Review Article

Sleep and Sleep Disorders

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ABSTRACT

Sleep is a complex neurological state, with its primary function of providing rest and restoring the body's energy levels. The importance of sleep could be seen from the fact that people spend about one-third of their lifespan in sleep. Normal human sleep is divided into non–rapid eye movement (NREM) and rapid eye movement (REM) sleep, and the alteration between NREM and REM occurs about 4-5 times during a night of normal sleep. Human NREM sleep could be classified into four stages, namely, stage I, II, III and IV, representing successively deeper stages of sleep. Sleep is an active rhythmic neural process produced by several brain areas, of which the preoptic and other basal forebrain areas play a major role in the generation of NREM sleep. Interaction of the pedenculo-pontine and lateral dorsal tegmental areas with the dorsal raphae nucleus and locus coeruleus, is important for REM sleep generation. Suprachiasmatic nucleus of the hypothalamus and the pineal gland ensure that sleep and wakefulness follow a circadian periodicity of nearly 24 hours.

Alterations in the quality, quantity and pattern of sleep result in sleep disorders. Persistent and repeated interruption of sleep affects the health of an individual. Undiagnosed and untreated wake/sleep complaints cause not only misery to the sufferer, but it also has socio-economic consequences. Sleep disorders cover a wide spectrum of diseases. Though there are more than 100 identified sleep/wake disorders, most sleep complaints can be categorised into five, namely, hypersomnia, insomnia, circadian rhythm disorders, parasomnias, and sleep disorders associated with mental, neurological, and other medical disorders. Researches during the last 50 years, and the advances made in clinical sleep medicine, have lead to more effective treatments for the myriad human sleep disorders. It is not possible to assign a specific reason for many of the sleep disorders, but some aspects of sleep and wakefulness are genetically influenced. But, most commonly, sleepiness during waking hours, results from volitional or forced sleep deprivation during previous nights, due to social, economic and environmental reasons. So, public awareness about sleep disorders should be an essential part of any programme aimed at global management of sleep disorders. **[Indian J Chest Dis Allied Sci 2008; 50: 129-135]**

Key words: Sleep, Apnoea, REM, Smoking, Neurology, Parkinson's disease, Electroencephalogram, Insomnia, Circadian rhythm, Parasomnias

INTRODUCTION

It is essential to spend sufficient period of time in sleep, as sleepiness from any cause can result in impaired attention with adverse disastrous results. Major disasters, such as Bhopal and Challenger were attributed to sleepiness-related impaired judgment at the work-place.[1] According to the National Institutes of Health, the prevalence of sleep disorders in USA is approximately among 14.71% of the population.[2] Though a clear-cut statistical data is not available about sleep disorders in India, the percentage of people suffering from it is not likely to be grossly different. A population-based survey conducted in Delhi had shown that 4% males and 2.5% females suffer from obstructive sleep apnoea.[3] Research has shown that bad sleep can affect not only a person's physical and mental health, but it can even impair civilised behaviour like moral judgments.[4]

The amount of sleep needed by each person is usually constant, although there is a wide variation among individuals. Sleep consists of a rhythmic (circadian) combination of the changes in physiological, biochemical, and psychological processes. When the circadian rhythm is disturbed, or when the individual processes are abnormal during sleep, it may result in a variety of disorders. The ability to cope up with circadian rhythm disturbances also does vary from person to person. Identification of the individual variation would be of importance in dealing with certain sleep disorders. It would also help in finding out the suitability of individuals for various jobs requiring unusual work schedules.

PHYSIOLOGY OF SLEEP

In adults, sleep of 7 to 8.5 hours is considered fully restorative, although there is a wide variation among

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individuals. In the elderly people, and in some cultures, total sleep is often divided into a mid-afternoon nap of about one hour, and an overnight sleep for the remaining period. Normal human sleep is divided into non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. The sleep cycle starts with a period of NREM sleep. Rapid eye movement sleep occurs after a short period of NREM sleep. This alteration between NREM and REM takes place about 4-5 times during a normal night's sleep. The first REM period may be less than 10 minutes in duration, while the last one may exceed 60 minutes. Awakening after a full night's sleep is usually from REM sleep. The sleep pattern changes as the child grows. Polycyclic sleep pattern of the newborn changes to a monocyclic adult pattern. In newborns, the total sleep duration can be 14 to 16 hours, in a day of 24 hours.

