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Sleep Medicine

Guest Editors

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V. Mohan Kumar

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March 18, 2014 *Prof. J.S. Bajaj*

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Sleep Medicine

Perspective, Potential, and Prospect

Prologue :

Taking cognizance of the rapid advances in the emerging specialty of Sleep Medicine, the National Academy of Medical Sciences planned and organized a Regional Symposium on the subject as a part of the Annual Conference of the Academy at the All-India Institute of Medical Sciences, Jodhpur. The Regional Symposium was aimed :

'to enhance knowledge of sleep physiology and raise awareness of the spectrum of sleep disorders that physicians may see in their patients and to enhance participants' understanding of the association of increasing prevalence of sleep disorders with the obesity epidemic in children and adults; consequences of sleep disorders; specific disease states associated with such disorders and the treatments available'.

Learning objectives in terms of cognitive, psychomotor and behavioural outcomes were articulated in order to achieve a positive outcome.

This special issue of ***Annals*** provides the scientific content of the presentations made at the Symposium. The pre- and post-symposium assessment as well as programme evaluation indicated most satisfactory outcome as summarized (page 185).

Nevertheless, Sleep Medicine is not just a compendium of clinical conditions dealing with etiology, pathogenesis, diagnosis and management. It has broader dimensions and wider ramifications which need to be amplified so as to generate awareness not only amongst healthcare providers but also in health planners, social and behavioural scientists as well as in the community at large so as to facilitate the emergence of a well considered collective and cohesive response and appropriate intervention strategies.

Historical Perspective :

Beginning in the middle of the 20th century, investigators both in the basic science laboratories as well as in multiple clinical disciplines have qualitatively and quantitatively added to our knowledge about sleep-wake functioning. Although sleep clinics were established in the United States and in some countries in Europe in the 1970s, most of these were confined to the diagnosis and management of Obstructive Sleep Apnea. No regulatory requirements of a training or certification were required and till the turn of the 20th century, any physician could open a Sleep Clinic and/or a Sleep Laboratory to provide specialized care for sleep disorders.

The situation was no different, perhaps worse in India. It was in September, 1992 that the International Conference on

'Sleep-Wakefulness' was held at the All-India Institute of Medical Sciences, New Delhi and provided an impetus to the Indian biomedical and clinical scientists who responded collectively to the unmet national needs in the specialty. It was at this conference that the '**Indian Society for Sleep Research**' was born and a classic Monograph "**SLEEP-WAKEFULNESS**" was published on behalf of the organizers of the conference with dynamic leadership of the past President of the National Academy of Medical Sciences, Dr. B. Ramamurthi as President and Dr. V. Mohan Kumar, a distinguished Fellow of the Academy as General Secretary of the newly constituted 'Indian Society for Sleep Research'. Long-term plans for the organizational structure and operational framework were nurtured. The second remarkable effort at this conference was the birth of a second organization "**The Asian Sleep Research Society**" with Professor T. Okuma from Japan as President and Dr. V. Mohan Kumar as Vice-President.

With the establishment of Indian Society for Sleep Research and the Asian Sleep Research Society, a mechanism of networking with other International Sleep Research Societies was established. This has now emerged as the World Federation of Sleep Research & Sleep Medicine Societies (WFSRSMS) with a large number of national associations affiliated to this organization. In some countries, there are more than one associations dealing with Sleep Medicine : separate organizations for dealing with biomedical research viz-a-viz associations involved in public health and education for sleep health care. For example, in the US, American Academy of Sleep Medicine (AASM) and National Sleep Foundation (NSF) deal with professional advancement and public interest, respectively.

Social demographics of Sleep Health Care :

The social demographics and economic cost to society as a result of disorders of sleep are now receiving major attention. The US National Transportation Safety Board, as a result of well conducted studies, observed that the leading cause of fatal-to-the-driver heavy truck crashes is fatigue-related (31%) and alcohol (29%), with sleep deprivation being a significant contributor. Indeed the later has been implicated in the nuclear incidents at Chernobyl and Three Mile Island and the explosion of the space shuttle Challenger.

There is a general agreement that a lack of adequate sleep is related to several adverse effects of health including some that may be of cognitive import. Therefore, seven to nine hours of sleep has been generally recommended for adults. As against this, a recent gallup poll conducted between December 05 and December 08, 2013, with a random sample of 1031 adults, aged 18 and older, living in all 50 US states has shown that 40% of American adults get less than 7 hours of sleep at night, the average being 6.8 hours. There is an average reduction of more than one hour when compared to data similarly obtained in 1942. It is argued that this significant reduction in sleep is on account of lifestyle changes i.e.

visiting discos / parting till late at night in higher socio-economic classes while in lower and middle classes it may be related to the demands of working and parenting.

It is axiomatic that for children a good night's sleep is an essential pre-requisite for good health, mental growth & development, scholastic performance as well as for desirable behavioural attributes. With focus on 'Sleep in Children' a National Sleep Foundation poll in 2014, aimed at ascertaining sleep practices and beliefs of the modern American family with school-aged children was conducted. The poll required the parents to provide an estimate of amount of sleep their child typically gets on a school night. The data showed that parents' estimates of sleep time were *8.9 hours* for children ages *6 to 10*, 8.2 hours for 11 and 12 year olds, 7.7 hours for 13 and 14 year olds, and 7.1 hours for teens ages 15 through 17. The data needs to be viewed in the context of the National Sleep Foundation recommendations which state that children ages *6 to 10* should get *10 to 11* hours of sleep per night. Parents were also asked as to how much sleep their child needs to have in order to be in optimal state of health and performance. 26% of parents estimated that their child's sleep must be at least one hour more than the child actually gets on the school nights. It is interesting to observe that parents do understand the importance of quality sleep : more than nine in ten parents think sleep to be extremely or very important for their child's performance in school, health and his/her well-being, and mood and behviour the next day.

A significant co-relation emerged between the availability of electronic devices in a child's bedroom and a reduction in night sleep. According to the parents' reports nearly three out of four (72%) children ages 6 to 17 year have at least one electronic device in the bedroom. Parents also have a more negative view of the quality of their child's sleep if the child leaves such an electronic device on while sleeping.

An interesting fact that emerged from the study was that the children whose parents have healthy sleep environments tend to have healthier sleep environments themselves. Nearly two-thirds (65%) of children whose parents have one or more "interactive" electronics (tablet or smartphone, laptop or desktop computer, and/or video game) in their bedroom also have at least one device in their own bedroom. Only 24% of children have a device in their bedroom if their parents do not.

The implications of such data are obvious in terms of contemporary relevance to emerging life style in upper and middle class families in India. Generating awareness is an urgent need : time is of essence.

Sleep and Nutrition :

It has been previously reported that there was a possible co-relation between poor sleep and low blood levels of omega-3 long chain polyunsaturated fatty acids (LC-PUFA) in infants as well as in children and adults with behavioural and learning difficulties. It was proposed to

investigate possible links between sleep pattern and fatty acids status in healthy children.

A randomized placebo-controlled study undertaken at the University of Oxford, England has shown that higher levels of omega-3 DHA, are associated with better sleep. The design of the study was based on investigating the effect of 16 weeks supplementation of daily 600 mg. of algal sources. The primary endpoint was improvement in the sleep of 362 children who were not selected for sleep problems but were struggling readers at a mainstream primary school. At the outset, the parents filled in a child sleep questionnaire, which revealed that four in 10 of the children in the study suffered from regular sleep disturbances. In the pilot study, it was shown that the children on a course of daily supplements of omega-3 had nearly 1 hour (58 minutes) more sleep and seven waking episodes per night compared with the children taking the corn or soybean placebo.

Sleep health care : Tasks ahead

The sound basis of health policy planning and implementation requires a system approach which includes determinants such as epidemiology, demography, human resources and appropriate technology. While studies of epidemiology and demography as cited above provide significant information for the population in the US, similar studies are lacking in India and in most of the developing countries. The obvious reason is the enormous disease burden due to communicable and non-communicable diseases, leaving little resources for additional undertaking. Nevertheless, there is an urgent need to focus on these emerging issues which are likely to be of concern in the near future. For example, a study by Panda et al (2012) reported prevalence of insomnia in 9% of the general population with about 30% reporting occasional insomnia. A higher prevalence of sleep disorders related to initiation and maintenance of sleep (28%) was reported in an urban population from north India. In a large study by Stranges et al. from the University of Warwick, the researchers examined the sleep quality of 50-year-olds from rural populations in Bangladesh, Ghana, India, Indonesia, Tanzania, South Africa, and Vietnam, as well as from an urban area in Kenya. They investigated potential links between sleep problems and social demographics, quality of life, physical health and psychiatric conditions in 24434 women and 19501 men included in the study. They found that a strong link existed between sleep-related problems and psychiatric conditions like depression and anxiety, similar to that reported from the developed world.

How do we respond to such problems in a realistic manner and prepare for the emerging issues in the future? A serious concern is lack of human resources which must play a key role in planning, designing and implementing sleep health care programmes in contrast to the felt but unmet needs of critical health manpower. The striking fact is that health and medical educators have neither paid any attention to the issues of sleep behavior nor to the morbidity associated with sleep disorders.

The lack of trained and skilled human resources for sleep health care is not confined to India alone. A survey in 1990-91 of 37 American medical schools showed that sleep and sleep disorders were 'covered' in less than two hours of total teaching time, on average. A 2002 survey of more than 500 primary care physicians in the US who self-reported their knowledge of sleep disorders as follows : Excellent – 0%; Good – 10%; Fair – 60%; and Poor – 30%. The link between lack of appropriate educational modules during undergraduate curriculum and the knowledge of practicing physicians is obvious.

In order to ascertain the situation in India, a well designed proforma with critical parameters was sent to 100 Government Medical Colleges in different states of the country. Early responses have been received from 23 Medical Colleges. To the question : '*Does your Institute conduct any structured course or module in any form, on Sleep Medicine in any of the departments/specialty*', 96% medical institutions have responded "NO" while only one institution (4%) has responded in the affirmative.

Notwithstanding obvious constraints there is need to initiate urgent action. An outline of a sleep health care programme stated below must keep in view these concerns : -

Goal :

The goal of a well-designed sleep health care programme must be aimed :

i) to generate the knowledge and technology required for the prevention and treatment of sleep disorders and associated co-morbidities;

ii) to devise, through service and psychosocial research, improved strategies for integrating sleep health care into primary health care, in a manner most appropriate to local needs, and taking into consideration socio-economic and other related factors;

iii) to promote local and national self-reliance in sleep health care by seeking support both from the governmental and non-governmental organizations, assessing the needs and incorporating training programmes for skilled human resources, and such physical, technical and technological facilities that will enable development of infrastructure and implementation of intervention strategies.

Enabling objectives :

The enabling objectives for such a sleep health care programme may generally include the following :

a) to generate awareness and provide technical inputs and manpower resources for integrating sleep health care in the primary health care system.

b) to provide upgraded facilities at the community health centres and sub-district (Taluka) hospitals.

c) to initiate and develop prototype of tertiary care facilities at district hospitals and medical colleges for diagnosis and management of sleep disorders and associated co-morbidities.

d) to innovate cost effective appropriate technologies and ensure a system of quality control.

e) to collate and disseminate new and relevant information on individual and family sleep behavior as well as sleep disorders especially in children, women, and aged.

f) to coordinate nationwide education and training programmes for public, patients as well as of all categories of primary health care providers including community health workers, allied health care professionals and physicians.

g) to assess current and future needs with regard to the need and supply of skilled human resources, drugs & devices, and procedures for the care and cure of sleep disorders and co-morbidities.

To summarize the strategic approach, it may be stated that :

"Health systems planning for, and research into, sleep health care must be adaptable to the wide variations in social, economic, and medical conditions and structures. Community-based primary health care schemes should be linked to specialized levels to optimize the quality of care, depending upon the requirements of the patient and the availability of resources. A group of experts should review alternative strategies including practice of Yoga and make specific proposals for health systems planning, and for the integration of sleep health care into national health services."

Epilogue :

Sleep is a blend of Scientist's narration and Artist's imagination :

'There is a drowsy state, between sleeping and waking, when you dream more in five minutes with your eyes half open, and yourself half conscious of everything that is passing around you, than you would in five nights with your eyes fast closed and your senses wrapt in perfect unconsciousness.'

- Charles Dickens

J.S. Bajaj*
Emeritus Editor

*The views expressed are entirely of the author and are yet to be discussed and endorsed at the appropriate Fora of the National Academy of Medical Sciences.

REFERENCES :**

** Can be available on request to the Publication Officer of the National Academy of Medical Sciences (meenakumari42@yahoo.com)

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Physiology of Normal Sleep: From Young to Old

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ABSTRACT

Human sleep, defined on the basis of electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG), is divided into rapid eye movement (REM) sleep and four stages of non–rapid eye movement (NREM) sleep. Collective monitoring and recording of physiological data during sleep is called polysomnography. Sleep which normally starts with a period of NREM alternates with REM, about 4-5 times, every night. Sleep pattern changes with increasing age. Newborns sleep for about 14-16 hours in a day of 24 hours. Although there is a wide variation among individuals, sleep of 7-8.5 hours is considered fully restorative in adults. Apart from restorative and recovery function, energy conservation could be one of the functions of sleep. The role of sleep in neurogenesis, memory consolidation and brain growth has been suggested. Though progress in medical science has vastly improved our understanding of sleep physiology, we still do not know all the functions of sleep.

Key words : electroencephalogram, electromyogram, electrooculogram, polysomnography, REM sleep, non–REM sleep, newborns, circadian rhythm, auto-regulation, sleep function

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Sleep is quantified and qualified on the basis of electrophysiological signals. There are definite changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) during sleep (**Figure 1 and 2**). Modern definition and classification of sleep was suggested by Nathaniel Kleitman, in 1939 in his seminal book titled *Sleep and Wakefulness* (1). Unfortunately, Kleitman is remembered today by many only for his discovery of rapid eye movement sleep (REM sleep) in 1953 (2). Classification of sleep is described in detail in a manual written by Rechtschaffen and Kales (3). Normal human sleep, divided into non–rapid eye movement (NREM) and REM sleep, could be classified into five stages. They are stages 1, 2, 3 and 4 of NREM sleep and REM sleep (**Figure 2**). The American Academy of Sleep Medicine (AASM) modified the staging rules in 2007(4). The major change that they have introduced was combining stages 3 and 4 of NREM sleep.

Sleep starts with a period of NREM sleep. REM sleep takes place after a short period of NREM sleep. This alteration between NREM and REM occurs 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. Usually, REM sleep is the last phase of a full night's sleep, and one usually wakes up during this stage of sleep.

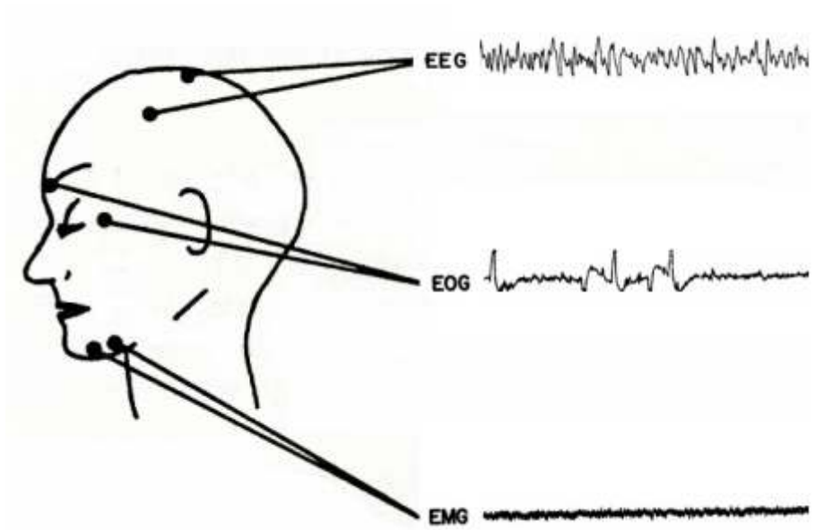

FIGURE 1 : Sleep-wakefulness, defined electrophysiologically, relies on changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). These signals are picked up from various sites using electrodes placed on the head.

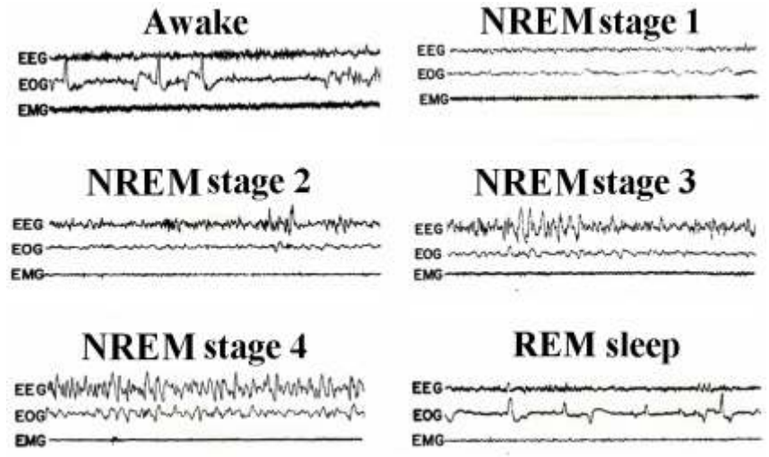

FIGURE 2 : There are distinct changes in electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) as the subject goes from wakefulness to stages I, II, III and IV of NREM sleep and REM sleep.

Polysomnography:

Collective monitoring and recording of physiologic data during sleep is called polysomnography. Traditionally three primary measures, namely EEG, EMG and EOG are used to assess different stages of sleep-wakefulness (**Figure 2**). Six electrodes (labeled C3, C4, A1, A2, O1, and O2) and one ground electrode are placed around the cranium to record EEG, using the 10-20 system of electrode placement. Some people think that it is sufficient to record from only four EEG electrodes (C3, C4, A1, A2) and one ground electrode. On the other hand, others use eight EEG electrodes (labeled C3, C4, F3, F4, O1, O2 , A1, and A2) and one ground electrode. Ear or mastoid process (A1, and A2) electrodes are used as reference electrodes. EOG is recorded by placing one electrode above and to the outside of the right eye, and another electrode below and to the outside of the left eye. EMG is actually recorded from two sites. In the classical recording for classification of sleep-wakefulness three EMG leads are placed on the chin (one in the front and center and the other two underneath and on the jawbone).

In the modern polysomnography many variables other than EEG, EMG and EOG are recorded. They include electrocardiogram (ECG), respiratory effort, nasal and/or oral airflow, oxygen saturation (SpO_2), body position, and limb movements. ECG is recorded with the help of two electrodes placed on the upper chest near the right and left arms. These

are recorded merely to note the heart rate and rhythm, and for alerting the technician to a possible emergency situation. They also demonstrate whether desaturation during apnea leads to arrhythmias or not. Airflow is monitored with the help of a thermistor or thermocouple sensor. This device looks similar to a nasal cannula and is secured just under the patient's nose. It senses the amount of air moving into and out of the airways and sends signals to the physiological recorder. This tracing is used to determine the presence and extent of apneic episodes. Respiratory effort is assessed using a piezo crystal. Two Velcro bands, one placed around the chest under the breasts and one around the abdomen, serve to determine chest wall and abdominal movements during breathing. Each band has a piezo crystal transducer. The force of chest or abdominal expansion on the bands stretches the transducer and alters the signals to the physiological recorder. These leads, combined with the airflow sensor, help to detect apnea. Limb movements are assessed by recording EMG. For that purpose two EMG leads are placed on the inside of each calf muscle, about 2-4cm apart. Oxygen saturation of blood is measured by a pulse oximeter probe placed on the finger, or earlobe of the patient.

Video cameras are used to monitor the patient. If the patient's activity is tape recorded while sleeping, the technician can review the tape at any time during the analysis. It helps to verify whether strange-looking waveforms were caused by the patient's movement, or due to any other reason. Though visual assessment of polysomnogram, and EEG in particular, is essential for any sleep-wake analysis, scoring of about 1400 pages (i.e. a patient's one night record) is time consuming. So, people often resort to computer scoring to come to a conclusion, which is not a healthy practice. But automation is superior to manual scoring in some ways, as the computer can use a lot of parameters, such as alpha rhythm, sleep spindles, delta waves, rapid eye movements or tonic chin EMG levels to make a hypnogram (**Figure 3**).

