abnormal limb movements. Dopamine activity follows a circadian rhythm that reflects a hyperfunctioning in the morning and hypofunctioning in the evening creating a state of dopamine deficiency at night when RLS symptoms are exacerbated. The dopaminergic medications correct this relative evening decrease in dopamine. In the long run down regulating the dopamine receptors may result in augmentation that occurs on dopaminergic therapy.

Periodic Limb Movements in Sleep

Periodic limb movements in sleep (PLMS) originally known as nocturnal myoclonus are repetitive stereotypical movements of the lower extremities. PLMS can present with sleep maintenance insomnia, daytime sleepiness and fatigue. PLMS are independently associated with atrial fibrillation and have an increased risk of elevation nocturnal blood pressure levels (non-dipping effect) and increased cardiovascular adverse outcomes[5] · PLMS can result in significant impairment in mental, physical, social and behavioral areas of functioning. Leg movement series consists of at least four movements with amplitude ≥8 uV occurs in a row, lasting 0.5–10 s in duration that recur every 5–90 s are considered Periodic limb movments. The Periodic Limb Movement Index (PLMI) assesses the frequency of PLMS and greater than five PLMI per hour is considered abnormal.

Parasomnias

Characterized by abnormal sleep-related complex motor or behavioral events, parasomnias may be associated with autonomic arousal activity. They may further characterized into phenomena arising from NREM and REM stages of sleep. Parasomnias are recurrent episodes, with incomplete awakenings, limited visual imagery and cognition, with partial or complete amnesia of the events.

ICSD-3 categorizes NREM-related parasomnias include confusional arousals. Sleep walking, sleep terrors, sleep related eating disorders.

REM-related parasomnias REM sleep behavior disorder, recurrent sleep paralysis, night mare disorder. Other parasomnias such as sleep-related hallucinations, exploding head syndrome .

Rem Behavior Disorder

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by prominent dream enactment behavior resulting from a loss of skeletal muscle atonia during rapid eye movement (REM) sleep. Patients with RBD are at risk for sleep-related injury (SRI), both to self and bed partners. A 30–81% prevelance of SRI reported in clinic in diagnosed RBD patients.

RDB is a precursor to neurodegenerative conditions hallmarked by alpha synucleionopathies. Up to 60% of Parkinson's disease (PD) patients, 80–100% of patients with dementia with Lewy bodies and only 33–61% of multisystem atrophy patients have RBD.[6] SPECT imaging on 20 patients with RBD reported decreased blood flow in the upper portions of the frontal lobe and pons and decreased striatal dopaminergic innervation in RBD patients.[7] On polysomnography, REM sleep without atonia and behaviors with sleep related vocalization and/or complex motor behaviors are observed. Substance use, alcohol abuse, medications and/or intrinsic sleep disorders such as obstructive sleep apnea that could contribute must be excluded.

Patient and family education and safety as well as extensive counseling in regards to association with synucleionopathies are to be addressed.

Treatment with Clonazepam at 0.5 mg at bedtime has shown to be effective in 90% of patients with gradually increasing the dosage until the symptoms are controlled. Other drugs, such as gabapentin, clonidine, carbamazepine, donepezil, levodopa, and melatonin have been anecdotally reported to be useful.

REM Sleep Behavior Disorder (RBD)

- 81–90% patients with RBD develop a neurodegenerative disorder.
- The prevalence of RBD is unknown, but occur mostly in men over age 50 years, common in patients with new-onset Parkinson's disease or multiple-system atrophy.
- RBD may be precipitated by most antidepressants in particular venlafaxine and mirtazapine (except bupropion).
- Patients with RBD should be treated with clonazepam 0.5–2.0 mg to reduce injury potential.

Hypersomnia

The term 'hypersomnolence' refers to the symptom of excessive daytime sleepiness that occurs in the absence of contributing nocturnal sleep complaints or misaligned circadian rhythms. Excessive daytime drowsiness is assessed through clinical history, questionnaires such as Epworth sleepiness scale, Stanford scales, sleep/wake diary logs and objective tests like multiple sleep latency or wakefulness tests and actigraphy. Careful evaluation helps exclude insufficient sleep syndrome which is the most prevalent sleep disturbance. Mean Wakefulness test can be helpful in assessment of treatment response.

Central disorders of hypersomnolence include narcolepsy with or without cataplexy, idiopathic hypersomnia and periodic hypersomnia–Kleine–Levin syndrome. Hypersomnias can also occur due to underlying medical/psychiatric disorder or medications. Hypersomnia associated sleep disorders are important to identify and the role of parents, caregivers, teachers, pediatricians in detecting them is crucial.

Narcolepsy

The prevalence of patients with narcolepsy varies widely between different populations and falls between 25 and 50 per 100,000 people.[8] Narcolepsy is caused by the loss of depletion of hypocretin (orexin). Hypocretin promotes wake and suppresses REM sleep, and functions as a stabilizing pathway between NREM, wake and REM sleep stages. Association with DQB1 0602, low CSF hypocretin levels, environmental triggers such as poststreptococcal infections

Table 1: Classification of narcolepsy

	Narcolepsy type 1 with cataplexy	*Narcolepsy type 2* without cataplexy
Cerebrospinal fluid (CSF) hypocretin-1	Low (110 pg/mL or less)	>110 pg/mL

and H1N1 vaccinations, anti-TRIB2 autoantibodies are identified to be contributing to the autoimmune etiology of narcolepsy. Table 1 depicts the two types of narcolepsy.