Sleep Stages

Human sleep could be classified into five stages. They are stage I, II, III and IV of NREM sleep and the fifth-one being the REM sleep. Traditionally, three primary measures are used to assess the different stages of sleep-wakefulness. These physiological measures are electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). The most important parameter required for sleep analysis is EEG. The different EEG waves found during sleep and wakefulness could be classified on the basis of their frequency and amplitude as delta (< 4 Hz, 150-250 μV), theta (4 - 8 Hz, 100-200 μV), alpha (8-13 Hz, 50 -100 μV), and beta (>13 Hz, < 50 μV). During NREM sleep the EEG shows increasing voltage and decreasing frequency, as the sleep progresses from stage I to IV. They represent successively deeper stages of sleep. The deeper stages of sleep are found predominantly during the first one-third of a night's sleep. The muscles are progressively relaxed during the deeper stages of sleep. Though the muscle activity is reduced, the sleeper makes postural adjustments after about every 20 minutes. During NREM sleep the heart rate and blood pressure decline, but the gastrointestinal motility and parasympathetic activity increases.

As mentioned earlier, NREM sleep alternates with REM sleep. The REM sleep is also called "paradoxical sleep", as the EEG during this phase becomes desynchronised (*i.e.* low voltage fast activity), similar to the wakeful stage. The eyeballs show rolling movement with superimposed bursts of rapid eye movements (REM) during this phase of sleep. Rapid eye movement sleep, which appears after 30 to 90 minutes of NREM sleep, is characterised by a profound loss of tone of muscles (except eye, middle ear and respiratory muscles). Muscle twitches, respiratory changes, increased heart rate and coronary blood flow are the other features of this stage. The subject recalls dreaming, when woken from REM sleep. Though, after a full night's sleep, one usually awakes up from REM sleep, dreaming is remembered only when the subject makes a conscious effort to recall the dream, within a few seconds after waking.

During the awake stage, the EEG alternates between beta and alpha activity. Alpha activity is observed when the subject is relaxed and the eyes are closed. Beta activity appears when the subject is alert with eyes open and scanning the visual environment. The amount of visual scanning would be reflected in the EOG. The EMG may be high or moderate, depending on the degree of muscle tension. The alpha activity suddenly decreases as the person enters the stage I of NREM sleep. The EEG consists mostly of low voltage, mixed frequency activity, with much of it in 3-7 Hz range. The EOG activity is mostly absent, but slow rolling eye movements would be present. The EMG is moderate to low during this period. As the person enters stage II, from stage I, sleep spindles (12-14 Hz sinusoidal waves) appear against the background of low voltage, mixed frequency EEG. Eye movements (EOG) are rare, and EMG is low to moderate during stage II. During stage III, delta waves appear in the EEG, but the EOG continue to remain as before. The EMG may also continue to remain as before, or show slight reduction as the sleep progress from stage II to stage III and IV. There is a quantitative increase in delta waves during stage IV, so that they come to dominate the EEG tracing. The EOG continues as before during this stage.

Rapid eye movement sleep is marked by the reverting of EEG to a low voltage, mixed frequency pattern, similar to that of awake alert stage. Bursts of prominent rapid eye movements appear in the EOG. The EMG is virtually absent, but small muscle twitches may occur against a background of low level of activity. Though REM sleep is associated with dreaming, some mental activity is also associated with NREM sleep. But, they are less vivid and not accompanied by full dream narrative. Dreams are usually visual, but the congenitally blind have auditory dreams. The REM sleep is also associated with penile erection and testosterone release.