Sleep stages :

The most important parameter required for sleep analysis is EEG. The different EEG waves found during sleep and wakefulness could be classified as delta (4Hz, 150-250V), theta (4 - 8 Hz, 100-200V), alpha (8-13 Hz, 50 -100V), beta (13Hz, 50V) on the basis of their frequencies and amplitudes. During the wakeful 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, either as abundant or as scarce activity. The EMG may be high or moderate, depending on the degree of muscle tension.

The alpha activity decreases during stage 1 of NREM sleep (**Figure 2**). The EEG consists mostly of low voltage, mixed frequency activity, with much of it in 3-7 Hz range. The EOG activity is

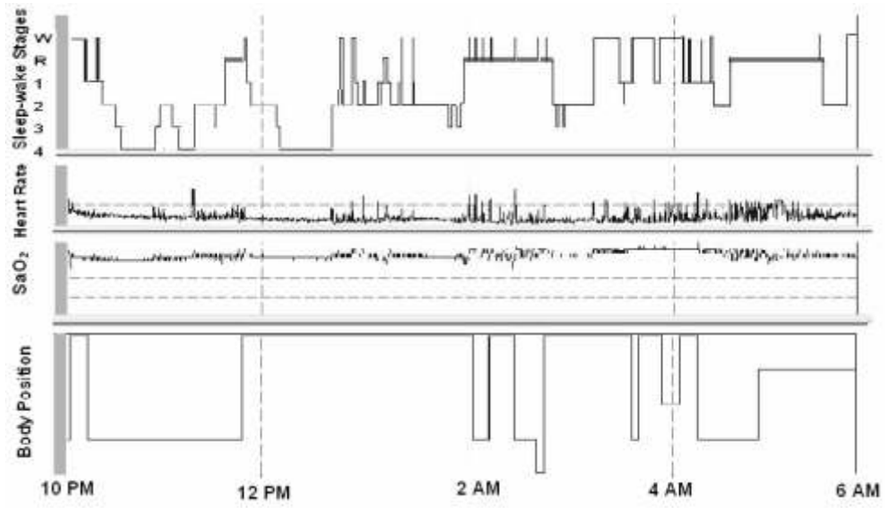

FIGURE 3 : Computer assisted scoring of sleep-wakefulness is shown in the upper graph. Simultaneous recording of heart rate, SaO_2 and body position are shown below that. W- wake stage; R- REM sleep; 1, 2, 3 and 4 are NREM sleep stages 1, 2, 3 and 4

mostly absent, but slow rolling eye movements would be present. The EMG is moderate to low during this period. Against the background of low voltage, mixed frequency EEG (of stage 1), sleep spindles (12-14 Hz sinusoidal waves) appear as the person enters stage 2 of NREM sleep. Eye movements (EOG) are rare, and EMG is low to moderate during stage 2. During stage 3, delta waves appear in the EEG, but the EOG and EMG continue to remain as before. There is a quantitative increase in delta waves during stage 4, so that they come to dominate the EEG tracing. The EOG continues as before, and EMG shows slight reduction. In a nutshell, as the sleep progresses to deeper stages, i.e. from stage 1 to 4, the EEG shows increasing voltage and decreasing frequency. Muscles are progressively relaxed during the deeper stages of sleep. Though muscle activity is reduced, the sleeper makes postural adjustments after about every 20 minutes. During NREM sleep, the heart rate and BP decline, but the gastrointestinal motility and parasympathetic activity increase.

NREM sleep alternates with REM sleep. Human REM sleep is marked by the EEG reverting to a low voltage, mixed frequency pattern, similar to that of NREM stage 1 sleep. The eyeballs show rolling movement, with superimposed bursts of rapid eye movements during this phase of sleep. So bursts of prominent REMs appear in EOG.The REM sleep is also called “paradoxical sleep”, as the

EEG (recorded from animals) during this phase becomes desynchronised (i.e. low voltage fast activity), similar to the wake stage. REM sleep, which appears after 30-90 minutes of NREM sleep, is characterised by a profound loss of muscle tone (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 REM sleep is associated with dream, some mental activity is associated with NREM sleep also. But it is less vivid and not accompanied by full dream narrative. Dreams are usually visual, but the congenitally blind have auditory dreams. REM sleep is associated with penile erection and testosterone release.

It is a common assumption that mammalian sleep and wake states are distinctly different. Though modern science identifies waking, NREM sleep and REM sleep, very objectively, by using physiological signs and behavioural correlates, studies have shown that each of these states can intrude into the other. Some components of REM sleep can, at times, appear in awake states in some clinical conditions. Similarly, wakeful behaviour can intrude into sleep, in some clinical conditions, resulting in striking consequences (5).

Sleep-wake cycle consists of inherent rhythmic changes with 24 hour (circadian) periodicity in physiological, biochemical, and psychological processes in the body. 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, with clues such as environmental variables (like light exposure) and activity schedule entraining it to a 24-hour cycle. Light, which entrains the circadian clock to a 24-hour rhythm, is called a "zeitgeber," a German word meaning "time-giver". 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 around 25 hours.

Sleep changes with age:

The amount of sleep needed by each person is usually constant, although there is a wide variation among individuals and cultures. In adults, sleep of 7-8.5 hours is considered fully restorative. In some cultures, total sleep often is divided into an overnight sleep period of 6-7.5 hours and a mid afternoon nap of about one hour. Sleep pattern changes with increasing age. Newborns show several sleep-wake cycles in a day of 24 hours. This polycyclic rhythm passes through a biphasic pattern before a monocyclic pattern is established in young adults. In newborns, the total duration of sleep in a day can be 14-16 hours. Most of it is REM sleep. During old age, total sleep is not only reduced, it is often divided into an overnight sleep period of less than 6-7.5 hours and a mid afternoon nap of about one hour.

Neural regulation of sleep:

According to traditional belief, prolonged activity of the brain during the day is followed by rest, at night, in the form of sleep. Sleep was considered as a passive process till the 1950s (6). This passive theory of sleep was replaced by the active sleep genesis concept, mainly after the realization that brain activity is only slightly reduced during sleep. Findings during the next 50 years emphasized that sleep is an active process of the brain. Employing various modern techniques, discrete areas were demarked by various scientists who assigned them the roles in the regulation of NREM and REM sleep (**Figure 4**). This led to the assertions about the roles of the preoptic and other basal forebrain areas in the generation of NREM sleep, and the interactions of the pedenculo-pontine and lateral dorsal tegmental areas with the dorsal raphae nucleus and locus coeruleus, for the generation of REM sleep (7). Unfortunately, overemphasis of localization of sleep regulating areas had led to a misunderstanding of sleep regulation itself. The emphasis on the active regulation of sleep cannot overlook the basic fact that the passive withdrawal of wakefulness plays a role in the initiation of sleep. There is now growing evidence to suggest that sleep is auto-regulatory and that it is not necessary to attribute sleep genesis to either an active or a passive mechanism (8,9).

Functions of sleep :

The importance of sleep is evident from the health problems resulting from

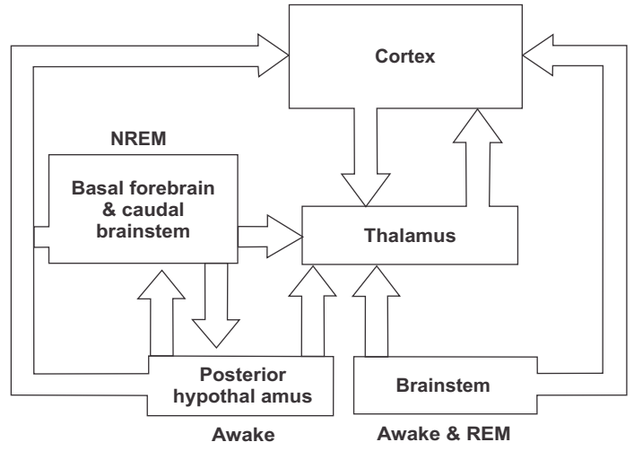

FIGURE 4 : The diagram shows the areas of the brain which are primarily implicated in the regulation of NREM and REM sleep and wakefulness. It also shows the major neural connections involved in the regulation of sleep-wakefulness.

sleep disorders. Some sleep disturbances can be described as temporary mild inconveniences, while others are far more serious with disastrous consequences. Persistent and repeated interruption of sleep affects the physical and mental health of the individual. Inadequate sleep causes not only misery to the sufferer, but it also has far reaching socioeconomic consequences. Sleep is considered essential for life as it is preserved through evolution. Moreover, both REM and NREM sleep show rebound after sleep restriction or deprivation. Sleep pressure after sleep deprivation is so strong that one falls asleep, even at the cost of one's own life. Sleep-deprived rodents die earlier than the food-deprived animals. Rats deprived of sleep die in 2-3 weeks, while food-deprived rats may survive for 4-5 weeks. Almost all mammals show NREM–REM cyclic alternation. Sleep must be having a universal functional significance, though it is still difficult to enumerate its functions. Some of the possible functions of sleep are listed below (10).

Sleep may be having a restorative and recovery function, especially for the brain. Sleep is said to prevent metabolic brain injury. Sleep time may be related to defense against oxidative stress. Normal metabolism produces high levels of reactive oxygen species (ROS) by mitochondria. ROS levels are reduced during sleep. Sleep facilitates the synthesis of molecules that protect brain cells from oxidative stress.

Energy conservation could be one function of sleep. Energy consumption during sleep is less by 15%. Energy intake (food intake) is increased on sleep deprivation. Sleep is more in newborns, infants and in small mammals with high surface to mass ratio. Energy cost of thermoregulation is high in small animals. Carnivores and omnivores, which are generally safe when asleep, may be using the energy-conservation aspects of sleep. Carnivores that eat meals with high calorific density can afford to have long periods of sleep.

Sleep may have a thermoregulatory function. Mild heating of hypothalamic sleep regulatory area & warm atmospheric temperature induce sleep in animals. Body heating prior to sleep increases slow wave sleep in man. Many sleep - active neurons in the brain are thermosensitive. Cooling of brainstem (REM generating areas) in experimental animals produces an increase in REM sleep. Brain temperature increases during REM sleep, even though thermoregulation is suppressed during this stage of sleep. REM sleep is maximum during early morning, when the body temperature is at the lowest level. This prevents the fall in brain temperature.

The role of REM sleep in brain growth has been suggested for long. Sleep, especially REM sleep, is more in newborns. Premature babies have higher REM sleep. REM sleep amount is strongly correlated with brain maturity at birth, in the animal kingdom. Guinea pigs have very little REM sleep at birth. New-born guinea pigs are born with teeth, claws, fur and open eyes. They thermoregulate and make locomotor movements within an hour of birth. They eat solid food within a day of birth. As their brain is relatively mature at birth the new-born guinea pigs have very little REM sleep. Similarly, sheep and giraffe are relatively mature at birth, and have very little REM sleep.

Sleep may also facilitate neurogenesis. Protein synthesis in the brain is increased during slow-wave sleep. Short-term (2–3-days) total sleep deprivation, blocks proliferation of cells in the dentate gyrus. Experimentally reducing light input in neonates reduced cells in the visual system. When neonates were also REM sleep-deprived, this shrinkage in the visual system was accelerated. It is suggested that the neuronal development proceeds according to genetic programmes, only when NREM sleep of neonates is interrupted by REM sleep.

Memory consolidation during sleep has been proposed by many investigators. There has been a manifold increase in publications on this topic during the last few years. Non-declarative memory (motor skill) is enhanced during sleep, probably during specific sleep stages. The role of sleep in declarative memory consolidation remains largely unproven. Sleep deprivation and disturbed sleep certainly reduce concentration and learning. Motor training and improved performance produce increased slow waves in the parietal cortex, during sleep. So slow-wave sleep may facilitate memory consolidation. Regions active during task performance in PET imaging, are more reactivated during REM sleep. Several genes that are believed to contribute to memory consolidation are up regulated during sleep.

Sleep is proposed to have many other functions. Discharge of emotions through dreaming is an age-old function ascribed to sleep. Those animals which are immature at birth benefit from the sleep-induced reduction in activity. Reduced activity would also lead to reduced exposure to danger. According to some studies man shows disturbed behaviour after REM deprivation. But, depressed persons show marked improvement on REM sleep deprivation.

Unanswered questions about sleep :

Sleep patterns of some animals make us doubt the validity of above mentioned statements regarding functions of sleep. There is near absence of sleep in postpartum marine mammals (whales, dolphins) and also their neonates do not sleep for several days. When on land, fur seals show both NREM and REM sleep. But when they are in water, they show no REM sleep. When they move back onto

land, after spending weeks in the water, they show no REM rebound. Cetacean mothers show no rebound increase in sleep after the postpartum period. Migratory birds also do not sleep during their long migration. This sleep reduction during the migration is not followed by sleep rebound. Moreover, it is not possible to assert that all animals sleep, though lower forms of animals show rest-activity cycles. Length of sleep also varies in different mammals. Giraffes and elephants sleep for 4-5 hrs, whereas opossum, bats and giant armadillos sleep for 18 hrs. Amount of NREM and REM sleep also varies in different animals. Platypus has more REM sleep than any other animal (about 10 hrs). Guinea pig has only 1 hour of REM sleep per day. Length of REM-NREM cycle varies from less than 12 min in rats to 90 min or more in man. Variation in sleep and its duration and pattern is not restricted to animals.

Mild body heating increases sleep, with no rebound insomnia, not only in animals but also in man. Heating the body, prior to sleep increases slow-wave sleep in man. Extending sleep time can slightly increase REM sleep in humans, with no rebound reduction during the subsequent night. Administration of monoamine oxidase inhibitors or brain lesions can suppress REM sleep for months or years (with no detectable cognitive or physiological symptoms). Sleep reduction in mania is also not followed by rebound sleep.

Conclusion :

It can be concluded that sleep is important for health and survival. Modern technology had made great advances in recording and analyzing sleep-wakefulness, and also the progress in medical science have vastly improved our understanding of the physiology of sleep. But, we still do not know all the functions of sleep. Though some sleep disturbances are temporary mild inconveniences, physical and mental health of the individual are grossly affected when there is persistent repeated interruption of sleep. Inadequate sleep causes not only misery to the sufferer, but it also has far reaching socioeconomic consequences.

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Sleep disordered breathing: OSA, CSA, Pathophysiology and Diagnosis

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a prevalent disorder that has been reported to occur in 2 to 4% of middle-aged adults. A similar prevalence of OSAS has been reported from India as well. However, this condition is frequently unrecognized and underdiagnosed. Important pathophysiological changes in patients with obstructive sleep apnea (OSA) is an alteration in human upper airway leading to a reduction in cross-sectional area of the upper airway contributing to the easy collapsibility of upper airway during sleep. Other pathophysiological changes in OSA are oxidative stress, systemic inflammation, sympathetic nerve activation, endothelial dysfunction, procoagulant activity, intrathoracic pressure changes and metabolic dysregulation. The gold standard for diagnosis of OSA is full polysomnography.

Key words: Obstructive sleep apnea, Central sleep apnea, Oxidative stress, Metabolic dysregulation, Polysomnography

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INTRODUCTION

Obstructive sleep apnea is a prevalent condition, but frequently unrecognized and undiagnosed. The important phases of sleep are Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep. There is decrease in sympathetic nervous system activity, heart rate, blood pressure, cardiac output, systemic vascular resistance and metabolic rate in NERM stage, but there is an increase in para sympathetic activity during NREM stage. However, there will be intermittent surges in sympathetic activity during Rapid Eye Movement (REM) sleep.

Obstructive sleep apnea :

The OSA is the repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. OSA is defined as reduction in airflow associated with upper-airway collapse or narrowing that occurs during the change from wakefulness to sleep. Apnea due to upper airway collapse is defined as nearly complete cessation of airflow associated with oxygen desaturation or an arousal from sleep and hypopnea is due to partial collapse of upper airways. Apnea is defined as cessation or near complete cessation that is more than 90% reduction of airflow $\geq$ 10 seconds despite continuing ventilatory effort with five or more such episodes per hour of sleep and is usually associated with a decrease of $\geq$ 4% in oxyhemoglobin saturation. Hypopnea is characterized by a reduction of > 50% in airflow for $\geq$ 10 seconds associated with a $\geq$ 3% decrease in oxygen saturation and/or arousal (1).

Central Sleep Apnea (CSA) :

The central sleep apnea (CSA) is the repetitive cessation of ventilation during sleep resulting from loss of ventilatory drive. The manifestations of CSA include high altitude induced periodic breathing, idiopathic CSA, narcotic-induced central apnea, obesity hypoventilation syndrome, and Cheyne-Stokes breathing (2).

Upper Airway Resistance Syndrome :

There will not be significant decrease in airflow in upper airway resistance syndrome, but snoring is usual, 15 or more episodes of arousal per hour of sleep with no significant decrease in oxyhemoglobin saturation are observed in Upper Airway Resistance Syndrome.

Pickwickian Syndrome - Obesity Hypoventilation Syndrome :

This entity consists of obesity, sleep disordered breathing, hypoxia and chronic hypercapnea during wakefulness in the absence of other known causes of hypercapnea. This was described as “Pickwickian Syndrome” in 1956 in a case report as the patient reported in this report resembled a character depicted by Dickens in his book “The posthumous papers of the Pickwick club” because both were obese with excessive hyper somnolence (3).

Apnea-Hypopnea Index :

Apnea-Hypopnea Index (AHI) is the number of apneas and hypopneas per hour of sleep confirmed by electro-encephalogram (EEG). Apnea-hypopnea index (AHI) is used to characterize OSA. Another index that is used is Respiratory Disturbance Index (RDI) and this is the number of apneas, hypopneas and respiratory effort related arousals per hour of sleep confirmed by EEG. The severity of OSA is classified based on apnea hypopnea index. AHI more than 5 and less than 15 events/hour of sleep is mild OSA, AHI between 15 to 30 events/ hour of sleep is moderate OSA and AHI more than 30 events/ hour of sleep is severe OSA. OSAS is defined as sleep disordered breathing associated with daytime symptoms most often excessive daytime sleepiness. It has been estimated that the OSAS affects 2 to 4% of middle-aged adults (4).

Risk factors :

Risk factors for development of OSA are classified as non-modifiable and modifiable factors (2, 3). The non-modifiable risk factors are age, gender (male), ethnicity (being black, Hispanic), anatomical abnormalities of craniofacial regions and upper airway, thick neck with circumference more than 17 inches in males and more than 16 inches in females and a genetic predisposition (5). The modifiable risk factors are excessive body weight (obesity), use of alcohol, sedatives or tranquilizers, narrowed airways due to enlarged tonsils or adenoids, smoking, chronic nasal congestion, hypertension, diabetes mellitus, myxedema and menopause (6). Wisconsin sleep study had identified baseline obesity, older age and presence of snoring as factors important in progression of disease (4).

Upper airway anatomy :

The human upper airway is composed of numerous muscles and soft tissue but it lacks bony support. It has been observed that the cross sectional area of the upper airway during wakefulness is reduced in patients with OSA compared with subjects without OSA, thereby leading to collapse of the upper airway during sleep (7).

Pathophysiology :

OSA-induced biological changes include intermittent hypoxia, intermittent hypercapnia, intra thoracic pressure changes, sympathetic activation and sleep fragmentation (8). Chronic intermittent hypoxia is the cardinal feature of OSA. During intermittent hypoxia, there will be repeated episodes of hypoxia and normoxia resembling ischemia/perfusion events (9). During hypoxic/ischemic phase, the cells adapt to low O2 environment and during reoxygenation/ reperfusion phase, there will be sudden increase of oxygen in the cells resulting in the production of reactive oxygen species (ROS) (9, 10).