The features of narcolepsy include uncontrollable sleep attacks and REM sleep onset phenomena such as

- Cataplexy—segmental or generalized flaccid paralysis that are provoked by strong emotions such laughter or excitement
- Hypnagogic hallucinations—that occur at sleep onset
- Sleep paralysis—unpleasant fearful phenomena occurring at the time of falling asleep or on awakening.

Frequently associated symptom makes up a narcolepsy "pentad" is disturbed nocturnal sleep.

Only 20–25% of narcoleptics have the complete narcoleptic tetrad.

Management of Narcolepsy

Treatment objectives should include control of sleepiness and other sleep-related symptoms. Reducing excessive daytime sleepiness, minimize nocturnal sleep disruption and managing cataplexy, hypnagogic hallucination (HH), and sleep paralysis (SP)

Role of Naps/Lifestyle Adjustments

Education and counseling at the work/school environment. Scheduled naps, optimizing work schedules can help improve daytime alertness, limit pharmacotherapy and improved efficiency.

Pharmacotherapy

Sodium oxybate is effective in the treatment of cataplexy, EDS and disrupted sleep in narcolepsy and is now considered the first-line therapy.

Modafinil, competitively binds to the dopamine transporter and improves mean sleep latency, clinical global impression outcome scores and has a low abuse potential. Other medicines that are prescribed are methylphenidate, amphetamines, mazindol, selegiline and pemoline.

Treatment of REM Symptoms

Sodium oxybate is used to REM intrusion and cataplexy. Antidepressants such as venlafaxine, atomoxetine, fluoxetine which suppress REM sleep are commonly used to treat REM intrusion.

Pitolisant has been well tolerated and efficacious in reducing cataplexy.

Insomnia

Insomnia is highly prevalent and poorly addressed societal issue, history frequently not addressed as patient's tend not to discuss with their physicians. The prevalence of insomnia symptoms may be estimated at 30% having a higher prevalence rate in women than in men. with a prevalence of 10% having chronic insomnia.

Insomnia is described as a sleep difficulty associated with sleep initiation, maintenance or early morning awakening despite adequate opportunity to sleep and resulting in impairment of daytime function.

ICSD 3 categorizes insomnia into acute and chronic if symptoms have persisted for greater than 3 months with symptoms occurring greater than 3 nights per week.

Insomnia sufferers are at an increased risk of mortality, cardiovascular disease, insulin resistance, increased motor vehicle accidents, falls, increased healthcare utilization and decreased survival rates. Insomnia is a precursor for mood disturbances and memory decline.

Insomnia may be primary or secondary and is often multifactorial with predisposing, precipitating and perpetuating factors that contribute to patient becoming symptomatic.

A 77-year-old female presented with h/o reduced total sleep time (approx. 4–5 hrs/at night) not very active during the day. She sleeps after breakfast ½ hr, after lunch lays down 1 hr. Stays home most of the day, estimated time in bed 14 hours/day

She has h/o snoring or apneas and no h/o suggestive of restless legs syndrome. No significant medical comorbid conditions. Social—recently lost her spouse, lived with her son, admits to low mood.

If we study the scenario, the presence of the stressor is identifiable. She has poor sleep hygiene as well as comorbid mood disturbance that may be contributing factors.

Etiopathogenesis

- Multifactorial genesis involving emotion, cognition, behavioral patterns, adaptation, species-specific stressor, psychosocial stressor, psychological vulnerability, and conflicts.
- Compounded by beliefs, attitudes, perfectionist standards and worries of consequences of lack of sleep.
- Genesis—Cortical and somatic hyperarousability influences total sleep time, sleep latency and wake after sleep onset and overall sleep efficiency.

Assessment

Comprehensive sleep history complemented by self-reported questionnaires and severity index scales that address potential causes and the impact on quality of life help in making the diagnosis of insomnia. Sleep history, sleep routines both on weekdays and weekends, medications, underlying medical/psychiatrist conditions are important factors in the assessment as well as screening for other intrinsic sleep disturbances such as obstructive sleep apnea, restless leg syndrome, periodic limb movement disorder that can contribute to the clinical presentation are essential.

Sleep diaries, actigraphy are used to assess the total sleep time, variable sleeping and waking times, spending excessive amounts of time in bed awake[10] Polysomnography is not routinely advocated in the assessment of insomnia except the evaluation mistake misperceptions or for evaluation of other intrinsic sleep disturbances.

Nonpharmacologic Therapy and Pharmacological Therapy

- *Nonpharmacologic therapy – cognitive behavioral therapy for insomnia (CBT-I)*: Sleep hygiene, stimulus control, sleep restriction, relaxation training, cognitive therapy, circadian rhythm entrainment on the cornerstones of cognitive behavior therapy for insomnia.[11]
- *Pharmacological therapy*: Insomnia is usually of multifactorial etiology, clinical situations and comorbidities help guide

clinicians to use one treatment over others. Patients who do not receive treatment from their physician for insomnia frequently seek over-the-counter remedies. Sleep aids to be administered the controlled setting alongside counseling. Dependence, tolerance, cognitive impairment and complex behaviors included "sleep driving", "sleep-walking", "sleep-eating" have been reported with the use of hypnotics.

Salient Points

- Treat the underlying etiology
- CBTi is the first line of management
- Pharmacotherapy in a monitored setting
- Polysomnography recommended only if intrinsic sleep disorders such as OSA, PLMD are suspected

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