Neural Control of Sleep

Sleep was considered as a passive process till the 1950's. Discovery of REM sleep in 1953 by Aserinsky and Kleitman[5] revolutionised the understanding of sleep. Sleep is an active rhythmic neural process. The ascending reticular activating system of the brainstem keeps the cortex and rest of the brain tonically active during wakefulness. Sleep is actively produced by the preoptic and other basal forebrain areas. Study of changes in the activity of the basal forebrain sleep regulating areas in conscious rats, by employing functional magnetic resonance imaging (fMRI), helped to localise the critical area for the maintenance of slow wave sleep at the medial preoptic area.[6] Selective

neuronal lesion of the basal forebrain has shown that the areas around the medial preoptic area play a major role in sleep initiation.[7,8] The thalamocortical loop is important for EEG slow waves of alpha frequency. Interaction of the brainstem areas, namely the pedenculo-pontine and lateral dorsal tegmental area, with the dorsal raphae nucleus and locus coeruleus, is important for REM sleep generation.

Circadian sleep rhythm is one of the several intrinsic body rhythms modulated by the suprachiasmatic nucleus of the hypothalamus, and the pineal gland. They set the body clock to approximately 25 hours, but environmental signals (like light exposure) and activity schedule entrain it to a 24-hour cycle. So, the light is called a "*zeitgeber*" a German word meaning "time-giver," because it sets the circadian clock to a 24-hour rhythm. Thus, the inherent circadian rhythm continuously interacts with the external environments. Sleep-wake cycle can continue even without external clues, but then the cycle length assumes a periodicity of 25 hours or more.

Though sleep is essential for life, it is difficult to enumerate its functions. It is stated that sleep is essential for restoration and recovery. Energy conservation is one function that is proposed for sleep. Sleep may help to discharge emotions through dreaming. Memory consolidation, brain growth and repair are other functions proposed for sleep.

SLEEP DISORDERS: CURRENT UNDERSTANDING

Though there are more than 100 identified sleep / wake disorders, as per revised international classification of sleep disorders,[9] most sleep complaints can be categorised into five, namely, hypersomnia, insomnia, circadian rhythm disorders, parasomnias, and sleep problems associated with other disorders.

Hypersomnia

The most common cause of day-time sleepiness is volitional sleep deprivation during previous nights. Sleepiness, not explained by volitional sleep deprivation, can be due to sleep disorders like obstructive sleep apnoea and narcolepsy.

Obstructive sleep apnoea. Obstructive sleep apnoea (OSA) is one of the most common medical disorders causing day-time hypersomnia, affecting over 2% of adult women and 4% of adult men. Though OSA is more frequent among middle-aged, overweight males, it may be seen even in children (3% of all children), and thin individuals. It is seen primarily in people who are loud snorers and is characterised by collapse of the upper airway during sleep. This upper airway collapse may be associated with a fall in the blood oxygen level and results in repetitive arousals (up to 100 per hour of sleep) to re-establish upper airway airflow. These brief arousals are not usually perceived by the individual, but the sleep disruptions result in excessive day-time sleepiness. Obstructive sleep apnoea is a risk factor for heart diseases and type 2 diabetes.

Narcolepsy. Narcolepsy is a neurological disorder affecting one in 2,000 individuals. It is characterised by the tendency to fall asleep during day time, despite having obtained an adequate amount of sleep the preceding night. Other symptoms of narcolepsy include cataplexy (sudden brief spells of muscle weakness), hypnagogic (occurring at the onset of sleep) or hypnopompic (occurring at the end of sleep) hallucinations, sleep paralysis and automatic behaviour.[10]

The study of narcolepsy has revealed some basic information about sleep. It has shown that wakefulness and sleep are not mutually exclusive states, and that one state can intrude into the another, often resulting in striking consequences. Narcolepsy has a clear genetic component, with over 90% of individuals with narcolepsy carrying the HLA-DR2 / DQ1 (current nomenclature HLA-DR15 and HLA-DQ6) gene (found in less than 30% of the general population). It is currently felt that DQ6, which corresponds at the genomic level to the sub regions DQB1*0602 and DQA1*0102 on chromosome 6, is one of the more reliable markers for narcolepsy across the ethnic groups.[11]

The most important discovery in the field of narcolepsy, which resulted from animal experiments, was the identification of the relationship between hypocretin-1 (also known as orexin) and narcolepsy. Hypocretin-1 is a neuropeptide confined to a small number of cells in the hypothalamus. Patients with narcolepsy have lost these hypocretin-producing cells.[12] Undetectable levels of hypocretin-1 in the cerebrospinal fluid (CSF) are claimed to be very specific for the patients of narcolepsy with cataplexy, and who are HLA DQB1*0602 positive.