OSA can cause sympathetic activation, metabolic dysregulation, endothelial dysfunction, systemic inflammation, oxidative stress, and hyper

coagulation and neurohumoral changes. These changes may lead to hypertension (both systemic and pulmonary), heart failure, arrhythmias, myocardial infarction, stroke and sudden cardiac death. Repetitive episodes of upper airway narrowing and / or occlusion cause hypoxemia, reoxygenation, swings in intra thoracic pressure and central nervous system arousals. These factors can cause acute stress on cardiovascular system and the cumulative effects from these can lead to disruption of cardiovascular homeostatic mechanisms. These may lead to daytime abnormalities in sympathetic nervous system function and to heart rate variability (11).

a) Oxidative stress :

Many studies have reported a role of oxidative stress in patients with OSA (12). Studies had demonstrated that there was an increase in thiobarbituric acid-reactive substances (TBARS) levels in patients with severe OSA compared with healthy control subjects and treatment with continuous positive airway pressure (CPAP) reduced the lipid peroxidation events (13-15). It was also reported that there was an increased level of oxidized low-density lipoprotein levels in OSA. Inhibition of xanthine oxidase by allopurinol and supplemental intake of vitamin C have been shown to improve endothelial function in patients with OSA. Glycation products, the end result of oxidative stress were also reported to be increased in OSA patients with normal glucose homeostasis. The demonstration that urinary 8 - hydroxy - 29 - deoxyguanosine excretion was significantly higher in patients with severe OSA versus control subjects suggests oxidative DNA damage in OSA. The antioxidant capacity in the blood which acts as defense against free radicals has also been found to be reduced in OSA compared to control subjects. In observational studies, a derangement in the oxidant-anti-oxidant balance with a shift towards oxidative stress was documented and treatment with the anti-oxidants (vitamin E, vitamin C and N-acetyl cysteine) had demonstrated a reduction in oxidative stress in OSA patients (15, 16). The results from these studies indicate the occurrence of oxidative stress in patients with OSA. However, there are studies that have not demonstrated increased oxidative stress in OSA (17).

b) Systemic inflammation :

It has been noticed that CD4 and CD8 T cells of patients with OSA undergo phenotypic and functional changes with a shift towards type 2 cytokines dominance and increased IL4 production (18). A marked increase in TNF-α and CD40 ligand in CD8 T cells from patients with OSA was also reported. CPAP treatment improved or reversed all these abnormalities in OSA patients (18, 19). Increased circulating levels of CRP have been consistently reported in both adults (20, 21), as well as in children with OSA (22) and are reduced on effective treatment (20, 23). It has been reported that there is an independent association between severity of OSA and elevated

CRP level in men without comorbidities (24). Nuclear factor kappa B (NF-kB), an important factor for activation of inflammatory pathways, has been found to be increased in OSA (25). Expression of adhesion molecules on circulating monocytes may indicate activation of systemic inflammation in OSA (26). It has been reported that TNF-α -308 polymorphism is associated with OSA (27).

c) Sympathetic Nerve Activation :

An increased sympathetic nerve activity has been reported in OSA (28). The increase in sympathetic activity during sleep may be due to the activation of peripheral chemoreceptors by hypoxia, hyper-capnea and apneas leading to peripheral vasoconstriction and increase in blood pressure (29). It has also been demonstrated that there is exaggerated sympathetic activity during daytime wakefulness despite normoxia (30). Increased concentrations of catecholamines in urine and elevated levels of norepinephrine in plasma were also seen in patients with OSA (31). Muscle sympathetic nerve activity (MSNA) has been found to be elevated in OSA during wakefulness (28) and CPAP therapy reduces the high sympathetic activity. An increase in resting heart rate during wakefulness has been observed in OSA patients suggesting that there is an increase in cardiac sympathetic drive in OSA (32). Thus chronic sympathetic activation may be an important factor for the development of cardiovascular disease in OSA (33).

d) Endothelial dysfunction :

Endothelial dysfunction in OSA is a risk factor for cardiac abnormalities in OSA (34). Endothelial dysfunction in OSA may be due to chronic intermittent hypoxia and to sleep loss and fragmentation. The endothelial dysfunction results in increased vasoconstriction and reduced vasodilation. Nitric oxide which is a powerful vasodilator is decreased in OSA and the decreased levels of nitric oxide may contribute to reduced vasodilation and platelet adhesion and aggregation. Treatment of OSA has been found to increase nitric oxide levels in OSA (35). Recurrent hypoxemia has been found to increase the endothelin levels in OSA and there is a reduction in endothelin levels on treatment with CPAP (36). Endothelin is a potent vasoconstrictor which causes elevated blood pressure. Endothelial dysfunction is one of the important factors that are responsible for cardiovascular diseases in OSA.

e) Procoagulant activity :

Several studies in OSA patients had shown that there are elevated levels of plasma fibrinogen, exaggerated platelet activity and reduced fibrinolytic activity suggesting that there is a hypercoagulable state in OSA (37). The exaggerated platelet activity has been found to be reduced following treatment with CPAP (38). There is also an increase in mean platelet volume which has been reduced by CPAP therapy in OSA patients.

f) Intrathoracic pressure changes :

During obstructive sleep apnea, the repetitive inspiratory efforts against a closed upper airway lead to increased negative intrathoracic pressure. As a result, there will be an increase in transmural gradients across the atria, ventricles and aorta. This is similar to the Muóller maneuver in which an individual inspires against closed glottis leading to a pleural pressure of -30 cm H_2O (39). These changes in transmural gradients can result in autonomic and hemodynamic instability (30, 40). An increase in aortic transmural pressure can cause aortic dissection in OSA patients.

g) Metabolic dysregulation :

There are evidences suggesting that OSA is independently associated with metabolic syndrome (41). Chronic intermittent hypoxia and sleep deprivation with sleep loss may play a role to trigger inflammation leading to metabolic syndrome. OSA may be a risk factor for metabolic syndrome. Obesity particularly central adiposity is a potent risk factor for sleep apnoea (42). An interaction of obesity-OSA-metabolic syndrome involving many mechanisms has been postulated (43). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report recommends the use of five variables (hypertension, insulin resistance or glucose intolerance, low serum high-density lipoprotein (HDL) cholesterol, elevated serum triglyceride, and abdominal obesity) with set threshold values for each variable for clinical characterization of metabolic syndrome. Subjects meeting three of these five criteria are classified as having metabolic syndrome. The cut off value for defining abdominal obesity may vary based on ethnicity (44). Features associated with metabolic syndrome are pro inflammatory state, prothrombotic state, hyperleptinemia, hypo-adiponectinemia, hyperuricemia, endothelial dysfunction and microalbuminuria (45).

Diagnosis :

Diagnosis of OSA is based on symptom assessment, clinical examination and laboratory investigations mainly by polysomnography.

a) Symptom assessment :

Symptoms can occur during sleep and during wakefulness. The most common symptoms during sleep are snoring, snorting, choking attacks terminating a snore and witnessed apneas by bed partner. Other nocturnal symptoms include non - restorative sleep, nocturnal restlessness, vivid dreams, gastroesophageal reflux, insomnia with frequent awakenings, nocturia, hyper salivation and diaphoresis. Symptoms reported during awake are excessive daytime sleepiness, lack of concentration, cognitive deficits, mood changes, morning headaches, dry mouth, impotence and decreased libido. The severity of excessive daytime sleepiness can be subjectively assessed by questionnaires; the most commonly used

questionnaire is Epworth Sleepiness Scale. Objective tests that can assess excessive daytime sleepiness include Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) and the Osler Test, but these tests are costly and time consuming (46). The interview of the partner is also important while assessing the patients with suspected OSA.

b) Clinical features :

The clinical features associated with OSA are obesity (particularly central, body mass index more than 30 kg/m^2), large neck circumference (more than 40 cm), narrow mandible, narrow maxilla, retrognathia, dental malocclusion, overbite, reduced nasal patency, high and narrow hard palate, elongated and low-lying uvula, enlarged tonsils, enlarged adenoids and macroglossia. Clinical examination of a patient suspected to be suffering from OSA includes measurement of blood pressure, cardiorespiratory auscultation, examination of the oral cavity and noting the presence of teeth and dentures. The assessment of the tonsils, tongue size, architecture of hard palate and faucal pillars are important. Mallampati score can be used to assess the upper airway in OSA.

c) Laboratory diagnosis :

The "Gold standard" for the diagnosis of OSA is full polysomnography and it provides detailed information on sleep state and respiratory and gas exchange abnormalities (47). Other variables assessed during polysomnography are body position, heart rate and rhythm, and muscle tone and contraction. Polysomnography is resource intensive requiring a full sleep laboratory and a trained technician. A minimum of 12 channels of recordings that include electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal airflow, chest wall effort, body position, snore microphone, electrocardiogram (ECG), and oxyhemoglobin saturation are usually used in polysomnographic (PSG) studies. The duration of the diagnostic study should be at least 6 hours.

However, when there is an obvious case of OSA, split-night studies, in which the first half of the study night is used for diagnosis and the second half to monitor treatment response using CPAP are also used. Because of the cost factor and the requirement of a trained technician, home-based sleep studies involving limited cardiorespiratory assessments are also advocated as an alternative to hospital based detailed polysomnographic studies. Cardio-respiratory monitoring which involves the measurement of airflow, respiratory effort, oxygen saturation and heart rate, but not EEG has been used to assess sleep apnea. Overnight oximetry is also used as a screening test to evaluate suspected cases of OSA by continuous recording of oxygen saturation (SaO2) during sleep. The characteristic pattern of desaturation in OSA is repetitive desaturation and oximetry may therefore be useful in evaluation of severe cases of OSA, but not in mild or moderate cases. There are many other conditions such as COPD, kyphoscoliosis, muscular dystrophy etc. that cause hypoxemia. Therefore, the observation of hypoxemia alone by oximetry cannot be taken as a diagnostic criterion of OSA.

A task force of the American Academy of Sleep Medicine has recommended the following criteria for the diagnosis of OSAS (48) and the patient suspected of OSAS must fulfil criterion A or B, plus criterion C:

A. Excessive daytime sleepiness that is not better explained by other factors

B. Two or more of the following that are not better explained by other factors:
Choking or gasping during sleep
Recurrent awakenings from sleep
Unrefreshing sleep
Daytime fatigue
Impaired concentration

C. Overnight monitoring demonstrates five or more obstructed breathing events per hour during sleep. These events may include any combination of obstructive apneas/hypopneas or respiratory effort–related arousals (49).

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Childhood Obstructive Sleep Apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is a common condition in childhood and can result in severe complications if left untreated. It is showing a rising trend in India. A significant association with obesity has been observed; however, some children with enlarged tonsils and/or adenoids may even be underweight. The patient usually presents with snoring and other respiratory problems like mouth breathing, choking and gasping episodes in night. Poor school performance and neurocognitive deficits have been reported. Pulmonary hypertension and cor pulmonale are seen in severe cases. Besides the history and clinical examination, for definitive diagnosis an overnight polysomnographic evaluation is the gold standard. In all cases, the specific treatment ranges from simple lifestyle modifications and medications to surgeries like adenotonsillectomy. Early diagnosis is vital.

Key words: Childhood OSA, Obesity, adenotonsillar hypertrophy

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INTRODUCTION

Sleep apnea forms a part of spectrum of sleep disordered breathing. It is defined as cessation of respiration for ten seconds or more OR cessation of respiration for two or more respiratory cycles (1). It can be Central, Obstructive or Mixed Apneas. Obstructive Sleep Apnea Syndrome (OSAS) is a sleep disorder characterized by recurrent episodes of narrowing or collapse of pharyngeal airway during sleep despite ongoing breathing efforts. Normally during sleep, the muscles which control the tongue and soft palate hold the airway open. If these muscles relax, the airway narrows, causing snoring and breathing difficulties. If these muscles relax too much or if obstruction is present, the airway can become completely blocked, preventing breathing. These often lead to acute derangements in blood gas disturbances, surges of sympathetic activation and periodic arousal from sleep causing fragmented sleep.

In recent years, the epidemic of obesity that is affecting the pediatric population all over the world has led to the emergence of a phenotypic variant of OSA in children that closely resembles that of adults with the disease. Dayyat et al. proposed that two types of OSA disease exist, namely one associated with marked lymphadenoid hypertrophy in the absence of obesity (type I) and the other being primarily associated with obesity in the presence of only mild lymphadenoid hyperplasia (type II) (2).

Epidemiology:

Though it occurs in all age groups from newborn to adolescents, the prevalence of sleep-disordered breathing in pre-school and school age children varies considerably from 3.2% to 27% for snoring (in most studies, 1/3 of the children aged 2-6 years have been claimed to snore occasionally and 10-14% to snore frequently) and from 0.5% to 3% due to OSAS (3, 4). Although only few studies have been conducted in India, yet the incidence was found to be higher than western studies (5). Seasonal variation is seen which might be due to variation in incidence of upper and lower respiratory problems (e.g. chronic rhinitis and asthma).OSA is more common in African-American & Asian children due to anatomic features of upper airway (6).

Pathogenesis:

Upper airway obstruction can be partial causing snoring or complete leading to OSA. In normal children, arterial oxygen decreases and CO2 increases only slightly during sleep. Episodes of partial or complete airway obstruction result in impaired gas exchange with hypoxemia and hypercarbia which stimulates arterial chemoreceptors leading to arousal or partial awakening. The impaired gas exchange in conjunction with decreased airflow is a potent stimulus for increased ventilatory effort and upper airway muscle activity. Arousal is associated with increased respiratory efforts and airway muscle tone which leads to resumption of airway patency. Arousals may appear in the form of movements, increased muscle tone or changes in EEG. Following the arousal, airflow is restored, blood gases are normalised and sleep resumes but the cycle of airway collapse starts again.

The most common functional process contributing to obstructive sleep apnea or hypoapnea is REM sleep, present in one-fourth of a typical night sleep. Apnea frequency, apnea duration and levels of hypoxemia are almost always more severe during REM sleep due to lack of "wakefulness" drive, decreased tone of pharyngeal muscles, intercostal and accessory muscle and depressed reflexes, minute volume and response to hypoxia.

Enlarged tonsils and adenoids are one of the common risk factors for OSA. Although one cause of OSA in children is adenotonsillar hypertrophy, yet tonsil size does not correlate with findings on sleep studies (7). One child with large tonsils may be without symptoms while another with modest tonsil enlargement may have significant symptoms. Increased resistance from swollen nasal turbinates or choanal stenosis places a greater negative collapsing pressure on the pharyngeal airway and may lead to worsening obstruction. Other anatomic factors such as micrognathia, retrognathia or macroglossia may force the tongue into the oropharyngeal portion of the airway and cause airway occlusion. Congenitally small midface or nasopharnyx also narrows the airway.

Diminished arousal responses can also impair the ability to restore upper airway patency. Children with CNS abnormality associated with impaired ventilator or arousal responses to hypoxemia, hypercapnia and/or airflow obstruction (e.g.Chiari II malformations) have increased vulnerability to severe OSAS and cardiorespiratory failure. Fat deposition from morbid obesity also narrows the airway. Sedative medicine or general anaesthesia can further compromise neural control of the upper airway.

Adenotonsillar hypertrophy, as a risk factor is now being replaced by obesity as a substantial cause of OSAS in children (8-13). For every increment in body mass index (BMI) of 1 kg/m^2 beyond the mean BMI for age and gender, the risk of OSAS increased by 12%. In obese, upper airway narrowing results from fatty infiltration of upper airway structures promoting pharyngeal collapsibility. Obesity reduces the intrathoracic volume and diaphragmatic descent during inspiration, particularly in the supine position, resulting in lower oxygen reserves and increased work of breathing during sleep. Obesity also results in blunted ventilatory responses to hypoxia and hypercapnea. Leptin, an adipocyte-derived hormone level appears to be determined by the degree of obesity. Leptin affect overall ventilatory drive, and influence peripheral chemoreceptor activity. Hypoxia induces an increase in both leptin gene expression and plasma leptin levels. Obesity is associated with peripheral and central leptin resistance. Thus, reduced bioavailability of leptin resulting in altered ventilatory responses also plays a role in the interaction between obesity and OSAS.

Sleep-disordered breathing (SDB) seems more common in boys (due to sex differences in airway structure and control of breathing) and African American children. Another putative risk factor is recurrent otitis media which is most likely related to chronic adenotonsillar hypertrophy. Disorders of the upper and lower respiratory system, including asthma and persistent wheezing are also risk factors. Environmental tobacco smoke exposure and maternal smoking during pregnancy not only exacerbate these other respiratory disorders but also have been shown to result in higher rates of snoring and likely SDB.

Symptoms (14-20):

Typically, loud snoring is the symptom that most disturbs and therefore alerts the parents. Though OSAS by definition is characterised by obstructive apneas terminated by arousals, OSAS in children present as partial continuous obstructive hypoventilation with fewer discrete obstructive apneas, fewer arousals and less disturbances of sleep architecture. For this reason day time hypersomnolence is much less frequent in children than adults. Children may sleep in unusual positions to help maintain a patent upper airway, e.g. with the neck hyperextended or prone with the bottom up in air. Thus the child presents with snoring, breathing pauses, choking or gasping arousal, restless sleep, nocturnal diaphoresis and enuresis at times.

Most children with OSA breathe normally while awake and have minimal day time symptoms. Daytime hypersomnolence results from sleep fragmentation that occurs when OSA is repeatedly terminated by arousals. So the child presents with morning headaches, excessive daytime sleepiness (EDS), dry mouth, chronic mouth breathing, poor appetite and failure to thrive. However, it is difficult to recognize EDS in young children who normally have daytime naps and early bedtimes. Most children do not present with daytime sleepiness and are more likely to be hyperactive or inattentive, often being diagnosed with Attention Deficit Hyperactivity Disorder.

Further, a child may have memory deficits and mood disturbances manifesting as poor school performance which is increasingly recognized as being associated with OSA. Lower academic performance has been described in young children as well as in adolescents who suffer from OSAS or from primary snoring. There is a debate as to whether the neurocognitive deficits are the results of poor night sleep secondary to frequent arousals (and hence inability to concentrate in school) or a result of spending every night in relative hypoxemia that could be predisposing the child to cerebral ischemia.

Signs (14-20):

The physical examination performed during wakefulness may be entirely normal and cannot be used to exclude OSAS when the clinical history suggests otherwise. Polycythemia and respiratory acidosis with metabolic alkalosis support the diagnosis of OSAS when present but are absent in majority of patients. Systemic hypertension may occur in advanced cases. In the past cor pulmonale with heart failure was a common mode of presentation for OSAS in children, but is rare now. Although overt heart failure occurs now less often, yet asymptomatic degrees of pulmonary hypertension may be common.

As stated by Dayyat et al Type I OSA is associated with hyperactive behaviour, enlarged tonsils/adenoids and recurrent ear infections contrary to Type II OSA which shows excessive sleepiness, truncal obesity, enlarged neck circumference, depression, low esteem, social withdrawal, left ventricular hypertrophy, systemic hypertension, insulin resistance, dyslipidemia and elevated C-reactive protein (2).

Diagnosis:

When snoring is associated with nocturnal breathing difficulties and witnessed respiratory pauses, this triad of symptoms is highly suggestive of OSA in children. An approach to a case of snoring is depicted in **Figure 1**

Total number of episodes of apneas and hypopneas averaged per hour of sleep is regarded as apnoea/hypopnoea index.

AHI < 5	: No OSA
AHI 5-15	: Mild OSA
AHI 15-30	: Moderate OSA
AHI > 30	: Severe OSA

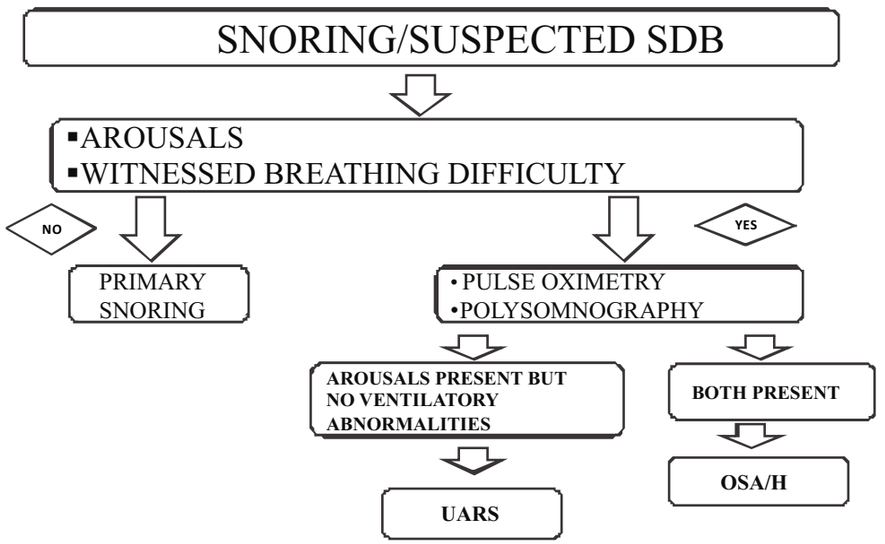

FIGURE 1. Diagnostic approach to a case of snoring

Polysomnography (PSG), an overnight recording of multiple physiologic sensors during sleep, is considered the gold standard for the diagnosis of OSA (20, 21). It is the only diagnostic technique shown to quantitate the ventilatory and sleep abnormalities associated with sleep disordered breathing. Variables that may be determined include:

1. EEG and EOG (for sleep state); EMG
2. Airflow at nose or mouth
3. End-tidal CO_2
4. Chest and abdominal motion (Impedance plethysmography)
5. ECG
6. Blood Pressure
7. Pulse oximetry
8. Esophageal Pressure (Intrapleural pressure)
9. Autonomic nervous system activity (Finger tonometer)

PSG can be performed satisfactorily in children of any age, provided that appropriate equipment and trained staff are available. Limitations of PSG are that it is a cumbersome, expensive, resource-intensive and inconvenient with limited accessibility and is an unreliable predictor of physical or psychological impairment in children with SDB.