But, hypocretin-producing cells were shown to be involved in several functions including the regulation of food intake. It was shown that local injection of hypocretin-1 (orexin A) at the medial preoptic area produced sexual arousal in male rats.[13] Sexual arousal is one of the physiological stimuli, which influences wakefulness. Sexual arousal may be responsible for increased wakefulness, on application of orexin A at the medial preoptic area / basal forebrain.[14] There are reports to show that pulsatile LH release is diminished in narcoleptic men.[15] So, sexual dysfunction in narcoleptic patients requires detailed investigation.

Insomnia

Insomnia is the most prevalent sleep complaint in

general population. It can be described as the inability to obtain sleep that is long enough to give a feeling of being rested or refreshed the following day. Although some insomnia may be constitutional in nature, there is evidence that untreated insomnia is a risk factor for the development of psychiatric problems, such as depression or substance abuse. There is convincing evidence to show that the depression may cause insomnia, and insomnia may cause depression. Insomniacs experience an overall increase in arousal and cortisol secretion.[16] Although numerous pharmacological treatments are available, the benzodiazepines and the newer, non-benzodiazepines are the two classes of medication approved for the treatment of insomnia. Behavioural treatment for insomnia, though time-consuming, can be effective. Combined behavioural and pharmacological treatments are often very effective.[17] Chronic exposure to a mild warm ambient temperature produces a persistent increase in sleep in rats.[18] It was even recommended that exposure to warm ambient temperature is a non-pharmacological method of producing significant increase in paradoxical sleep in the rat.[19] The changes in sleep induced by long periods of exposure to mild warm ambient temperature need to be studied in man before drawing a firm conclusion on the non-pharmacological method for producing a sustained increase in sleep.

Identification of sleep/wake-related neuro-transmitters will certainly lead to the development of the newer and more effective sleep-promoting agents. It was demonstrated that the noradrenergic inputs to the preoptic sleep regulating area are hypnogenic in function in rats.[20,21] This finding is in marked contrast to the common concept that the noradrenergic system of the brain is part of the arousal mechanism. But it has been experimentally demonstrated that the stimulation of postsynaptic alpha adrenergic agents at the preoptic area could induce sleep.[20,22] This finding cannot have an immediate application as the available alpha adrenergic agents have many side effects, and they cross the blood brain barrier with difficulty. So, efforts are required to be initiated to find an alpha-adrenergic agent, which could have selective action on postsynaptic receptors, especially at the preoptic area.

Restless legs syndrome. Restless legs syndrome (RLS) is one of the most common causes of severe insomnia. It is a neurological sensory/movement disorder affecting 5% to 15% of the general population.[23] Restless legs syndrome is characterised by a vague and difficult-to-describe unpleasant sensation in the legs. Patients often have difficulty in describing the unpleasant sensations. Restless legs syndrome sensations are unlike any experienced by unaffected individuals. This discomfort appears particularly during the transition from wake to sleep. Patients exhibit "restlessness of their legs" as movement of the legs relieves these distressing sensations. Recent studies suggest that there is a susceptibility gene locus, which would explain why RLS is often found to be familial.[24] Most cases of RLS respond to anti-parkinsonian agents, benzodiazepines, opiates and anti-convulsant medication. Further studies on the relationship between dopamine and RLS will be of great interest and value to neurophysiologists, neurochemists, neuropharmacologists and, of course, patients.