As per International Classification of Sleep Disorders Edition 2 diagnostic criteria (1) for the childhood OSA is as follows:
Diagnosis = A + B + D or C + D

A. At least one of the following applies:
   i. Complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia.
   ii. Awakenings with breath-holding, gasping, or choking.
   iii. Bed partner reports loud snoring and/or breathing interruptions during the patient's sleep.

B. Polysomnography shows the following:
   i. Scoreable respiratory events (apneas+ hypopneas + respiratory effort–related arousal RERAs)/hr of sleep ≥5/hr.
   ii. Evidence of respiratory effort during all or a portion of each respiratory event (in the case of RERAs, respiratory effort is best detected by esophageal manometry).

C. Polysomnography shows the following:
   i. Scoreable respiratory events (apneas+ hypopneas + RERAs)/hr of sleep ≥15/hr.
   ii. Evidence of respiratory effort during all or a portion of each respiratory event.

D. The disorder is not better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder.

Overnight oximetry may be useful if it shows the pattern of cyclic desaturation. Brouillette et al performed oximetry in a group of children with suspected OSAS and compared it with simultaneous full polysomnography (patients with complex medical conditions were excluded) (22). Compared with polysomnography, they found that oximetry was useful when results were positive. However patients with negative oximetry required full PSG for definitive diagnosis. False positive results were found in patients with mild coexistent medical problems, such as obesity and asthma, suggesting that this technique is useful only in otherwise healthy children. Other investigations that need to be done are:

Lateral neck radiograph: To evaluate the size of the adenoids.

Complete blood count: To detect polycythemia suggestive of chronic hypoxemia.

ECG & ECHO: For evidence of Cor Pulmonale or Right Ventricular Hypertrophy.

Treatment :

Lifestyle modifications include positional therapy (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in supine position) and weight loss.

Previously, nonsurgical treatment, including the use of either intranasal or oral steroids, was used largely as a bridge to surgery. Medications are now are being considered as a viable, routinely used treatment option for those with mild SDB or snoring. However, pharmacologic management has only a limited role in paediatric OSAS patients. Treatment of nasal obstruction with topical nasal steroids can reduce snoring and OSAS severity in some children.

Steroids and antibiotics may be a useful adjunct in the acute management of infected pharyngeal tissues that have compromised upper airway patency. Nasal decongestants help in treatment of allergic rhinitis. Earlier beneficial effects of systemic corticosteroids on OSA were not proven but now a substantial decrease in the frequency of apnea and hypopnea events among children treated with fluticasone have been observed however no improvement in parents' symptom scores or reduction in tonsillar and adenoidal size is seen (23, 24).

Oral appliances: Continuous Positive Airway Pressure (CPAP) is useful as a treatment option. Though most common treatment in adults, medical management with nasal CPAP can be used in children also. It is indicated for patients with specific surgical contraindications, minimal adenotonsillar tissue, or persistent OSA after adenotonsillectomy or for those who prefer non-surgical alternatives. CPAP is delivered using an electronic device that delivers constant air pressure via nasal mask, leading to mechanical stunting of the airway and improved functional residual capacity in the lungs.

Among the surgical options available adenotonsillectomy is the most

common therapy for OSAS in children with adenotonsillar hypertrophy. When adenotonsillar hypertrophy is present, the majority of otherwise healthy children without major risk factors experience resolution or significant improvement after adenotonsillectomy. However, children with underlying problems, such as trisomy 21, craniofacial disorders, extreme obesity, or neuromuscular disorders, or who present before 2 yrs of age are at risk for incomplete resolution of OSAS even after adenotonsillectomy (25). Other surgical options used are as follows:

1. Uvulopalatopharyngoplasty
2. Tracheostomy
3. Mandibular distraction

Tracheostomy is treatment of choice if severe upper airway obstruction is present in both wakefulness & sleep (particularly when vocal cord dysfunction, impaired swallowing, or absent laryngeal protective reflexes exists). It may be necessary for severe OSA complicated by cor pulmonale when CPAP is unsuccessful or not tolerated. Alternative is mandibular distraction osteogenesis/maxillomandibular reconstruction surgery. The management approach to a case of sleep disorder breathing is depicted in **Figure 2**.

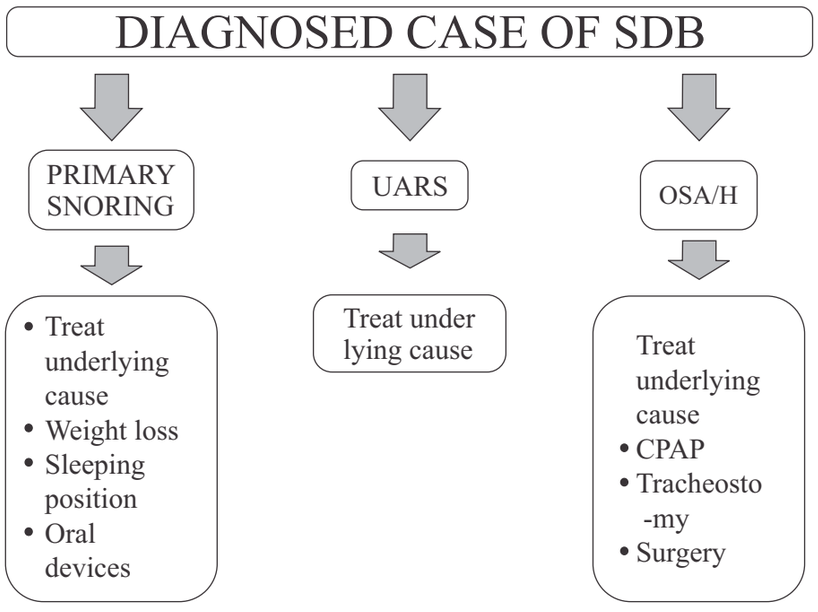

FIGURE 2. Management of case of Sleep Disorder Breathing

Conclusion:

Childhood OSA is on the rising trend in our country. Significant association is now being observed with obesity. Adenotonsillar hypertrophy remains the most important cause of this problem. It is vital to take a good history and conduct a thorough clinical examination of such children. Although polysomnography is the gold standard for making a definitive diagnosis yet in those centres where this facility is lacking, clinical evidence supported by basic investigations helps in making a diagnosis. Medical treatment should always be attempted before resorting to surgical treatment.

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Co-morbidities associated with obstructive sleep apnea

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ABSTRACT

There are many co-morbid conditions that are associated with obstructive sleep apnea (OSA). Though a causative relationship between OSA and some of the co-morbidities is well established or strongly associated, many risk factors of OSA (age, male gender and obesity) are also known risk factors especially for cardiovascular diseases. Other important co-morbid conditions associated with OSA are neurocognitive dysfunction and, erectile dysfunction. Recently there are reports that ocular manifestations are associated with OSA. It is expected that more co-morbidities will be reported in OSA as the research in this area progresses.

Key words: Co-morbidities in OSA, Hypertension, Cardiac arrhythmias, Stoke, Erectile dysfunction

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INTRODUCTION

OSA is the repetitive interruption of ventilation during sleep as a result of collapse of the pharyngeal airway. The most important co-morbidities associated with OSA are cardiovascular and cerebrovascular diseases, and neurocognitive dysfunction. The main cardiovascular morbidities reported in OSA are systemic hypertension, pulmonary hypertension, cardiac arrhythmias, cardiovascular mortality, heart failure and stroke. Motor vehicle accidents are also important consequences in OSA (1).

OSA and cardiovascular diseases :

OSA has been shown to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebral vascular disease, congestive heart failure and arrhythmias (1, 2). However, a causal relationship remains controversial. Many risk factor of OSA (age, male gender and obesity) are also known risk factors for cardiovascular disease. OSA is also associated with conditions (diabetic mellitus and hypertension) that are known to increase the risk for cardiovascular disease. Therefore, it is difficult to prove whether OSA independently causes cardiovascular disease or not in these conditions.

a) Systemic hypertension :

In normal individuals, sleep is associated with a reduced blood pressure compared to wakefulness and this is known as "Dipping" phenomenon. In normal individuals, systolic and diastolic blood pressure may decline as much as 10-15%. Sleep apnea has been found to blunt the dipping of blood pressure during sleep. Disordered breathing during sleep has also been found to be associated with acute peripheral vasoconstriction and rise in blood pressure during sleep (3). Several studies have shown that OSA increases the relative risk of hypertension independent of other confounding factors. Sleep Heart Health Study (SHHS) in a cross sectional analysis of > 6000 patients has shown a linear relationship between systolic and diastolic blood pressure and OSA severity (4). A Canadian population based study involving 2677 adults aged 20-85 years, had shown that each apneic event per hour increased the odds of hypertension by 1% and each 10% reduction in nocturnal O_2 saturation increased the likelihood of hypertension developing by 13% (5). As the above studies were cross sectional in nature linking sleep-disordered breathing to chronically elevated blood pressure, a prospective, population-based study was conducted to know the association between objectively measured sleep-disordered breathing and hypertension (6). This Wisconsin sleep cohort study in 709 participants had demonstrated a dose-response association between sleep disordered breathing at baseline and the presence of hypertension four years later. This was independent of known compounding factors. Peppard et al found a dose-response association between sleep-disordered breathing at base line and the presence of hypertension four years later that was independent of known confounding factors (6). This study suggested that sleep disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population (6). In another prospective study of 2470 participants of SHHS aged > 40 years without baseline hypertension and not on antihypertensive medication, it has been shown that there is a significant relationship between the risk of developing hypertension and OSA. However, this association was lost after adjustment for BMI. A moderate influence of an AHI > 30 on hypertension could not be excluded in this study (7). Continuous positive airway pressure (CPAP) has been shown to acutely attenuate sympathetic drive and nocturnal BP in OSA (8). Observational studies from uncontrolled and highly selected populations have suggested improvement in BP control with CPAP (9). A meta-analysis of 12 placebo-controlled randomized trails (n = 572) found a statistically pooled reduction in mean BP of 1.69 mm Hg with CPAP treatment (10). Most of these trials were limited to normotensive individuals. The seventh report of the Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-VII) has listed sleep apnea as a significant cause of secondary hypertension (11).

b) Pulmonary hypertension :

Pulmonary hypertension is defined as a mean pulmonary arterial pressure>25 mm Hg at rest or >30 mm Hg with exercise as measured by right heart catheterization. It has been demonstrated that hypoxic vasoconstriction over time may result in pulmonary vascular remodeling, contributing to the development of pulmonary hypertension, as seen in patients with chronic lung diseases. It may therefore be possible that repetitive upper airway collapse and oxyhemoglobin desaturation characteristic of OSA could also provide a pathophysiologic basis for elevations in pulmonary arterial pressure (12). Data from case series mainly in male patients have suggested that the prevalence of pulmonary hypertension in OSA varies from 17 to 53%. However, there are no population based data to know the prevalence of pulmonary hypertension in OSA. In a study of patients with OSA with no clinically significant cardiac and pulmonary disease, 41% had pulmonary hypertension. There was no difference in AHI, BMI, smoking history and lung function between patients with pulmonary hypertension and those without pulmonary hypertension (13). A placebo-controlled randomized cross-over trial of CPAP and sham CPAP over 12 weeks has been reported in 23 patients with OSA and CPAP therapy reduced pulmonary arterial systemic pressure in all patients with pulmonary hypertension at baseline (14). The revised "Clinical Classification of Pulmonary Hypertension" has identified sleep-disordered breathing as part of the category of respiratory disorders associated with pulmonary hypertension (15).

c) Cardiac arrhythmias and cardiovascular mortality :

The prevalence of cardiac arrhythmias in two samples of participants from the Sleep Heart Health study showed that compared with subjects with Respiratory Disturbance Index (RDI) < 5, those with severe OSA (RDI > 30) had higher rates of atrial fibrillation, non-sustained ventricular tachycardia, complex ventricular ectopy (bigeminy, trigeminy and quandrigeminy). Compared with those without sleep-disordered breathing and adjusting for age, sex, body mass index, and prevalent coronary heart disease, individuals with sleep-disordered breathing had four times the odds of atrial fibrillation (odds ratio [OR], 4.02), three times the odds of nonsustained ventricular tachycardia (OR, 3.40), and almost twice the odds of complex ventricular ectopy (OR, 1.74) (16). Bradyarrhythmias are also reported in OSA and can occur with a structurally normal heart. Effective CPAP therapy has been shown to attenuate bradyarrhythmias (17). People with sudden death from cardiac causes from midnight to 6 a.m. had a significantly higher apnea-hypopnea index than those with sudden death from cardiac causes during other intervals. The relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 for people with obstructive sleep apnea. In contrast, the risk of sudden death from cardiac causes in the general population peaks from 6 a.m. to noon and has a nadir from midnight to 6 a.m. (18). However, a causative role for sleep apnea in serious arrhythmias or sudden death has not been proven (16, 19). In an observational study to compare incidence of fatal and non-fatal cardiovascular events in simple snorers, patients with untreated obstructive sleep apnoea-hypopnoea, patients treated with CPAP, and healthy men, it has been shown that severe obstructive sleep apnoea-hypopnoea significantly increases the risk of fatal and non-fatal cardiovascular events in men and CPAP treatment reduces this risk (20). In an observational study, it has been reported severe OSA is associated with cardiovascular death in Women as well, and adequate CPAP treatment may reduce this risk (21).

d) OSA and heart failure :

There is a close link between OSA and heart failure by their close association with aging and obesity. The Framingham study had shown that increasing BMI is directly correlated with incident heart failure and may be mediated in part by OSA. Incident atrial fibrillation, an important risk factor for heart failure is also associated with the degree of oxyhemoglobin desaturation in OSA (22-24). Repetitive upper airway closure in OSA can have deleterious effects on cardiac function. In a study of subjects randomly assigned to receive medical therapy either alone or with the addition of continuous positive airway pressure for one month, it has been shown that treatment of coexisting obstructive sleep apnea by continuous positive airway pressure reduces systolic blood pressure and improves left ventricular systolic

function in medically treated patients with heart failure (25). In another randomized study of patients with congestive heart failure and OSA receiving 3 months of CPAP, it has been shown that there is significant improvements in left ventricular ejection fraction (LVEF) and reductions in urinary catecholamines, but no changes in BP (26). However in another rigorous, placebo-controlled cross-over study sing auto-titrating CPAP, Authors found no improvement in any parameter of cardio-vascular function, including left ventricular ejection fraction, blood pressure and exercise tolerance (27). Further trials are required to know the exact role of CPAP in patients with heart failure and OSA. High sensitivity troponin T (hs-TnT) levels have been shown to be predictor of coronary artery disease and heart failure (28). In a study of 1645 participants from Atherosclerosis Risk in Community (ARIC) and Sleep Heart Health Study (SHHS), it has been observed that there is an association between severity of OSA and high levels of hs-TnT suggesting that subclinical myocardial injury caused by OSA may play a role in subsequent risk of heart failure (28).

e) OSA and incident stroke :

The incidence of stroke was studied in a geographically diverse, community based sample of male and female participants in SHHS. Based on 8 years of prospective data from the study, it has been observed that modest to severe levels of sleep apnea are associated with an approximately three-fold increased risk of ischemic stroke in men (29). A prospective study had shown that self-reported snoring was an independent risk factor for stroke in women (30). Data from the Wisconsin Sleep Cohort had demonstrated that moderate to severe sleep-disordered breathing is a risk factor for prevalent stroke and that the preexisting sleep disorder may be a risk factor for incident stroke (31). Longitudinal data with a mean follow-up of 3.4 yr on mortality from stroke and other causes in patients with preexisting OSA, it has been shown that there is an increasing risk of events with OSA severity (32). It is feasible that stroke may itself predispose to sleep-disordered breathing. The strong association with atrial fibrillation may confer a heightened risk of embolic events. OSA has been shown to promote thrombosis and doppler measurements have suggested that apneic events are associated with reduced cerebral blood flow (33).

f) Erectile dysfunction :

A high prevalence of erectile dysfunction in OSA patients has been reported (34). It has been suggested that the nocturnal oxygen saturation observed in OSA may be an important factor contributing for the occurrence of OSA (34). Treatment with nasal CPAP has been found to resolve erectile dysfunction resulting in improvement in quality of life (35).

g) Aortic aneurysm :

Abdominal aortic aneurysm has

been found to be highly prevalent in OSA and it has been reported that there was further expansion of abdominal aortic aneurysm in patients with severe OSA (36).

Ocular manifestations :

Recently reported ocular manifestations in OSA are floppy eyelid syndrome (FES), glaucoma, papilledema, non-arteritic anterior ischemic optic neuropathy and retinal vein occlusion (37). Papillary conjunctivitis and a rubbery, redundant upper eyelid tissue is the characteristic features of FES and frequently manifests unilaterally affecting the eyelid on the side the patient most often sleeps on. Although the specific etiology of this association is not well described, one proposed mechanism suggests. It has been suggested that damage to the optic nerve head caused by apnea-induced ischemic events may be responsible for glaucoma in OSA patients, as it has been reported that glaucoma severity correlates with both the frequency and duration of apnoeic episodes. There is forced inspiration against a closed airway in OSA and this can lead to an increase in venous pressures and impaired venous return with subsequent increase in intracranial pressure resulting in papilledema. Papilledema can also result from hypercapnea which has been reported to occur in OSA. Though the mechanism of nonarteritic ischemic optic neuropathy is not well understood, it is possible that intermittent apnea-induced increases in blood pressure and intracranial pressure and nocturnal hypoxemia may result in optic nerve edema leading to optic neuropathy. Retinal vein occlusion in patients with OSA may be to the consequences of impaired venous return of the retina and atherosclerotic defects of the feeding arterioles.

Other medical consequences :

Other medical consequences of OSA include excessive daytime sleepiness, loss of alertness, memory deficit, reduced vigilance, impaired executive function, increased risk for automobile and occupational accidents and decreased quality of life (38).

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Endocrine and Metabolic Aspects of OSA

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ABSTRACT

Obstructive sleep apnea (OSA) is characterized by repeated spells of apnea. Collapsibility of hypopharynx due to multiple factors involving pharyngeal dilator muscles and deposition of fat or fluid in the surrounding soft tissues are important contributing factors in its pathogenesis. OSA commonly affects obese individuals. Males are more commonly affected than the females probably due to the disturbing effect of testosterone on sleep.

The impact of OSA on human health include disturbances in endocrine and metabolic system affecting hypothalamic-pituitary-gonadal axis, adrenocorticotrophic-cortisol axis, growth hormone, antidiuretic hormones and insulin resistance. There is a tendency for predisposition of the metabolic syndrome or its components including glycemic dysregulation, hypertension, hyperlipidemia and physical parameters related to adiposity. On the other hand, several endocrine disorders such as hypothyroidism, growth hormone excess, polycystic ovarian disease and testosterone replacement are associated with increased prevalence of OSA.

There is limited information on the effect of treatment of OSA by continuous positive airway pressure (CPAP) on the endocrine and metabolic disturbances. There is a need to conduct randomized controlled trials using CPAP therapy in patients with OSA and to study its cause and effect relationship with endocrine and metabolic disturbances**.**

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OVERVIEW

Deposition of fat and fluid in the soft tissues of the airways are important contributing factors in the pathogenesis of OSA (1,2). As expected, OSA is more common in obese individuals but can also be seen in non-obese subjects and children (3,4). Males are more commonly affected than the females probably due to disturbing effect of testosterone on sleep. With advancing age the protective effect of estrogen is lost leading to increased prevalence of OSA in postmenopausal women. OSA has been associated with increased incidences of diseases related to endocrine, nutritional and metabolic, nervous conditions, respiratory, skin and musculoskeletal system.

The problem of OSA and associated syndrome is also common in Indians with prevalence rate similar to that reported in the western population (5). Recently, Sharma and Ahluwalia summarized salient studies from India (5). The prevalence of OSA in North Indians and Western Indians was 9.3% and 19.5% respectively (5,6). The prevalence rates of OSA syndrome in these cohorts were 2.8% and 7.5% respectively. The trend of higher prevalence in males than females was also observed in the Indian subjects. However, these studies cannot be taken as representative of the whole Indians in view of the wide variation in the socioeconomic differences and prevalence of obesity in Indians from different geographic regions.

The purpose of the present review is to provide an overview of the endocrine manifestations covered in the Annual meeting of the National Academy of Medical Sciences held at AIIMS, Jodhpur in 2013. The endocrine implications of OSA have been covered recently in two excellent reviews by Attal and Chanson (1) and Kamenov *et al.* (2). The present review is based on relevant information on OSA summarized in these reviews and other published data. The search period was focused for studies available during 2008 to 2013. Broadly, the information can be categorized as (A) effect of OSA on endocrine disturbances (B) effect of endocrine disorders on OSA and (C) disorders where the cause and effect relationship is not clear i.e. obesity, diabetes, insulin resistance and polycystic ovarian disease (PCOD).

(A) Effect of OSA on endocrine disturbances

Effect of OSA on hypothalamic-pituitary-gonadal axis :

There is sexual dimorphism in the prevalence of OSA. This indicates the role of testosterone in sleep disturbance and protective effect of estradiol in females. Despite sexual dimorphism in the prevalence of OSA, alteration in sex hormone is a common feature in male and female patients with OSA. The low serum total testosterone level observed in OSA could be an effect of hypoxia on hypothalamic-pituitary-gonadal axis. Alternatively, it could be a confounding effect of obesity commonly associated with the OSA syndrome and related

alteration in sex hormone binding globulin (SHBG). There is insufficient data on sex hormone status (serum total and free testosterone) along with SHBG in subjects with OSA. Similarly, the effect of testosterone replacement and treatment with continuous positive airway pressure (CPAP) either alone or in combination has not been extensively studied using well-designed placebo controlled randomized control trials (RCT). Recently, Hoyos *et al.,* reported a RCT on the effect of 1000 mg of testosterone undecanoate given for 18 weeks in a group of 67 males. Testosterone supplemented group had worsening of O_2 desaturation index at 7th week. The study concluded worsening of sleep disorder breathing in time dependent manner with testosterone in obese males with severe OSA (7). Meston *et al.,* reported a RCT on the effect of nasal CPAP therapy in 101 male subjects with OSA. Testosterone and SHBG showed a negative correlation with the OSA severity at baseline. Active intervention group had a significant elevation of SHBG and reversible change in serum testosterone (8).

Changes in serum prolactin levels have also been documented in patients with OSA (9). The high serum prolactin level led to a negative effect on hypothalamic-pituitary-gonadal axis in them. Recently, Macrea *et al.,* reported the effect of CPAP therapy after 11 to 39 months on serum prolactin, estradiol, FSH, LH, testosterone, glucose, cortisol and leptin (9). The CPAP therapy led to significant fall in serum prolactin levels with no change in other hormones. The higher serum prolactin values observed seems to be a consequence of OSA and not a cause of OSA as patients with prolactinoma do not have increased prevalence of OSA syndrome (10). Thus, hypothalamic-pituitary gonadal axis is impaired in patients with OSA, but the causal role of obesity, SHBG and prolactin needs further evaluation. The effect of such disturbances on quality of life, infertility and sexual dysfunction is an important area requiring further studies.

Effect of OSA on hypothalamic pituitary-adrenal and thyroid Axis:

Henley *et al.,* assessed ultradian patterns of serum ACTH and cortisol using repetitive blood sampling in 10 patients with moderate to severe OSA at baseline and at 3 months after CPAP therapy (11). The mean total ACTH and cortisol production were significantly increased at baseline and the levels of both the hormones decreased after CPAP therapy. Pre-CPAP therapy, the subjects had significantly elevated cortisol response to a single breath of 35% CO_2. Lanfranco *et al.,* observed increased ACTH response to CRH in patients with OSA, which was not explained by obesity (12). However, unlike the study by Henley *et al.,* this study could not find any significant difference in the serum cortisol and ACTH levels in obese subjects with or without OSA. The increased serum cortisol level observed in OSA has also been implicated in the pathogenesis of metabolic syndrome associated with OSA. However, the variable data obtained for the ACTH-cortisol axis in various studies, as exemplified in the above two studies, indicates a need for further studies on this aspect. The thyroid axis has been found to be normal in most patients with OSA except for the pattern of sick euthyroid syndrome in severe OSA (2).

Effect of OSA on fluid and electrolyte disturbances :

The increased effort of breathing in OSA creates a situation of excessive negative intra-thoracic pressure. This is analogous to increased volume load to the heart resulting in increased secretion of atrial natriuretic peptide from the heart. This peptide has inhibitory effect on the arginine vasopressin and renin angiotensin aldosterone system, which can result in increased glomerular filtration. Thus, OSA favours suppression of vasopressin which could be the possible reason for the increased nocturia observed in some of the patients with OSA (2,13,14). Patients with OSA are also prone to resistant hypertension. Recently, Pimenta *et al.,* evaluated 97 patients with resistant hypertension by overnight polysomnography and assessed 24-h urinary sodium and aldosterone excretion (15). 28.9% of the patients had hyperaldosteronism and 77.3% had OSA. Urinary sodium level was found to be an independent predictor of severity of OSA only in patients with hyperaldosteronism. The authors suggested restriction of dietary salt as a treatment strategy for management of OSA in resistant hypertension.

(B) Effect of endocrine disorders on OSA

Growth hormone excess and OSA :

Acromegaly is associated with a remarkably high prevalence of OSA. Recently Roemmler *et al.,* assessed the prevalence of sleep apnea by polysomnography in 52 patients with acromegaly (16). Twenty three of them had controlled disease activity with GH levels <1 µg/l and normal IGF-1 levels and 12 had active acromegaly despite use of somatostatin analogues. The prevalence of OSA was 66% in patients with active disease and 48% in the cured group. Patients with acromegaly and OSA had higher mean HbA1c and higher prevalence of hypertension than those without OSA. Though the OSA correlated with BMI, age and disease activity, it showed no significant correlation with duration of the disease and serum growth hormone. Interestingly, five subjects had evidence of central sleep apnea either in isolated form or mixed with OSA. Thus, patients with and without active acromegaly are prone to OSA as well as central sleep apnea. The facial skeletal defects associated with acromegaly such as prognathism, widened angle of the jaw due to mandible position, thickened soft tissues of the nasopharynx including soft palate and uvula, with fluid retention due to salt retaining effect of growth hormone are major factors responsible for increased prevalence of OSAS in the acromegaly. Besides, excess body weight and central hypothyroidism associated with pituitary mass lesion, hyperprolactinemia leading

to hypogonadism and changes in the neuromuscular structure of the pharyngeal muscle also possibly contribute in increased prevalence of OSA in acromegaly. Irreversibility of several of these changes especially skeletal structure might explain the persistence of the OSA syndrome after successful medical or surgical therapy (2).

Paradoxically, adult patients with isolated growth hormone deficiency as exemplified by patients with panhypopituitarism who were adequately replaced with all hormones except growth hormone also demonstrate increased prevalence of OSA. Replacement with growth hormone resulted in improvement in OSA in some of these patients but also had a worsening effect in others (2, 17).

Hypothyroidism and OSA :

Increased sleepiness and weight gain are features common to both OSA and hypothyroidism. The prevalence of OSA has been found to be 25-35% in patients with hypothyroidism (2,18). Kapoor *et al.,* studied 336 consecutive adult patients undergoing polysomnography for suspected OSA and similar age and sex matched controls (18). The prevalence of hypothyroidism was only 1.4% in OSA. Moreover, all the subjects had only subclinical hypothyroidism indicating lack of case for routine screening for hypothyroidism in patients with OSA. Narrowing of the pharynx due to infiltration of the soft tissue by mucopolysaccharides might alter the control of the respiration (2). Presence of large goitre and macroglossia are the possible contributory factors for the pathogenesis of OSA in hypothyroidism (19). Medical replacement therapy with L-thyroxin or surgery can reverse features of OSA syndrome specially when there is no obesity. Reiher *et al* has recently shown the important role of goitre in the pathogenesis of OSA (19) 71% of patients had Berlin questionnaire suggestive of OSA before thyroidectomy, which was decreased to 51% after surgery.

Obesity, metabolic syndrome and OSA:

Prevalence of obesity is high in patients with OSA. Peppard *et al.,* showed that a 10% weight gain would result in 32% increase in AHI (20). Similar relationship between obesity and OSA is observed in childhood obesity also (21). Moraleda-Cibrián and O'Brien investigated the association between short sleep duration, obesity and OSA in 306 children undergoing polysomnography and observed prevalence of obesity, short sleep duration and OSA as high as 32 %, 39.5 % and 78 % respectively (21). Children with OSA had a similar frequency of short sleep duration than those with no OSA. However, in children with short sleep duration, the odds ratio for obesity was 2.5 (95 % CI 1.3-4.9) compared to children with normal sleep duration even after accounting for the presence of OSA. The authors concluded that reduction in total sleep duration by 1 h was associated with a higher risk for obesity in children. Various aspects of obesity which could determine the

presence of OSA include (a) degree of fat deposition around upper airways and lateral wall of nasopharynx as reflected by neck circumference (b) reduced pulmonary volume consequent to abdominal obesity and increased respiratory effort leading to decrease pulmonary traction of the upper airways and (c) impairment of the dilator muscle (2). Use of different criteria to define obesity such as BMI, waist or neck circumference and visceral fat in various studies could explain the variable prevalence of metabolic syndrome in OSA (2,3). Reduction of obesity by bariatric surgery can reverse or improve OSA (22). Greenberg *et al.,* reported up to 75% reduction in prevalence of OSA after bariatric surgery. However, there is a tendency of relapse for OSA after surgery. This could be related to that fact that despite successful surgery, some of the patients continue to have significant fat deposition in the neck tissues (2, 22).

Patient with OSA have high prevalence of metabolic syndrome with incidence as high as 60% (2,3). The prevalence of various components of metabolic syndrome such as dyslipidemia (hyper cholesterolemia in males and decreased HDL/increased triglycerides in females) waist to hip ratio, hypertension, insulin resistance and impaired fasting glucose have been found to be high in OSA. However, the independent link of metabolic syndrome with OSA after adjusting for obesity is not clear. Kamenov *et al.,* reviewed various studies on the prevalence of metabolic syndrome in patient with OSA (2). Several observational studies indicated association of OSA with metabolic syndrome or its individual components. Coughlin *et al.,* carried out an RCT on the effect of CPAP on metabolic syndrome in 34 subjects with OSA (23). Though arterial pressure decreased after 6 weeks of CPAP, there was no change in the insulin resistance or lipid profile (23). Hoyos *et al.,* recently studied 65 CPAP naïve adult men without diabetes who had moderate to severe OSA (24). Subjects were randomized to receive either real or sham CPAP for 12 weeks. Though the AHI was lower on CPAP after 12 weeks, there were no between-group differences after 12 weeks in the visceral fat, insulin sensitivity index and liver fat. The authors concluded that CPAP therapy in men with OSA would not lead to significant reduction of visceral adiposity (24).

The pathogenesis of metabolic syndrome in OSA is not clear but could be related to pro-inflammatory cytokines and hormones produced from visceral fats including leptin, omentin, IL-6 and TNF-alpha. Kurt *et al*., studied 46 patients with newly diagnosed OSA patients and 35 normal subjects (25) and observed elevated circulating omentin in OSA. Both obesity and OSA can independently result in hyperleptinemia. Successful treatment of OSA by CPAP is predicted to decrease hyperleptinemia. Recently, Zirlik *et al.,* studied 10 patients with newly diagnosed OSAS and healthy volunteers. Patients had significantly higher plasma omentin-1 than healthy volunteers which decreased towards the values observed in the controls after three

months of CPAP therapy (26).

The plasma melatonin peaked at 2.00 a.m. in the healthy volunteers but at 6.00 a.m. in patients with OSA. The abnormality in melatonin returned to normal after CPAP therapy. Whether these abnormalities associate with OSA independent of insulin resistance is not clear. Thus, there is a need to generate further data based on placebo controlled randomized trial with CPAP.

Diabetes and OSA :

Cross sectional and experimental studies suggest a link between OSA and increased prevalence of diabetes. However, the issue related to false association between OSA and DM exists in view of co-linear association between obesity and DM. Moreover, the methods used to rule out diabetes or to adjust obesity vary in different studies (2,3). These factors therefore do not allow firm association of diabetes with OSA. Tassone *et al.,* studied insulin dynamics and glucose metabolism in 30 obese patients with OSAS and matched controls (27). The composite insulin sensitivity index values were significantly lower in OSAS than in the obese and normal subjects. The authors concluded that obese patients with OSA syndrome had higher insulin resistance than patients with simple obesity, independent of the degree and distribution of adiposity. Recently, Bozkurt *et al.,* assessed 190 non-diabetic subjects grouped as controls, mild OSA, moderate OSA and severe OSA after polysomongraphy (28). Subjects with more severe OSA tended to have lower vitamin D levels which also correlated with increased prevalence of insulin resistance, pre-diabetes and diabetes status (28). Thus, vitamin D deficiency might also play a role in the OSA associated glycemic dysregulation.

West *et al.,* carried out a RCT in patients with OSA and DM and observed no significant effect on the HbA1c values (29). The pathogenesis of diabetes in OSA is similar to that of Type 2 DM with predominant effect on insulin sensitivity. Though data on insulin sensitivity in human is limited, there is strong support from animal studies on the pathogenetic mechanism of diabetes in OSA (30,31). Restriction of sleep in animal resulted in increased prevalence of glucose intolerance, hypertension and impaired pancreatic beta cell regenerative capacity especially in animal with hyperglycemia. Yokoe *et al.,* developed a chronically catheterized, unhandled, lean adult male C57BL/J model to examine the effects of intermittent hypoxic exposure and exogenous glucose infusion on the diurnal pattern of blood glucose, and pancreatic beta-cell growth and function (31). Intermittent hypoxia impaired glucose homeostasis only during periods of hypoxic exposure. Presence of hyperglycemia increased the hypoxic susceptibility of beta-cells. The pathogenesis of increased prevalence of diabetes in OSA in human could also be related to increased serum cortisol, oxidative stress and its effect on lipid peroxidation, up-regulation of nuclear factor-kB (2,3).

Polycystic ovarian syndrome and OSA:

There has been increasing awareness about the association of PCOD with OSA (2,32,33). The prevalence of OSAS is increased by 10 fold in these patients (2). Vgontzas *et al.,* observed 30 times higher risk of OSA among patients with PCOD compared to age matched controls (33) which was also associated with higher degree of insulin resistance, waist hip-ratio and glucose intolerance. The increased association between the two disorders is not clear but could represent a common pathogenesis such as insulin resistance or could be due to increase in serum testosterone in patients with PCOD and its destabilizing effect on sleep.

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Quality of Life in Obstructive Sleep Apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with significant cardiovascular and cerebrovascular morbidity and mortality. Usual parameters studied in sleep laboratory are unable to measure overall impact of OSA on human life. Consequently, it is important to measure Quality of Life (QoL) in OSA. QoL can be measured with generic instruments like SF-36 or OSA specific questionnaires like Calgary Sleep Apnea Quality of Life (SAQLI) questionnaire. Most of the studies suggest that there is significant impairment of QoL in patients of OSA. But the present evidence suggests that impairment in QoL is not proportional to severity of OSA. There is no consensus on the question of improvement in QoL with Continuous Positive Airway Pressure (CPAP) therapy. A recent Cochrane review concluded that CPAP improves QoL in people with moderate and severe OSA.

Key words : Obstructive sleep apnea, Quality of Life, Continuous Positive Airway Pressure

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Sleep apnea is defined as repetitive episodes of decreased or total cessation of respiratory airflow during sleep, leading on to desaturation and sleep fragmentation. There are two types of sleep apnea - OSA and Central Sleep Apnea. In OSA the cessation of respiration during sleep is caused by upper respiratory obstruction and the apnea is followed by strenuous breathing effort.

The site of occlusion varies, and it can occur at several levels or at various sites during different stages of sleep. Any disorder that produces or contributes to upper airway narrowing is a risk factor for OSA, including obesity, enlarged tonsils, anatomical malformations of the jaw/pharynx and pharyngeal muscle weakness caused by neuromuscular disorders. When the OSA is accompanied by daytime sleepiness, it is referred to as the OSA syndrome(OSAS)(1).

In a population based study of employed adults between 30 and 60 years of age in the western world, the prevalence of OSA (which was defined as at least five apneas and hypopneas per hour of sleep accompanied by excessive daytime sleepiness) was 4% for males and 2% for females (2). Indian prevalence studies estimated disease prevalence rates of 3.5-13.7% (4.4-19.5% in males and 2.5-7.4% in females) (3,4,5,6). Prevalence of OSAS in India is 1.7-3.6% (2.4-7.5% in males and 1-2.1% in females). Although the number of OSA prevalence studies in India is not sufficient and there is major difference in the prevalence among different studies but all the studies indicate that it is an important public health concern in India also.

Research on sleep-disordered breathing, including sleep apnea syndromes, has grown tremendously in recent years. Many studies have indicated an association between sleep apnea and cardiovascular / cerebrovascular related morbidity and mortality (7,8). Sleep apnea has also been linked to an increased risk of road accidents and changes in personality. These symptoms have been attributed to nocturnal oxyhaemoglobin desaturation and to the chronic sleep deprivation caused by sleep fragmentation. Even patients with comparatively mild OSA with Apnea-Hypopnea Index (AHI) < 20 report impairment in social functioning, and limitations in function because of physical and emotional factors, as well as a lowered sense of well being for mental health and energy than in normal subjects(9).

With successful treatment, quality of life may improve with nasal continuous positive airway pressure (nasal CPAP). However, so far, disease severity prior to nasal CPAP treatment does not clearly relate to post-treatment improvements in health related QoL (10). Conventionally, the impact of the disease in OSA cases is often measured in term of physiological response on control sleep recordings and severity of symptoms. But these symptomatic measures and the physiological scales e.g. AHI have failed to measure adequately the rather broader impact of the disorder on human life. As symptoms are usually a subset of overall

QoL of patient, it is important to measure overall impact of the disease on life per se. Several researchers have highlighted the importance of measuring QoL in OSA patients(11).

Measuring Quality of life in OSA :

Health Related Quality of Life (HRQoL) is a concept developed on the lines of the WHO definition of health (including physical, emotional, social and spiritual well being) by including both personal health status and social well being when assessing health. HRQoL is evaluated subjectively; that means it is assessed by the person himself and it is evaluated with the help of Questionnaires. These Questionnaires have multiple domains representing different aspects of life. There are two types of Questionnaires which can be used to measure QoL in patients of OSA. (Table 1)

1) Generic Questionnaires – These Questionnaires can be used to measure QoL in all kind of clinical conditions.
2) OSA Specific Questionnaires – These Questionnaire can be used to determine QoL in OSA patients only.

Which type of Questionnaire should be used for measuring QoL :

Generic and the OSA specific Questionnaires have different advantages and disadvantages. The structure of Generic questionnaires is more comprehensive. They can allow comparison between studies, populations, or diseases but they may have some domains which are not related to OSA. Thus they may be less sensitive as compared to the disease specific Questionnaires (12). In case a person is suffering from more than one disease, Generic Questionnaires are more appropriate.