Circadian Rhythm Disorders

Daily rhythm of rest-activity cycles of all living creatures is linked to the geophysical light-dark cycle. The primary symptom of circadian rhythm disorders is the inability to sleep during the desired sleep time. The individual's biological clock finds it difficult to adjust to the demands of the geophysical environment. Wake-sleep schedule disorders could be primary, where there is malfunction of the biological clock *per se*, or it could be secondary, which results from environmental effects upon the underlying clock. Delayed sleep-phase syndrome (DSPS), and advanced sleep-phase syndrome (ASPS) are the common primary circadian rhythm disorders. In DSPS, the patient falls asleep late and rises late. Individuals suffering from ASPS fall asleep early and awaken earlier than desired. Human genetic studies have identified specific genes associated with both advanced and delayed sleep-phase syndromes.

Until recently, the circadian rhythm disorders were only of academic interest, as no effective treatments existed. Fortunately, this has changed, and many patients with these incapacitating disorders do benefit from accurate diagnosis and appropriate treatment. The mainstay of the treatment is chronotherapy and phototherapy. In addition, there are promising new pharmacological treatments on the horizon.[25]

In chronotherapy, the desirable total sleep time is determined by sleep logs during a 'free-running' period. The patient then delays or advances sleep onset, by a few hours every day and sleeping only during the pre-determined period until the sleep onset time comes to the desired time. The patient then attempts to maintain his sleep schedule during that time.[26]

Phototherapy (exposure to bright light) has a potent effect upon the biological clock, and exposure at strategic times of the wake/sleep cycle results in a change in the underlying rhythm. This has afforded an opportunity to treat circadian dysrhythmias effectively. The timing and duration of the phototherapy depend upon diagnosis and individual response. The patient sits at a prescribed distance from a bright light producing 2,500 lux at the point where it reaches him. The effect of light upon human rhythms varies with intensity, wavelength, timing and duration of exposure. Much remains to be learned regarding these variables and the effectiveness of phototherapy in the clinical settings.[27] Once the desired sleep period time has been

achieved, continued light exposure must be maintained.

Drugs that shift biological rhythms are called chronobiotics. One promising chronobiotic is melatonin, which is a hormone, normally secreted by the pineal gland. Melatonin secretion is coupled to the wake sleep cycle and to the circadian cortisol rhythm. It is a valuable marker of the underlying wake-sleep period. It is likely that melatonin plays an important role in biological rhythms. Circadian dysrhythmias are common, and are disabling in terms of academic, employment or family consequences, and so the sleep medicine field is eagerly awaiting the development of effective chronobiotics.

Parasomnias

Parasomnias are defined as the unpleasant or undesirable behavioural or the experiential phenomena that occur predominantly or exclusively during sleep. The common parasomnias result from an overlap of "awake behaviour" during sleep. The admixture of wakefulness and NREM sleep result in the most common NREM parasomnia called "disorders of arousal" such as sleep walking or sleep terrors. Admixture of wakefulness and REM sleep result in REM sleep behaviour disorder.

NREM parasomnias. The disorders of arousal are the most impressive, and most common, of the NREM sleep parasomnias. They occur during stages III and IV of NREM sleep. As these sleep stages are present in abundance during the first third of the sleep cycle, the disorders of arousal are also more common during this period. They are common in childhood, usually decreasing in frequency with increasing age. Occurrences of stages III and IV of NREM sleep also decrease with advancing age. Disorders of arousal include confusional arousals, somnambulism (sleep walking) and sleep terrors. Some take the form of 'specialised' behaviours such as sleep-related eating and sleep-related sexual activity. Confusional arousals are often seen in children and are characterised by movements in bed, occasionally thrashing about or inconsolable crying. The prevalence of confusional arousals in adults is approximately four percent. Sleep walking is prevalent in childhood (1–17%), peaking at 11–12 years of age, and is common in adults (nearly 4%). The sleep terror is the most dramatic disorder of arousal, frequently initiated by a loud, blood-curdling scream associated with extreme panic, followed by prominent motor activity such as hitting the wall, running around or out of the bedroom, even out of the house, resulting in bodily injury or property damage. A universal feature of this condition is inconsolability. As with sleep walking, sleep terrors are also more prevalent in childhood. But it is also prevalent in adults (up to 3%). Although usually benign, some of these behaviours may be violent at times, resulting in considerable injury to the victim or to others.