Table 1- List of Generic and OSA specific QoL Questionnaires

Generic Questionnaires	OSA Specific Questionnaires
MOS(Medical Outcome Survey)	**Calgary SAQLI (Sleep Apnea Quality of Life Questionnaire)**
SF-36(Short Form-36)	**FOSQ (Functional Outcome of Sleepiness Questionnaire)**
NHP (Nottingham Health Profile)	**QSQ (Quebec Sleep Questionnaire)**
EuroQoL	**OSAPOSI (OSA Patient Oriented Severity Index)**
SIP (Sickness Impact Profile)	
MLDL(Munich Life Quality Dimension List)	

Disease specific questionnaires are more sensitive to detect subtle changes in QoL in patients having that disease. These questionnaires have Questions related to the disease so these tend to have higher acceptability and completion rates. But disease specific Questionnaires don't allow inter disease comparisons.

Thus, the choice of Questionnaire should be based on research question. If the researcher wants to compare QoL among two conditions then obviously only generic questionnaires can be used. Otherwise the recent trend is towards use of OSA specific questionnaires because of their better acceptability and completion rates.

Discussion :

The symptoms of OSA have been recognized for many years. Interestingly, the first observation of disease was not made by a physician but a famous writer. Charles Dickens described an obese, hypersomnolent boy in his novel “The Posthumous Papers of the Pickwick Club" where he wrote "... and on the box sat a fat and red faced boy, in a state of somnolency" or "Joe damn that boy, he's gone to sleep again" is a classic portrayal of an OSA patient (13). William Osler, who was a famous physician of early 20th Century also observed the association of obesity and hypersomnolence when he described the obesity-hypoventilation syndrome or Pickwickian syndrome in 1918(14). Despite the description of these observations and associations, it was only in 1973 that Guilleminault described the disease as obstructive sleep apnea syndrome (15). Subsequently several reports appeared regarding pathophysiology, diagnosis and treatment of OSA. Although OSA is relatively recent disease as far as the discovery is concerned, it is a disease with high prevalence and carries significant morbidity associated with it.

Like any other chronic medical conditions OSA also impair normal human life extent of which can be measured quantitatively in form of HRQoL index. Various scales such as the Nottingham Health Profile and SF 36 have been used in patients with OSA to evaluate the QoL. Measurement of QoL has become an important part of management of patients with OSA.

Although WHO recognised as early as in 1947 that health encompassed physical, mental and social well being, the use of QoL measurement started mostly in 1980s (16). QoL measurement was even more appropriate in case of OSA as AHI, the index of OSA severity, was inadequate in measuring the overall impact of OSA on human life. The First study of QoL in OSA was published by Gall et al which used SF-36 questionnaire to measure QoL (9). The study recruited 42 males and the researchers observed that QoL was significantly impaired in OSA patients. Interestingly in some severe OSA patients there was little impairment of QoL. After that there have been many studies exploring QoL in patients of OSA which has been summarised in table-2. The initial studies used only generic instruments to measure HRQoL in these patients. In 1998 Flemons et al in their instrument validation study used Calgary SAQLI, an OSA specific

Questionnaire to measure QoL in OSA patients (17). After this other OSA specific Questionnaires like Functional Outcome of Sleepiness Questionnaire (FOSQ), OSA Patient Oriented Severity Index (OSAPOSI) and Quebec Sleep Questionnaire (QSQ) have also been used. Among the Generic Questionnaires SF-36 has been used most. Jenkinson et al. used SF-36 to assess QoL and observed that there is significant deterioration of QoL in patients of OSA and it improved with CPAP treatment. The generic instruments studies have shown significant variability in QoL assessment even among same patients (18). Jenkinson et al used SF-36, ***respiratory disturbance index*** (RDI) and EuroQoL among same group of OSA patients and observed that while SF-36 and PGI showed significant life impairment in OSA, in contrast to the EuroQoL, which showed little QoL impairment(19).

Table 2 – Summary of studies exploring QoL in OSA

Study	Sample size	AHI	Instrument used	Setting	Observation
Gall et al. (1993)(9)	OSA patients = 42 (All Males)	AHI	SF-36	Untreated	Mild OSA patients had impairment in Social Functioning, Role Limitations-Physical and Emotional, lowered mental health and well-being.
Fornas et al. (1995) (20)	OSA Patients = 103 Healthy controls= 40	38± 27	NHP	Untreated	SAHS patients showed a deterioration of general health status parameters in comparison with healthy subjects, these parameters do not correlate with the physiological disturbances of SAHS, expressed as the number of respiratory events per hour
Bolitschek et al. (1998)	OSA patients treated with CPAP=21 Untreated OSA patients = 21 Healthy controls =113	47.08/49.94 (Treated/ Untreated)	MLDL	Untreated	OSA patients treated with CPAP had 'life satisfaction' ratings comparable to that of the healthy controls. Untreated OSA patients had impairment in all 4 domains of MLDL.
Jenkinson et al. (1998)(18)	n = 89 for PGI and EuroQol, n= 86 for SF-36		PGI, EuroQoL SF-36	Before and after 3 months CPAP	Before CPAP SF-36 scores were low which increased to levels similar to general population after 3 months of CPAP therapy. Change in EuroQol scores were not significant. The PGI scores in accordance with SF-36 scores showed substantial improvement after CPAP.

Study	Sample size	AHI	Instrument used	Setting	Observation
Piccrillo et al. (1998)	119 OSA patients- 71 given CPAP, 48 underwent surgery	Mean= 40.0	SF-36, OSAPOSI	Before and after CPAP/Surgery	Scores on the role-physical, vitality, and emotional wellbeing subscales of the SF-36 increased significantly. OSAPOSI awake and sleep subscales and total instrument score increased
Flemons et al. (1998)	SAQLI was tested in 24 OSA patients.	N.A.	SAQLI SF-36	Before starting and 4 week after CPAP	SAQLI had a high correlation with SF-36 among patients successfully completing CPAP
Bennett et al. (1999)	51 OSA patients (46 M and 5 F)	Median apnea/ hypopnea index [AHI] 25, 90% central range: 1 to 98	SF-36	Before and after 4 week CPAP	In OSA patients SF-36 subscale scores for role-physical and vitality were impaired prior to CPAP as compared to normal population, which improved to normal levels after CPAP therapy.
D'Ambrosio et al. (1999)	OSA patients = 29 (23 M, 6 F)	77 + 9	SF-36	8 week CPAP	All domains of SF-36 were impaired in OSA patients when compared with an age and sex matched population. Eight weeks of treatment improved Quality of life to the level of normal population. Improvement was maximum in domains of vitality, social functioning and mental health.
Engleman et al. (1999)	OSA patients = 34 (21 M, 13 F) Cross over trial- patients on 4 weeks of CPAP and 4 weeks of oral placebo therapy alternatively Mild sleep apnea patients (5-15)	NHP	SF-36	Before and after 4 week CPAP or oral placebo	In OSA patients SF-36 scores were impaired on all subscales except general health perceptions. After CPAP treatment, significant improvements were seen in general health, role-phy ical, bodily pain, social functioning, and vitality. Social functioning and vitality were significantly greater on CPAP than on placebo. There was no change in QoL after CPAP therapy on NHP for health and functional status.

Study	Sample size	AHI	Instrument used	Setting	Observation
Yang et al. (2000) (25)	OSA patients -37 Controls- 46		SF-36	Untreated	After controlling for age, gender, body mass index, and number of comorbid conditions, the association between sleep apnea and QOL was significant in the domains of physical functioning and role limitation due to physical health problems and was borderline in vitality.
Stepnowsky et al. (2000) (26)	n = 69 (29 M, 40 F)	22 ± 19	MOS QWB	Untreated	OSA patients with RDI< 15 had significant impairment in general physical functioning and mental health functioning (not those with RDI>15).
Walker-Engstrom et al. (2000) (27)	84 OSA patients- 41 in oral appliance group 43 in UPPP group		MSE-P	Before and 1 year after UPPP or dental Device	The mean values for the three dimensions vitality, contentment and sleep improved significantly 1 year after intervention in the dental appliance and UPPP groups. One year after intervention the UPPP group showed significantly more contentment than the dental appliance group. In contrast, vitality and sleep dimensions did not differ between the two treatment groups. No significant correlations were observed between the QOL scores and somnographic values.
Baldwin et al. (2001)(28)	2398 OSA patients 5-14 AHI=1473 15+= 916		SF-36	Untreated	Sleep disturbances are associated with worse physical and better mental HR-QOL than the U.S. norm.
Akashiba et al. (2002) (29)	60 OSA patients, 34 healthy controls(entry criteria AHI > 20/h and severe arterial oxygen desaturation (arterial oxygen saturation [Sao_2] < 80%) accompanied by EDS	51.6 ± 26.6	SF-36	Untreated	Six of eight domains and the total score on the SF-36 were significantly lower than those in the control subjects.

Study	Sample size	AHI	Instrument used	Setting	Observation
Glebocka et al. (2006)(30)	29 OSA patient, 34 healthy controls	33.3 ±15.8	Satisfaction With Life Scale (SWLS)	Untreated	No difference in satisfaction with life score between OSA patients and Controls.
Dutt et al. (2013)(30)	69 OSA patients (57 M+12 F) 41 healthy controls	26.39 ±16.62	SAQLI	Untreated	QoL was impaired in OSA patients in all the four domains of Calgary SAQLI. QoL impairment not directly proportional to severity of OSA.

Most of the studies suggest that there is significant impairment of QoL in OSA patients but interestingly the QoL impairment has not been found to be directly proportional with the severity of OSA as determined by AHI (10, 20, 25). Only Indian study conducted on this issue also observed significant impairment of QoL in OSA and no association of severity of impairment with severity of OSA (31). No other polysomnographic variable has also been consistently found to be associated with QoL impairment. It has been suggested that HRQoL deteriorates only to a certain level with increasing RDI, but then plateaus(32).

The question of effect of CPAP treatment on QoL in OSA patients has not been answered convincingly. Different studies have shown divergent results. Some studies have shown that CPAP treatment improves QoL so much so that it reaches the level of healthy controls but some studies did not observe significant improvement in QoL. In many CPAP trials the issue of compliance has not been addressed properly and proper adjustment to take compliance has not been done. A 2006 Cochrane review on Continuous positive airways pressure for OSA in adults concluded that CPAP improves QoL in people with moderate and severe OSA(33).

Thus, it is important to measure QoL in patients of OSA as it gives the clear picture of sufferings of the patients and helps in formulating holistic treatment strategy.

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Management of Obstructive Sleep Apnea

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ABSTRACT

Obstructive Sleep Apnea (OSA) is an important public health problem and is associated with considerable morbidity and mortality. Therefore, treatment of this condition is of paramount importance. The treatment of OSA includes general and behavioural measures, mechanical measures including continuous positive airway pressure (CPAP), Bilevel positive airway pressure (BiPAP) and Oral Appliances (OA), pharmacological treatment and surgical procedures. Continuous positive airway pressure (CPAP) treatment reverses the repetitive upper airway obstruction of sleep apnea and associated daytime sleepiness and is the most effective treatment for OSA. However maintaining patient adherence to CPAP therapy is a challenge. Weight loss should be recommended to overweight patients with OSA, as it has been shown that weight reduction has additional health benefits. Treatment of underlying medical conditions such as hypothyroidism or acromegaly has profound effect on apnea/hypopnea index. A subset of patients with OSA may benefit from supplemental oxygen and positional therapy. Presently, there are no effective pharmacotherapeutic agents for treatment of patients with OSA and the role of surgical treatment in OSA is controversial. However, pharmacological treatment of persisting residual sleepiness, despite adequate positive airway pressure therapy delivery and adherence, is indicated and may improve daytime sleepiness.

Key words : CPAP, Oral appliances, Modafinil, CPAP compliance Uvulopalatopharyngoplasty, positional therapy

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INTRODUCTION

There are several consequences that are associated with obstructive sleep apnea (OSA) (1). Life threatening cardiovascular complications can occur in patients with OSA. The treatment of OSA is of utmost importance not only to prevent serious consequences, but also to improve the quality of life of such individuals. The treatment of OSA includes general and behavioural measures, mechanical measures including continuous positive airway pressure (CPAP), Bilevel positive airway pressure (BiPAP) and Oral Appliances (OA), pharmacological treatment and surgical procedures.

General and behavioural measures :

General measures include weight reduction, avoidance of alcohol at least 4 to 6 hours prior to bed time, avoidance of sedative drugs that are known to make apnea worse, smoking cessation, sleeping on one's side rather than on the back or stomach and avoiding sleep deprivation. As obesity is an important factor in the causation of OSA, it has been observed that a 10% reduction in weight was associated with clinically significant improvement in apnea-hypopnea index (2, 3). There are several benefits from reduction of weight in OSA and these include decrease in respiratory disturbance index (RDI), lowering of blood pressure, improvement in sleep structure and snoring and improvement in pulmonary function and arterial blood gas values. There is also a possibility that weight reduction may reduce the optimum CPAP pressure required. Longitudinal studies are required to assess the long-term effects of methods of weight loss (e.g. bariatric surgery and carbohydrate-restricted diets) on the severity of OSA (4, 5).

Mechanical measures :

Mechanical measures include positive airway pressure with a CPAP or bilevel positive airway pressure (BiPAP) and oral appliances (OA). The standard treatment of OSA is with CPAP. The treatment of OSA should start from least invasive and effective to most invasive and effective. All patients with OSA should be offered nasal CPAP first. Patients with mild-to-severe OSA who refuse or reject CPAP therapy may be offered the next choice, i.e. BiPAP therapy. If BiPAP therapy also fails, OA therapy may be considered (5). Oral appliances can be the first line therapy in mild OSA, if they are unwilling to use CPAP.

a) CPAP therapy :

CPAP therapy is the first-line standard of care for treating OSA and this is the only intervention shown to have a favourable impact on both cardiovascular and neurobehavioral morbidities. A "pneumatic splint" is created by delivering a fan-generated flow and thus CPAP maintains airway patency. CPAP dramatically reduces or eliminates apnea and hypopnea in most patients (6). The effectiveness of CPAP depends on the utilization of the machine and mask by the patients. Approximately, 25-50% of patients either will refuse CPAP therapy or cannot tolerate it. Of the patients who accept CPAP, about 40-60% of them continue to use it for one year or longer. Nonadherence to the use of CPAP is therefore a major therapeutic challenge. When adherence is defined as greater than 4 hours of nightly use, 46 to 83% of patients with obstructive sleep apnea have been reported to be nonadherent to treatment. Evidence suggests that use of CPAP for longer than 6 hours decreases sleepiness, improves daily functioning, and restores memory to normal levels. No single factor has been consistently identified as predictive of adherence. Emerging data suggest that various behavioural interventions may be effective in improving CPAP adherence (7, 8).

Patients who have been diagnosed as having OSA and who require CPAP treatment, have titration of pressure over an entire night (full-night polysomnogram (PSG) titration) during a technician-attended PSG. Titration is usually done by a trial and-error process and the technician adjusts the applied pressure until respiratory and sleep parameters that are considered to be clinically important are reduced to the degree judged by the clinician to be acceptable (9). The pressure needed typically is 5-20 cm H_2O. Auto adjusting CPAP (A-CPAP) devices are intended to detect breathing disturbances or absence of such disturbances over specified intervals and modify the applied positive airway pressure upward or downward, respectively, in real time, according to a device-specific algorithm. Split-night PSG titration is an attended, in-laboratory, overnight procedure during which sleep and breathing variables are recorded for diagnostic purposes during the first hours of the sleep period, after which, if specific criteria are met, CPAP titration is performed during the remainder of the night. Split-night PSG titration may provide a pressure prescription that is comparable to that of full-night PSG titration in patients who demonstrate frequent obstructive events early in the sleep period (6). Patients with moderate to severe sleep disordered breathing (apnea-hypopnea index greater than 15) should be treated with CPAP irrespective of their symptoms because these patients are at increased risk of cardiovascular morbidity. Patients with mild form of OSA (AHI 5 to 14.9) can be treated with CPAP if they have one of the following i.e. excessive daytime sleepiness, hypertension or coexistent cardiovascular disease. Conventional CPAP therapy applies fixed pressure continuously to the patient. Since respiration is a dynamic process applying a fixed pressure continuously may not be appropriate. Therefore, CPAP devices are currently available that automatically change pressures based on the presence and/or absence of OSA (auto-positive airway pressure, auto-PAP). CPAP has been reported to improve daytime sleepiness, cognitive function and quality of life and also has been found to decrease blood pressure and health care costs (6). Important drawback of CPAP therapy is

the poor adherence to CPAP therapy. Many patients do not accept CPAP devices and many do not regularly report for follow up visits (8). Complications of CPAP therapy include a sensation of suffocation or claustrophobia, musculoskeletal discomfort, aerophagia and sinus discomfort. Rarely pneumothorax, pneumomediastinum and tympanic membrane rupture have been reported.

b) BiPAP Therapy :

Whereas CPAP delivers a constant pressure during both inspiration and expiration, BiPAP allows independent adjustment of the pressures delivered during inspiration and expiration. BiPAP therapy is prescribed in patients with OSA who cannot tolerate high CPAP pressure or have complications following CPAP therapy i.e. ear infections, bloating etc. (5). There is no distinct advantage of BiPAP over CPAP therapy.

c) Oral appliances :

The indications for oral appliances are OSA patients with mild-to-moderate OSA who prefer OA to CPAP therapy, who do not respond to CPAP therapy and in whom the CPAP therapy had failed. Therefore OA is not indicated in patients with severe OSA (5). There are three basic designs of OAs. These are mandibular repositioners, tongue retaining devices and palatal lifting devices. There are more than 40 OAs available to manage sleep related breathing disorders and obstructive sleep apnea. Contraindications to the use of OAs are less number of teeth, patient is unable to protrude the mandible forward and open jaw widely, pre-existing tempero-mandibular joint problems, severe bruxism and patients with full dentures. Complications of oral appliances include excessive salivation, dental misalignment with bite change, tempero-mandibular joint disease, gum irritation, salivation and tongue pain (5).

Pharmacologic treatment :

a) Serotonergic agents :

It has been observed that serotonin contributes to upper airway patency and that serotonergic agent reduces sleep-related breathing events both in rapid eye-movement (REM) and non-REM sleep in an animal model of OSA. Selective serotonin reuptake inhibitors (fluoxetine and paroxetine) have been shown to decrease apnea-hypopnea index (10). Mitrazapine is a piperazinoazepine-derivative tetracyclic antidepressant and is also a 5-HT antagonist. It is thought to act as a central ventilatory stimulant as it has effects at noradrenergic and histaminergic receptors. Though it has been shown to reduce AHI by almost 50%, its antihisaminergic properties compromises its utility in OSA. It causes weight gain in many subjects. However these selective serotonin reuptake inhibitors are not currently recommended for treating OSA.

b) REM suppressants :

As atonia is a feature of rapid eye movement (REM) sleep interfering with thoraco-abdominal muscles of respiration, REM suppressants have been suggested as therapeutic agents for treatment of OSA. A subset of patients develops OSA and hypopnea events almost exclusively during REM sleep. These patients may be candidates for REM suppressant therapy. It has been observed that many drugs including fluoxetine, paroxetine, tricyclic antidepressants, alcohol and stimulants (dexoamphetamine) have REM-suppressing effects. Two other REM suppressants evaluated for treatment of OSA are protryptiline and clonidine. Protryptiline is a tricyclic antidepressant having anticholinergic, serotonin and noradrenergic reuptake inhibitory effects. Protryptiline has been found to significantly reduce apnea/hypopnea index (AHI), however there was no reduction in REM AHI. Though protryptiline may reduce AHI, the reduction is not sufficient to recommend its use in OSA. Clonidine is a noradrenergic alpha $_2$ agonist and is used as an antihypertensive drug. Clonidine was evaluated for the treatment of OSA because of its REM suppressant effect. However, clonidine is not recommended for treatment of OSA as it has major side effects such as CNS depression and orthostatic hypotension (11, 12). The effectiveness of REM suppressants in the treatment of OSA is not determined (10).

c) Ventilatory stimulants :

Methyl xanthines, opioid antagonist (naloxone), doxopram and nicotine are the drugs evaluated as ventilatory stimulants for treatment of OSA. Nicotine is used as a smoking cessation drug and it has both CNS and respiratory stimulant effects. However none of these drugs are having promising effects to be recommend for OSA treatment (13, 14).

d) Wake promoting substances (e.g. Modafinil and armodafinil) :

Despite treatment with CPAP, many patients demonstrate residual sleepiness. Wake promoting substances are advocated as an adjunctive treatment for such residual sleepiness. Modafinil is a wake-promoting agent which has been approved for the treatment of narcolepsy. Modafinil was therefore evaluated in patients with excessive daytime sleepiness and this drug has no effect on AHI. In a randomized, double blind, placebo-controlled parallel group trial, modafinil was evaluated in a group of patients who were treated with CPAP and with residual sleepiness (dose 200 mg/day week 1 and then 400 mg/day weeks 2-4). It was observed that modafinil significantly improved daytime sleepiness (15). The common adverse events are headache, nausea and infection. It has been reported that life-threatening skin reactions may occur with modafinil. Other adverse events reported are psychiatric symptoms. Modafinil may be given to adult patients with OSA having excessive somnolence

despite well treated with CPAP (10).

e) Hormonal treatment :

There are no randomized prospective studies that have evaluated hormonal replacement (e.g. Medroxyprogesterone and oestrogen) treatment on prevention of OSA. It has been hypothesized that increased incidence of OSA in postmenopausal women is due the loss of protective effect of estrogen and progesterone. Several studies evaluated the role of these hormones in the treatment of OSA. However, there are no consistent data to show the beneficial effects from hormone replacement treatment in OSA (16).

f) Endocrinological disorders :

i) Thyroid hormone replacement therapy :

Hypothyroidism is an important risk factor for development of OSA. All patients with OSA require evaluation to exclude hypothyroidism. . Thyroid hormone replacement therapy completely reverses OSA due to hypothyroidism. Reversal of OSA in such situation may take one year (17).

ii) Growth hormone suppressant therapy in acromegaly :

Patients with OSA may require evaluation for acromegaly as it is associated with OSA. If acromegaly is suspected, such patients require appropriate endocrine evaluation. Bromocriptine and octreotide (a somatostatin analog) have been found to significantly reduce AHI in patients with acromegaly (18, 19).

g) Supplemental Oxygen :

Intermittent hypoxia has been implicated as the underlying mechanism for the systemic manifestations seen in OSA. Supplemental nocturnal oxygen therapy was evaluated in patients with OSA. It was observed that oxygen administration improved nocturnal oxygen saturation levels but does not improve airway patency (20).

h) Improvement of nasal patency :

Patients with OSA and coexisting rhinitis may benefit from the use of nasal corticosteroids. However this alone will not be sufficient to treat OSA (21).

I) Positional therapies :

Lateral positioning therapy has been found to improve AHI (22). Use of specially designed pillows to improve neck and body position in sleep requires further evaluation (23).

j) Antioxidants :

An imbalance in the oxidant-anti-oxidant status has been implicated in the development of cardiovascular abnormalities in patients with OSA. There is not only an increase in pro-oxidants but also a decrease in anti-oxidants. It is recognised that when there is oxidative stress, there is an increase in the production of the inflammatory cytokines which in turn would produce further free radicals, thus forming a vicious cycle and worsening the disease condition. Oral N-acetylcysteine (NAC), an antioxidant, administration appears to have a therapeutic potential in the treatment of OSA (24). Compared to a previous investigation in which the anti-oxidants used were vitamins E and C, there was a greater increase in total reduced glutathione (GSH) level in the NAC group (24, 25).

Surgical Treatment :

The role of surgery in the treatment of OSA is controversial. Patients with reversible upper airway obstruction such as adenotonsillar hypertrophy or mass lesions are candidates for surgery with beneficial effects. Uvulopalatopharyngoplasty is a commonly performed surgery in OSA in which soft palatal tissue is excised, but with suboptimal results (26). Mandibular advancement devices have been found to be effective in mild apnea and may improve daytime symptoms (27). Other surgical procedures attempted for treatment of OSA are septoplasty, nasal polypectomy, radiofrequency ablation of turbinates, uvulopalatal flap, palatal advancement, radiofrequency ablation of the soft palate, genioglossal advancement, hyoid suspension, partial glossectomy, tongue radiofrequency ablation, lingualplasty, maxillo-mandibular advancement and epiglottoplasty. It has also been reported that bariatric surgery may be useful. However, there are no randomised trials showing the efficacy of bariatric surgery in OSA. Tracheostomy, though very effective in the treatment of OSA, is a disfiguring procedure and decreases the quality of life of the patients. Tracheostomy is therefore reserved for patients with severe OSA in whom other medical and surgical procedures have failed (5).

Hypoglossal Nerve Stimulation :

Since hypoglossal nerve stimulation (HGNS) recruits lingual muscles and reduces pharyngeal collapsibility, it is possible that stimulation of hypoglossal nerve may be used to treat sleep apnea. A Hypoglossal Nerve Stimulation System (HGNS) was implanted in patients with OSA to test this hypothesis. It has been shown that hypoglossal nerve stimulation produced marked dose-related increases in airflow without arousing patients from sleep, suggesting that hypoglossal nerve stimulation is a potential novel therapeutic approach for patients with OSA (28).

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Causes of Hypersomnia – Narcolepsy

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ABSTRACT

The causes of hypersomnia or excessive daytime sleepiness (EDS) besides volitional sleep deprivation and obstructive sleep apnea are principally due to primary central nervous system abnormalities. Most common amongst these is Narcolepsy, a primary disorder of the neural control of wakefulness and sleep. The recent discovery of hypocretin/orexin deficiency as the main cause of narcolepsy will lead to important therapeutic advances for patients with narcolepsy and further to understanding of the control of sleep and wakefulness in general. Importantly, the excessive daytime sleepiness is not due to psychiatric conditions, but rather is always due to sleep deprivation or an underlying diagnosable and treatable sleep disorder.

Key words : EDS, Sleep, Narcolepsy

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Volitional sleep deprivation and obstructive sleep apnea are the most common causes of hypersomnia. The remaining causes are primarily due to primary central nervous system abnormalities, the most common of which is narcolepsy, a primary disorder of the neural control of wakefulness and sleep.

NARCOLEPSY :

It is the prototypic example of dissociated sleep-wake phenomenon in which components of one state, ie rapid eye movement (REM) sleep, appear in another (wakefulness) (1).

Narcolepsy is a relatively frequent disorder with a prevalence of 0.09%. A clear genetic component is indicated by the fact that over 90% of individuals with narcolepsy carry the HLA DR15 and HLA DQ6 gene, which is found in less than 30% of the general population. Siblings of individuals with narcolepsy have a 60-fold increased likelihood for developing the disease. Narcolepsy if thought to result also from abnormal neurotransmitter functioning and sensitivity and abnormal immune modulation (1,2,3).

The male to female ratio in narcolepsy is 1.64:1. The usual age of onset of narcolepsy is adolescence or early adulthood, although it ranges from early childhood to senescence (3 to 72 years of age), with a primary peek in the teens and a lesser peak in the early 30s.

Signs and Symptoms :

Manifestations of narcolepsy are as follows: (1,2)

1. EDS
2. Cataplexy
3. Hypnogogic hallucinations
4. Sleep paralysis

Excessive Daytime Somnolence (EDS) :

EDS is the primary symptoms of narcolepsy with unwanted and unanticipated sleep episodes lasting seconds to minutes and occurring at inappropriate times, particularly during periods of reduced environmental stimulation, such as reading, watching television, riding in or driving or attending a class or meeting. During periods of excessive sleepiness, a brief (10 to 30 minute) nap is frequently very refreshing, if only for a short period of time. The symptom of sleepiness is accompanied by failing performance due to impairment of sustained attention, at times reflected in a complaint of impaired memory. The apparent memory disturbance is secondary to impaired attention (1,2,4).

Ancillary symptoms of narcolepsy include cataplexy, hypnogogic hallucinations, and sleep paralysis.

Cataplexy :

Cataplexy, which occurs in 65% to 70% of these patients, comprises of sudden loss of muscle tone, typically triggered by emotion such as laughter, anger, excitement, delight or surprise. The muscle weakness of cataplexy may be complete, resulting in the patients falling or being forced to sit, much more commonly, the weakness is milder and more focal, taking the form of facial sagging, slurred speech or localized weakness of an extremity. Cataplexy may never occur in 30% of patients with narcolepsy or may precede the onset of EDS (1,2,4).

Hence the salient features of Cataplexy are:

1. If severe and generalized, cataplexy may cause a fall.
2. More subtle forms exist with only partial loss of tone (eg., head nod and knee bucking)
3. Respiratory and extraocular movements are preserved.
4. Cataplexy is usually triggered by emotions (especially laughter and anger)

Sleep Paralysis :

Sixty percent of individuals with narcolepsy experience sleep paralysis upon awakening from REM sleep (usually from a dream). At times, this frightening manifestation consists of total-body paralysis, with sparing of respiration and of eye movements, lasting from seconds to minutes (1,2,4).

The salient features of Sleep paralysis are:

1. Usually the patient is unable to move upon awakening.
2. Less commonly, the patient is unable to move upon falling asleep with consciousness intact.
3. Paralysis is often accompanied by hallucinations
4. Respiratory and extraocular muscles are spared
5. Paralysis occurs less frequently when the person sleep in an uncomfortable position
6. Paralysis can be relieved by sensory stimuli (eg. touching or speaking to the person)

Hallucinations :

Hypnogogic (at sleep onset) and hypnopompic (upon awakening) hallucinations are noted in 12% to 50% of cases. The hallucinations are extremely vivid and often frightening dreams that occur during the transition between wakefulness and sleep. They may be associated with total body paralysis and sensations of oppression and dread. These hallucinations are more frightening than conventional dreams because the dream imagery arises from the real (waking) environment, making differentiation between reality and dreaming difficult (1,2,4,5).

The following are also common features of narcolepsy:

1. A tendency to take short and refreshing naps during the day; these may be accompanied by dreams.
2. Trouble sleeping at night
3. Nocturnal compulsive behaviours (sleep related eating disorder and nocturnal smoking)
4. Obesity

Features of Narcolepsy in children are : (6)

1. Restlessness and motor over activity may predominate
2. Academic deterioration, inattentiveness and emotional lability are common
3. At disease onset, children with narcolepsy and cataplexy may display a wide range of motor disturbances that do not meet the classic definition of cataplexy.
4. Motor disturbances may be negative (hypotonia) or active.
5. Motor disturbances may resolve later in the course of the disorder.

Diagnosis :

The DSM-5 defines narcolepsy as recurrent episodes of irrepressible need to sleep, lapsing or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months. There must also be presence of at least one of the following (1,2,5).

1. Episodes of cataplexy occurring at least a few times per month
2. Hypocretin deficiency
3. REM sleep latency < 15 minutes or a mean sleep latency < 8 minutes and two or more sleep-onset REM periods (SOREMPs).

Narcolepsy can be categorized as mild, moderate or severe based on the frequency of cataplexy, need for naps, and disturbance of nocturnal sleep. In addition, the DSM-5 identifies five subtypes as follows:

1. Narcolepsy without cataplexy but with hypocretin deficiency
2. Narcolepsy with cataplexy but without hypocretin deficiency
3. Autosomal dominant cerebellar ataxia deafness and narcolepsy
4. Atuosomal dominant narcolepsy, obesity and type 2 diabetes
5. Narcolepsy secondary to another medical condition

Whenever possible, the diagnosis of narcolepsy should be confirmed by polysomnography (PSG) followed by a multiple sleep latency test (MSLT). The MSLT should show sleep latency 8 minutes or less and 2 or more SOREMPs. An alternative criterion is a CSF hypocretin level of 110 pg/ml or lower. The hypersomnia must not be explained as another sleep, neurologic, mental or medical condition, or induced by medicine /substance use.

Pathophysiology :

Narcolepsy is thought to result from genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation. Current data indicate certain human leukocyte antigen (HLA) subtypes and abnormal hypocretin (orexin) neurotransmission, which leads to abnormalities in monoamine and actylcholine synaptic transmission, particularly in the pontine reticular activating system (3,7).

Understanding of the neurochemistry of narcolepsy began with research involving narcoleptic dogs. In these animal models, the disorder is transmitted in an autosomal recessive fashion with full penetrance and is characterized mainly by cataplexy. Muscarinic cholinergic stimulation increases cataplexy in these animals, and cholinergic blockade eliminates the symptom. Nicotinic agents have no effect on the cataplexy (8).

Receptor subtypes such as the alpha-1-noradrenergic receptor appear to mediate cataplexy. Prazosin, an alpha-1-antagonist, worsens symptoms in canine and human subjects. The pons is not the only neuroanatomic site that is responsible for mediating cataplexy. The mesocorticolimbic dopaminergic system also has been implicated. This connection with the limbic system in part explains the relationship of cataplexy to emotion.

The centrality of hypocretin transmission in the pathophysiology of narcolepsy was demonstrated when hypocretin knockout mice displayed cataplexy and sleepiness. Further evidence for impaired hypocretin functioning in humans was found with the discovery of low levels of hypocretin in the CSF of narcoleptic patients (9,10).

Subsequently, abnormal immune modulation was associated with the clinical development of narcolepsy in children in Scandinavia and Finland. After vaccination against H1N1 influenza virus with a vaccine using a potent ASO3 adjuvant, narcolepsy in Finish children increased 8 to 12 fold. All affected children who underwent HLA typing were found to have the HLA DQB*0602 allele (3,7).

REM Sleep :

Dysfunction and inappropriate regulation of REM sleep are thought to exist in narcolepsy. Neuroanatomic control of REM sleep appears to be localized to the pontine reticular activating system.

The brain contains REM-on cells, which fire selectively during REM sleep periods, and REM-off cells, for which the converse holds true. Most REM-on cells function through cholinergic transmission whereas REM-off cells are noradrenergic or serotonergic. In narcolepsy, monoamine-dependent inhibition of REM-on cells may be defective (5,4).

Symptoms can be viewed as REM sleep components intruding into wakeful states. For example, cataplexy and sleep paralysis represent an intrusion of REM sleep atonia, whereas hallucinations represent an intrusion of dreams.

Hypocretin :

Hypocretin plays an important role in the pathophysiology of human narcolepsy. Patients with narcolepsy have been found to have little or no hypocretin in their CSF. Postmortem pathologic examination of the brains of people with narcolepsy with cataplexy has

demonstrated dramatically reduced numbers of hypocretin neurons. Hypocretin deficiency is theorized to produce instability of sleep and wake states, thereby preventing the persons from sustaining more continuous sleep or wakefulness. A large majority of patients with narcolepsy without cataplexy have normal CSF hypocretin levels (9,10).

Investigators have also found low levels of histamine (that helps maintain wakefulness) in the CSF of patients with hypocretin-deficient narcolepsy. They are also seen in narcolepsy patients with normal CSF hypocretin levels and in patients with idiopathic hypersomnia. Low CSF histamine levels have not been found in patients with hypersomnia secondary to obstructive sleep apnea syndrome. The CSF histamine level may serve as a biomarker reflecting the degree of hypersomnia of central origin (9,10).

CNS nuclei for wakefulness and the relevant neurotransmitters generated in those nuclei include the following:

1. Locus ceruleus – Norepinephrine
2. Raphe nucleus – Serotonin
3. Tubomammillary nucleus – Histamine
4. Ventral tegmental area – Dopamine
5. Basal forebrain – Acetylcholine

These areas also inhibit REM sleep.

Hypocretin neurons thought to be autoexcitatory project from the lateral hypothalamus into these regions and serve to maintain wakefulness. A deficiency of hypocretin neurons may decrease the threshold for transitioning between wakefulness and sleep. This is a proposed explanation for the sleepiness and REM intrusion into wakefulness found in narcolepsy (9,10).

Destruction of hypocretin-producing neurons appears to be an autoimmune process. A specific autoantigen against Tribbles homolog 2 (Trib2) have been found to be higher in narcolepsy patients with cataplexy than in normal controls. The autoimmune model of narcolepsy inspired trials of intravenous immunoglobulin therapy in narcoleptic patients with low levels of hypocretin – 1. In these trials, IVIG reportedly improved cataplexy and sleepiness in many cases, but the effects did not last long (11).

Genetic Factors:

The genetics of Narcolepsy are complex. The risk is as high as 40% in the first-degree relatives.

There is a striking association between narcolepsy and the HLA haplotype DQA1*01:02-DQB1*06:02. A genome wide association study proposed a protective variant DQB1*06:03. GWA studies in Caucasians with replication in 3 ethnic groups have revealed associations between SNP in the T cell receptor alpha locus and narcoplepsy. This association further supports the autoimmune basis of narcolepsy (3,7).

An SNP in the purinergic receptor subtype P2Y11gene also appears to be associated with Narcolepsy. A GWA study that investigated 202 candidate genes in a replication study in 222 narcoleptic patients and 380 controls identified 6 genes that were associated with narcolepsy: NFATC2, SCP2, CACNA1C, TCRA, POLE and FAM3D (3,7).

Management :

Treatment of Narcolepsy has both nonpharmacologic and pharmacologic components. Sleep hygiene is important. Most patients improve if they maintain a regular sleep schedule, usually 7.5 to 8 hours of sleep per night. Scheduled naps during the day also may help (1,2,11).

Pharmacologic treatment of narcolepsy involves the use of central nervous system stimulants such as methyphenidate, modafinil, dextroamphetamine sulphate, methamphetamine and amphetamine. These medications help reduce daytime sleepiness, improving the symptom in 65% to 85% of patients. In patients for whom stimulant treatment is problematic, subjective benefit from treatment with codeine has been reported (1,2,11).

Methylphenidate was the stimulant most frequently used for treatment of narcolepsy. It improves sleep tendency in a dose-related fashion. Undesirable side effects include headache, nervousness, and gastrointestinal complaints. Nocturnal sleep may be impaired with a resulting decrease in total sleep time (11).

Modafinil is novel wake-promoting agent. The mechanism of action is not understood, but it does not appear to involve altering levels of dopamine or norepinephrine. Unlike traditional medications, modafinil does not appear to affect total sleep time or suppress REM sleep; the most common adverse effect is headache. Its safety in children has not been established (11).

Armodafinil has fewer side effects. It is indicated for the treatment of EDS associated with narcolepsy. TH most common side effects are headache, nausea, dizziness and difficulty in sleeping (11).

Cataplexy in patients with narcolepsy can be treated with the CNS depressant sodium oxybate. Other agents that are used off-label for cataplexy are tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. The strongest evidence is for clomipramine, fluoxetine and sodium oxybate (11).

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Sleep in Epilepsy

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ABSTRACT

The relationship between sleep and epilepsy is bidirectional. While certain types of seizures occur almost exclusively during sleep, sleep deprivation can precipitate seizures and can activate interictal epileptiform discharges (IEDs) in the electroencephalogram (EEG). While non-rapid eye movement sleep is an activator of IEDs and seizures, rapid eye movement sleep suppresses them. Nocturnal seizures need to be distinguished from parasomnias. Epileptic seizures and IEDs result in changes of sleep architecture, while antiepileptic drugs have variable effect on sleep and wakefulness. Nearly one-third of patients with epilepsy complain day time somnolence. In addition to nocturnal seizures and antiepileptic drugs (AEDs), associated sleep disorders such as sleep apnoea and restless leg syndromes might be responsible for daytime sleepiness in persons with epilepsy.

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INTRODUCTION

It has been known since antiquity that sleep and epilepsy are intimately related. The relationship between sleep and epilepsy is bidirectional **(Table 1).** Certain types of seizures occur almost exclusively during sleep, and sleep deprivation can precipitate seizures and can activate IEDs in the EEG. While non-rapid eye movement (NREM) sleep is an activator of IEDs and seizures, rapid eye movement (REM) sleep suppresses them **(Table 2).** Nocturnal seizures can mimic parasomnias. Epileptic seizures and IEDs result in changes of sleep architecture, while AEDs affects sleep and wakefulness in different ways.