REM sleep parasomnias. The most common and best-studied REM sleep parasomnia is the REM sleep behaviour disorder (RBD). In patients with RBD, somatic muscle atonia (which is one of the defining features of REM sleep) is absent, permitting the acting out of dream mentation, often with violent or injurious results.

REM sleep behaviour disorder in humans occurs in both acute and chronic forms. The acute form is often due to undesirable side effects of antidepressant medicines, like serotonin reuptake inhibitors. The chronic form of REM sleep behaviour disorder is usually either idiopathic or associated with neurological disorders. One of the most interesting implications of chronic RBD is its association with neurodegenerative disorders, particularly Parkinson's disease, multiple system atrophy and dementia with Lewy body disease. Rapid eye movement sleep behaviour disorder may be the first manifestation of these conditions, and may precede any other manifestation of the underlying neurodegenerative process by more than 10 years.[28]

The RBD may be a very early harbinger of Parkinson's disease. When new neuroprotective pharmacological agents are developed for Parkinson's disease, it may be found very useful for RBD also. In keeping with the fact that both narcolepsy and RBD represent state boundary dyscontrol conditions, it should be no surprise that there is a higher incidence of RBD in patients with narcolepsy. Benzodiazepine clonazepam is a highly effective treatment for RBD.[29]

Sleep Problems Associated with Other Disorders

A large number of mental, neurological, and other medical disorders are associated with disturbances of sleep and wakefulness. The division into mental and medical categories is somewhat arbitrary. Most mental disorders can have an associated sleep disturbance. Psychoses, mood disorders, anxiety disorders, panic disorders, and alcoholism are commonly seen in patients presenting with sleep complaints. Most psychotic patients experience some degree of sleep disruption during exacerbations of their illness.

Neurological disorders that are commonly associated with sleep disturbance are degenerative disorders, epilepsy and headaches. Cerebral degenerative disorders, dementia, and Parkinson's disease are commonly recognised neurological disorders that are associated with sleep disturbance. Parkinson's disease is even preceded by day-time sleep attacks, nocturnal insomnia, REM sleep behaviour disorder, hallucinations and depression, which are frequently as troublesome as the motor symptoms of Parkinson's disease. It has recently been reported that there is substantial loss of hypothalamic hypocretin neurons and melanin concentrating neurons in Parkinson's disease.[30]

Epilepsy may be exacerbated by sleep disturbance, and may occur predominantly during sleep. Therefore, the term "sleep related epilepsy" is used to denote those forms of epilepsy that are highly associated with the sleep state. Electrical status epilepticus of sleep has a high degree of association with non-REM (NREM) sleep. Headaches, particularly migraine and cluster headaches, can occur predominantly in sleep. Though the sleep disturbance increases over the duration of these diseases, the coincidence of sleep disturbance has not been systematically studied.[9] Fibromyalgia, is a disorder associated with abnormal electroencephalographic patterns during sleep and is called alpha sleep or alpha-delta sleep.

There are a variety of other medical disorders that have features occurring during sleep or that can cause sleep disturbance. Nocturnal cardiac ischemia, sleep-related asthma and gastroesophageal reflux are medical disorders that occur during sleep. The discomfort associated with chronic obstructive pulmonary disease and peptic ulcer occurs commonly during the major sleep episode.

Sleeping sickness (Von Economo's disease/ encephalitis lethargica) is one disease, which is rare outside the continent of Africa. Sleeping sickness is a parasitic disease, caused by the protozoa Trypanosoma. The parasites enter through the blood and lymph systems, and cause swollen lymph glands. In the advance stage, the parasite passes through the blood-brain barrier and enters a neurological phase which gave the disease its name. The symptoms include disturbed sleep cycle, with day-time slumber and night-time insomnia. Studies on patients of encephalitis lethargica is of historical importance as it had later led to the discovery of a "waking center" in the posterior hypothalamus and brainstem. [31]

FUTURE DIRECTIONS IN THE APPROACH TO SLEEP MEDICINE

Progress in clinical sleep medicine and basic science of sleep physiology is rapid at the moment. Knowledge gained from sleep research, and the progress made in clinical sleep medicine, should lead to more effective treatments for the myriad human sleep disorders. Knowledge gained from sleep research in animals will undoubtedly lead to more effective treatments. Studies on hypocretin deficiency in narcoleptic dogs, and identification of sleep and circadian abnormalities in transgenic mouse models of Alzheimer's disease and Huntington's disease are a few examples. Many aspects of sleep and wakefulness are genetically influenced. Studies on biochemical markers and genetics will not only provide diagnostic tools, but it will also help in obtaining important information regarding genetic influences in sleep disorders. Applied clinical research and the knowledge gained from experiments would result in practical human application. In addition, questions raised by human sleep disorders will help to direct research in basic science. A close collaboration between basic science and sleep medicine will result in positive contribution to medical science and patient care.

One cannot underestimate the importance of programmes aimed at community service and public awareness of sleep disorders. Though it is not possible to assign specific reason for many of the sleep disorders, it is seen that some people are more likely to have (or develop) sleep problems. They include people who are overweight, habitual drinkers and night-shift workers. But the most common cause of sleepiness during working hours is volitional sleep deprivation for social or economic reasons. The present generation gets 20% less sleep than previous generations. There is no evidence that earlier generations required more sleep than ours. So a public awareness programme can also help a lot in dealing with several sleep disorders. In spite of the progress made in the treatment of sleep disorders, people in India do not receive proper diagnosis and treatment of sleep disorders. There are several obstacles in delivering effective new therapies, and translating scientific advances into clinical practice in this country. The major reason for inadequate diagnosis and treatment of sleep disorders in India are the lack of facilities and prohibitive cost of treatment. Poor awareness of sleep disorders among public, inadequate emphasis on sleep medicine in the medical curriculum and shortage of personnel trained in management of sleep disorders are the other reasons.

REFERENCES

1. National Commission on Sleep Disorders Research. *Report of the National Commission on Sleep Disorders Research (Research DHHS Pub. No. 92)*. Supplier of Documents, U. S. Government Printing Office, Washington, DC, 1992.
2. National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, USA. *Available from:* (http://www.wrongdiagnosis.com/s/sleep_disorders/basics.htm).
3. Vijayan VK, Patial K. Prevalence of obstructive sleep apnea syndrome (OSAS) in Delhi, India. *Chest* 2006 130: 92S.
4. Killgore WDS, Killgore DB, Day LM, Li C, Kamimori GH, Balkin TJ. The effects of 53 hours of sleep deprivation on moral judgement. *Sleep* 2007; 30: 345-52.
5. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena during sleep. *Science* 1953; 118: 273-4.
6. Khubchandani M, Jagannathan NR, Mallick HN, Mohan Kumar V. Functional MRI shows activation of the medial preoptic area during sleep. *Neuroimage* 2005; 26: 29-35.
7. Srividya R, Mallick HN, Kumar VM. The changes in thermal preference, sleep-wakefulness, body temperature and locomotor activity in the rats with medial septal lesion. *Behav Brain Res* 2005; 164: 147-55.
8. Srividya R, Mallick HN, Kumar VM. Differences in the effects of medial and lateral preoptic lesions on thermoregulation and sleep in rats. *Neuroscience* 2006; 139: 853-64.

9. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Revised: Diagnostic and Coding Manual*. Chicago, Illinois: American Academy of Sleep Medicine, 2001.
10. Guillemiault C, Framherz S. Narcolepsy: diagnosis and management. In: Kryger MH, Roth T, Dement WC, editors *Principles and Practice of Sleep Medicine.* Philadelphia: W.B. Saunders & Co.; 2005: pp 780-90.
11. Bassetti C, Aldrich MS. Narcolepsy. *Neurol Clin* 1996; 14: 545-71.
12. Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000; 27: 469-74.
13. Gulia KK, Mallick HN, Kumar VM. Orexin A (hypocretin-1) application at the medial preoptic area potentiates male sexual behavior in rats. *Neuroscience* 2003; 116: 921-3.
14. Thakkar MM, Ramesh V, Strecker RE, McCarley RW. Microdialysis perfusion of orexin-A in the basal forebrain increases wakefulness in freely behaving rats. *Arch Ital Biol* 2001; 139: 313-28.
15. Kok SW, Roelfsema F, Overeem S, Lammers GJ, Frolich M, Meinders AE, *et al*. Pulsatile LH release is diminished, whereas FSH secretion is normal, in hypocretin-deficient narcoleptic men. *Am J Physiol Endocrinol Metab* 2004; 287: E630-6.
16. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, *et al.* Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab* 2001; 86: 3787-94.
17. Hajak G, Bandelow B, Zulley J, Pittrow D. 'As needed' pharmacotherapy combined with stimulus control treatment in chronic insomnia: assessment of a novel interventional strategy in a primary care setting. *Ann Clin Psychiatry* 2002; 14: 1-7.
18. Mahapatra AP, Mallick HN, Kumar VM. Changes in sleep on chronic exposure to warm and cold ambient temperatures. *Physiol Behav* 2005; 84: 287-94.
19. Rosenthal MS, Vogel GO. The effect of a 3-day increase of ambient temperature towards the thermo neutral zone on rapid eye movement sleep in the rat. *Sleep* 1993; 6: 702-5.
20. Kumar VM, Vetrivelan R, Mallick HN. Alpha-1 adrenergic receptors in the medial preoptic area are involved in the induction of sleep. *Neurochem Res* 2006; 31: 1095-102.
21. Kumar VM, Vetrivelan R, Mallick HN. Noradrenergic afferents and receptors in the medial preoptic area: neuroanatomical and neurochemical links between the regulation of sleep and body temperature. *Neurochem Int* 2007; 27: (in press).
22. Vetrivelan R, Mallick HN, Kumar VM. Tonic activity of α_1 adrenergic receptors of the medial preoptic area contributes towards increased sleep in rats. *Neuroscience* 2006; 139: 1141-51.
23. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Intern Med* 2000; 160: 2137-41.
24. Desautels A, Turecki G, Montplaisir J, Xiong L, Walters AS, Ehrenberg BL, *et al*. Restless legs syndrome: confirmation of linkage to chromosome 12q, genetic heterogeneity, and evidence of complexity. *Arch Neurol* 2005; 62: 591–6.
25. Sack RL, Lewy AJ, Hughes RJ. Guidelines for prescribing melatonin for sleep and circadian rhythm disorders. *Ann Med* 1998; 30: 115–21.
26. Czeisler CA, Richardson GS, Coleman RM. Chronotherapy: resetting the circadian clocks of patients with delayed sleep phase insomnia. *Sleep* 1981; 4: 1-21.
27. Reid KJ, Zee PC. Circadian rhythm disorders. *Semin Neurology* 2004; 24: 315-25.
28. Boeve BF, Silber MH, Parisi JE, Dickson DW, Ferman TJ, Benarroch EE, *et al*. Synuceinopathy pathology often underlies REM sleep behavior disorder and dementia or Parkinsonism. *Neurology* 2003; 61: 40-5.
29. Schenck CH, Mahowald MW. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. *Cleveland Clin J Med* 1990; 57 (Suppl.): S9–S23.
30. Thannickal TC, Lai Y, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* 2007 (in press).
31. Von Economo C. Sleep as a problem of localisation. *J Ner Ment Dis* 1930; 71: 249-59.

Clinical Trials Registry-India

A Clinical Trials Registry-India has been set up jointly by the Department of Science and Technology (DST), World Health Organisation (WHO) and Indian Council of Medical Research at the National Institute of Medical Statistics (NIMS), New Delhi. This Registry will provide a platform for registration of all clinical trials. The objective of the Registry is to establish a public record system by registering all prospective clinical trials of any intervention (drug, surgical procedure, preventive measures, lifestyle modifications, devices, educational or behavioural treatment, rehabilitation strategies and complementary therapies) conducted in India involving human participants. The Registry will be made publicly available on the internet at no cost. The website of the Indian Registry is www.ctri.in.