Table 1: The bidirectional relationship between sleep and epilepsy

Effects of sleep on epilepsy
- Activation of interictal epileptiform discharges (IEDs)
- Activation of epileptic seizures

Effects of sleep deprivation
- Activation of IEDs
- Activation of epileptic seizures

Effects of epilepsy on sleep
- Disruption of sleep by IEDs and seizures

Effects of antiepileptic therapy on sleep
- Antiepileptic drugs
- Vagus nerve stimulation

Effect of sleep disorders on epilepsy
- Obstructive sleep apnoea syndrome
- Restless leg syndrome
- Parasomnias

Effects of sleep on epilepsy :

Interictal epileptiform discharges :

Sleep is a potent activator of IEDs in the EEG. A number of studies have examined the frequency of IEDs in different stages of sleep in patients with temporal lobe epilepsies (1-7). Focal IEDs become more frequent and tend to become bilateral and generalized during sleep (3,5,6). The IEDs are most frequent during stages 3 and 4 NREM sleep and least frequent during REM sleep (4,5). The ability of NREM sleep to activate IEDs appears to be related to the intense neuronal synchronization that occurs between brainstem, thalamus and cortex in this state. The sleep activation of IEDs

Table 2: Effect of sleep stages on epilepsy

NREM sleep	REM sleep
Synchronization of EEG	Desynchronization of EEG
Activation of IEDs	Suppression of IEDs
Generalization of focal IEDs	More localized IEDs
Increased likelihood of seizures	Decreased likelihood of seizures

is profound in certain epilepsy syndromes such as benign childhood epilepsy with centro-temporal spikes (benign rolandic epilepsy) (8,9) and in epilepsy with continuous spike and waves during slow-wave sleep (10,11). The essential feature of the latter disorder is a diffuse 2-3 Hz spike-wave discharges occurring throughout NREM sleep and occupying at least 85% of slow-wave sleep (10,11). In children with benign rolandic epilepsy, marked activation of centro-temporal spike discharges occurs during NREM sleep, while awake EEG record may show few or occasionally no IEDs at all (8,9). The capacity of sleep to activate IEDs indicate the importance of obtaining EEG recording during sleep, in addition to wakefulness, in patients with suspected diagnosis of epilepsy.

Epileptic seizures :

As with IEDs, nocturnal focal seizures occur predominantly in NREM sleep and seldom during REM sleep. However, in contrast to IEDs, seizures are more common in stages 1 and 2 rather than in slow-wave sleep (12,13). Partial seizures generalize more often during NREM sleep than wakefulness (12,13).

In patients with nocturnal frontal lobe epilepsy (NFLE), the seizures occur exclusively during sleep. NFLE is often familial, autosomal dominant in inheritance and the gene locus has been mapped to the nicotinic acetylene receptor α4 subunit on chromosome 20 (14). The motor behaviour in nocturnal frontal lobe seizures often mimics parasomnias (15). Furthermore, IEDs are often absent in frontal lobe epilepsies and ictal EEG is usually obscured by muscle artefacts. The brief duration, stereotypy of the spells and lateralizing features would favour epileptic events than parasomnias (15).

In children with benign rolandic epilepsy, the seizures occur almost exclusively during sleep (8,9). The AED treatment is often differed in children with benign rolandic epilepsy because of the infrequent nocturnal occurrence of seizures and the tendency of the disorder to spontaneously remit by adolescence.

Ring chromosome 20 should be suspected in patients with nocturnal frontal lobe nonconvulsive status epilepticus and normal brain magnetic resonance imaging (16). Individuals with ring chromosome 20 syndrome may have

normal cognition despite poorly controlled seizures and no dysmorphic features, making the diagnosis difficult unless there is a high index of suspicion (17).

Effects of epilepsy on sleep :

Interictal epileptiform discharges :

A number of studies have shown that IEDs during sleep unassociated with clinical seizures could disrupt the nocturnal sleep and could contribute to daytime sleepiness (18,19). Suppressing the IEDs during sleep by bedtime benzodiazipine group of AEDs often improves daytime alertness and school performance in selected children with certain epilepsy syndromes such as benign rolandic epilepsy and in epilepsy with continuous spike waves during slow-wave sleep (11,19).

Epileptic seizures :

Both focal and generalized seizures at night cause considerable disruption of sleep (12,13). Compared to patients with epilepsy without nocturnal seizures, in those with nocturnal seizures, the total sleep time decreases and the number of nocturnal awakenings increase (12,13). The most striking change in sleep architecture in patients with nocturnal seizures is an absolute and relative reduction in REM sleep. Patients with drug-resistant nocturnal generalized seizures are more prone to sudden unexpected death in epilepsy (20).

Antiepileptic drugs :

The AEDs in general improves sleep efficiency by decreasing sleep latency and nocturnal awakenings (21,22). An exception is phenytoin, which increases awakenings and decreases sleep efficiency. Phenobarbitone, carbamazepine and benzodiazipines decrease REM sleep whereas gabapentin and lamotrigine enhance REM sleep. Most of the AEDs cause daytime sleepiness; however, felbamate and lamotrigine can result in insomnia. Benzodiazipines and phenobarbitone can aggravate obstructive sleep apnoea (OSAS) syndrome. The OSAS can also be worsened by vagus nerve stimulation used to treat certain AED-resistant epilepsies (23).

Daytime sleepiness and epilepsy :

Nearly one-third of patients with epilepsy show elevated scores on the Epworth Sleepiness Scale (18). The factors that contribute to day time somnolence in persons with epilepsy are listed in **Table 3.** It should be remembered that associated sleep disorders such as OSAS and restless leg syndrome might be responsible for daytime somnolence in persons with epilepsy. Additionally, OSAS may increase the frequency of seizures by producing sleep deprivation or by inducing hypoxemia, and treatment of OSAS can improve seizure control.

Table 3: Causes of daytime sleepiness in persons with epilepsy

Antiepileptic drugs
Nocturnal seizures
Associated sleep disorders
▪ Obstructive sleep apnoea syndrome
▪ Restless leg syndrome

Sleep deprivation and epilepsy :

Sleep deprivation can aggravate IEDs and seizures. Sleep deprivation is widely used in EEG laboratories and epilepsy monitoring units as a method of inducing IEDs and seizures (24). The influence of sleep deprivation in precipitating seizures is most evident in patients with juvenile myoclonic epilepsy. Patients with this disorder exhibit myoclonic jerks of the upper limbs and generalized tonic-clonic seizures usually within one hour after awakening in the morning, especially following sleep deprivation (25).

Evaluation of the patient with nocturnal spells :

The differential diagnosis of nocturnal events, especially between NFLE and parasomnias can be very difficult. More than one-third of patients with NFLE present with personal or family history of parasomnias, thereby complicating the differential diagnosis between these two disorders (15). An Australian group of researchers demonstrated that clinical history alone can accurately discriminate between NFLE and parasomnias (26). In the test battery they developed, called FLEP scale, later age at onset, longer duration (>2 minutes) of events and occurrence during later part of sleep favored parasomnia, while stereotypy, clustering and ability to recall were more frequently associated with NFLE (26). A recent study that compared the diagnostic value of FLEP scale against nocturnal polysomnography showed that FLEP scale failed to give a diagnosis of NFLE in only 4 out of 71 (5.6%) patients (27).

The correct characterization of nocturnal spells requires collaboration between an epileptologist and a sleep specialist. When the spells also occur during wakefulness, especially if the interictal EEG is abnormal, the diagnosis of epilepsy is usually straightforward. When the spells occur only during sleep and the clinician suspects that seizures are more likely than parasomnias, an awake and sleep EEG, often preceded by sleep deprivation, often settles the diagnosis. The brief and stereotypic nature of the nocturnal spells favour epilepsy (26,27). If the interictal EEG is normal, prolonged recording to capture the spells in an epilepsy monitoring unit (EMU) become necessary. If parasominas are more likely than seizures, poysomonography with full

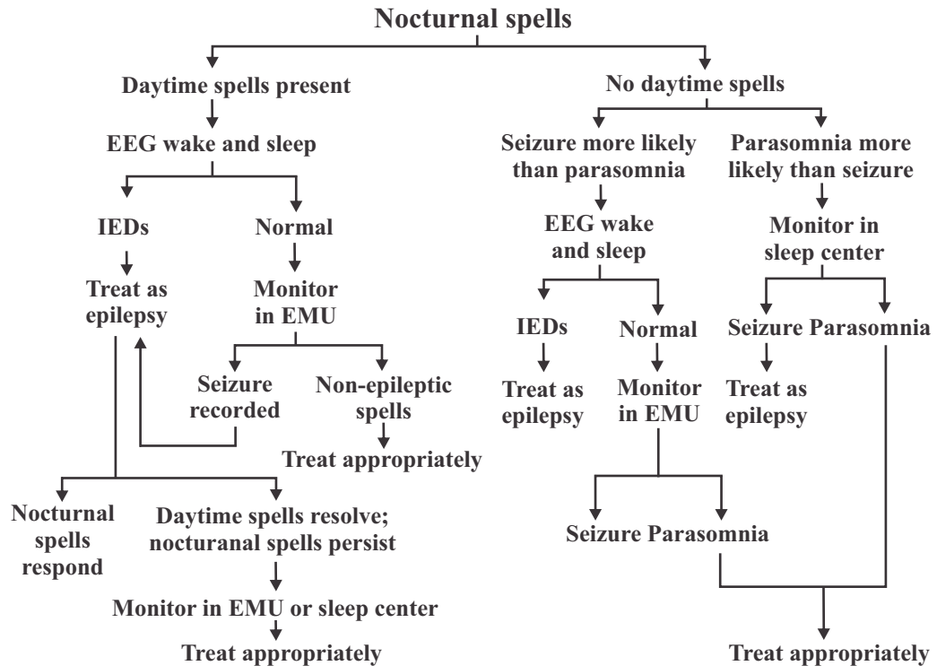

FIGURE 1 : Algorithm for evaluation of patients with nocturnal spells

EEG montage will be a better option. An algorithm for the evaluation of a patient with nocturnal spells is illustrated in **Figure 1.**

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Sleep and Stroke

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ABSTRACT

Circadian variations in conjunction with sleep-related heart rhythm changes and sleep disordered breathing (SDB) are contributing risk factors for stroke. Strong scientific evidence now exists indicating that SDB contributes to systemic hypertension, a prominent risk factor for stroke, and compelling circumstantial evidence is present suggesting that SDB raises the risk for development of stroke through other circulatory mechanisms as well. Preliminary evidence indicates that post-stroke patients have a higher prevalence of SDB, which is likely to compromise their rehabilitation outcomes. Since SDB is modifiable with the application of CPAP and other treatment modalities, there is practical value in investigating patients at risk of stroke or post stroke for presence of SDB. Successful application of CPAP or BiPAP therapy may improve the outcome in both instances.

Key words : Sleep, Stroke, SDB, CPAP

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Most strokes occur as a result of the concerted action of risk factors, prominent among which are age, hypertension, ischemic heart disease, diabetes and smoking. The awareness of new risk factors provides the opportunity to activate more preventive measures. Such is the case with obstructive sleep apnea (OSA). The role of sleep apnea disorder in circulatory alteration and vascular injury is a recently developed concept.

Circadian Variations Influential in Circulatory and Vascular Phenomena :

Many physiological systems directly involved in functions of the circulatory system are affected by the circadian rhythm and interact in a chain of events with far-reaching ramifications. Such are the endocrine secretions, thermoregulation, renal functions, respiratory control, heart rhythm, hematologic parameters, immune system and drug metabolism.

Plasma catecholamine levels rise from 6 AM to noon in parallel with an increase in heart rate and blood pressure. Fibrinolytic activity is reduced in the mornings while platelet aggregability is elevated. These phenomenons have been linked to increased vascular morbidity during morning hours.

A number of studies have shown that stroke onset is more common between 6 AM and non during the 24 hour cycle; the most critical period occurs 1 hour after awakening. Several factors have been proposed as possibly influential in this cyclical occurrence, including cortisol rhythm, hemodynamic variability, increased platelet aggregability, changes in blood viscosity and decreased fibrinolytic activity (1).

Snoring :

Pathologic snoring can be described as the habitual harsh and loud vibratory sound produced by respiratory effort in the sleeping individual. Most individuals past middle age are snorers, but of importance to the clinician should be habitual, unabating, intensely loud snoring that is disturbing to others. Habitual snoring has been associated with arterial hypertension, ischemic heart disease and stroke. Sleep Disordered Breathing (SDB) can have serious cardiovascular and cerebrovascular consequences.

SDB and Stroke :

Abundant circumstantial evidence points to a causal association between SDB and stroke. Vascular risk factors, such as systemic hypertension, provide a slowly evolving indirect link to stroke in untreated SDB patients, while heart disease in any of its forms, as is widely appreciated, is a more direct pathway, if not a trigger, for stroke.

Sleep disordered breathing is a rubric under which OSA, snoring, upper airway resistance syndrome and central hypoventilation/apnea are included. OSA is the most common form of SDB and is characterized by intermittent and repetitive episodes of partial or complete obstruction of the upper airway, accompanied by elevated airway resistance leading to apneas and hypopnoeas during sleep, both of which cause intermittent hypoxemia (2).

Epidemiology of OSA :

Sleep apnea is a common disorder, affecting up to 20% of the general population according to some reports. With two of the greatest risk factors for OSA being age and obesity, the prevalence should increase with time as the population ages and waistlines bulge. Sleep apnea severity is measured by the apnea-hypopnea index (AHI). The AHI is a measure of the number of apneas, complete cessation of airflow and the number of hypopneas, reduction in airflow with desaturation or arousal, per hour of sleep. An AHI > 5 events/hour with symptoms of daytime somnolence, snoring or waking with gasping or choking or an AHI > 15 events/hour regardless of symptoms is considered diagnostic of OSA. The prevalence of sleep apnea is high in stroke patients – estimated to be between 50% and 70%. The most common type of sleep-disordered breathing found after stroke or transient ischemic attacks (TIA) is OSA. It may predate the stroke, worsen during the acute stage and persist after the acute phase (2,3,4,5).

OSA and Stroke: Shared risk factors vs independent association :

The relationship between OSA and stroke is a complex one with shared risk factors as well as a likely independent association. Several studies have established OSA as a strong risk factor for hypertension, one of the leading risk factors for stroke. Studies have linked OSA to other major stroke risk factors, including insulin resistance, coronary artery disease, heart failure, and arrhythmias. Individuals with OSA have a fourfold increased risk of atrial fibrillation and a two to three fold higher risk of other complex arrhythmias, even after adjustment for potential confounders. Sleep apnea has also been suggested as an independent risk factor for stroke. Postulated mechanisms of OSA as an independent risk factor for stroke include tachyarrhythmias related to sympathetic activation; impaired cerebral hemodynamics as a consequence of blood pressure fluctuations; enhanced inflammation and oxidative stress associated with hypoxemia, including evidence for OSA activating nuclear factor kappa-B-mediated inflammatory pathways leading to systemic inflammation; promotion of atherosclerosis and thrombosis; abnormal coagulation markers, including plasma fibrinogen levels and platelet reactivity and increased right-to-left shunting through a patent foramen ovale (2,3,4,5,6,7,8).

Various studies also support casual association between hypertension

and OSA. The autonomic and hemodynamic responses of OSA lead to acute surges in heart rate and blood pressure. Sleep heart health study demonstrated that sustained diurnal hypertension is a consequence of chronic OSA. The relative risk of hypertension in severe OSA (AHI> 30) compared with the mildest category (AHI < 1.5) in this study was 1.37 (95%, CI: 1.03-1.83), and the odds for hypertension increased with AHI in a dose-response manner. Another compelling evidence for OSA leading to hypertension is available from Wisconsin sleep cohort study, in which even after adjusting for baseline hypertension, age, gender, BMI, weekly cigarette and alcohol consumption, the risk of developing hypertension in people with an AHI of > 15 remained higher compared with those without OSA. Treatment of OSA with CPAP (Continue Positive Airway Pressure), compared to sham CPAP, reduced the hypertension, which further supports an association between OSA and hypertension. OSA may raise the systemic blood pressure significantly and thus can be one of the most important mechanism by which OSA leads to cerebrovascular morbidity (2,3,4,5,6,7,8).

Mechanism of interaction between OSA and normal blood pressure leading to hypertension has been studied and it is observed that patients with OSA have considerably higher sympathetic activity compared with controls, even during wakefulness. A modification caused in renal physiology in the form of an augmentation of the rennin-angiotensin system in chronic OSA-induced hypoxia has also been forwarded as an explanation for the genesis of hypertension in OSA. OSA is also been implicated in contributing to medically refractory hypertension.

The cardiac response to apnea consists of reduction of stroke volume, decreased heart rate and reduced cardiac output. These changes occur in convergence with progressive oxyhemoglobin desaturation and in prolonged apneas, with gradual hypercapnia. In patients with advanced SDB, cardiac arrhythmias, which are more abundant in older patients, appear when the oxyhemoglobin saturation falls below 65%. REM sleep is a most vulnerable time of the night for subjects with cardiovascular and cerebrovascular risk factors since cerebral blood flow normally increases and cardiac rhythm variability is at a maximum in this stage. In SDB, REM sleep related atonia of dilator oropharyngeal muscles and loss of respiratory drive dependency on chemoreceptor reflex activity result in more prolonged episodes of obstructive apnea. In consequence, the accompanying hypoxemia is more profound and the cardiac rhythm changes are more prominent, creating a dissociation between an increasing demand and a progressively faltering supply of blood flow to the brain. (2-11)

TIA and silent infarctions may also occur at night while individuals are asleep, but proof is still missing. The most compelling circumstantial evidence that SDB affects cerebral hemodynamic mechanisms comes from studies investigating cerebral blood flow velocities with ultrasound techniques in the middle cerebral artery (MCA) territory in patients with SDB. During the apnea event, significant reduction in MCA blood flow velocity occurs that correlates with the duration of the apnea that correlates with the duration of the apnea rather than with the depth of oxyhemoglobin desaturation. These intracranial hemodynamic changes occurring repeatedly night after night in patients with marginal circulatory reserve may contribute to a raise in the risk of stroke. (2-11)

Acute Stroke and Sleep :

Inversion of the sleep-wake rhythm is commonly observed in the days that follow a large hemispheric stroke and is manifested by agitation during the night and lethargy during the day. The early presence of REM sleep and normal sleep cycles is a good prognostic sign. Location and extent of the stroke determine the type of sleep-related alteration. Neuronal centers controlling respiratory drive, pharyngeal motility, and some sleep functions are located in anatomic proximity in the tegmentum of the pontomedullary junction. Vascular injury to the respiratory centers in the lateral medullary syndrome may precipitate SDB. Other patterns of respiratory dysfunction noted with infratentorial lesions include apneusis or apnea during sustained inspiration, nonobstructive, obstructive and mixed apneas and failure of automatic breathing (so called Ondine's Curse). Sleep apnea events of the obstructive or non obstructive varieties with oxyhemoglobin desaturations may require administration of oxygen through a nasal cannula (12-16).

Patients with mesencephalic or paramedian thalamic lesions may exhibit excessive daytime somnolence as a result of loss of alerting mechanisms due to damage to reticular activating pathways and nuclei rather than development of OSA as such. Patients with hemispheric infarction demonstrate reduction of REM sleep during the acute stage proportional to the severity of neurologic deficit. In bilateral hemispheric lesions, Cheyne-Stokes respiration may be observed.

The reported frequency of OSA in stroke patients varies between 30% and 80%. In recent meta- analysis of ischemic or hemorrhagic stroke and TIA patients, the frequency of SDB with AHI of >5 was 72 %, and with an AHI of >20 was 38%, it was reconfirmed by a previously reported higher prevalence of SDB (AHI>10) in men compared with women (65% vs. 48%; p-0.001), and also a higher percentage of SDB (AHI>10) in patients with recurrent stroke than initial stroke (74% vs. 57%; p-0.013). Patients with cardio embolic strokes had a lower percentage of SDB compared with patients with strokes due to unknown etiologies (15,16).

OSA as a predictor of poor outcome after stroke :

If sleep apnea increases the risk of stroke, either directly or indirectly,

untreated patients with co-morbid OSA may have worse functional outcomes and higher mortality after acute stroke. Several observational studies suggest that OSA is a predictor of poor functional outcome after stroke, increasing the likelihood of dependency, and poststroke mortality. Potential mechanisms of OSA contributing to poor neurologic recovery include direct effects of reduced cerebral blood flow and modulation of blood pressure and oxygen saturation associated with apneic episodes, resulting in further neurologic injury due to a compromise in perfusion to the ischemic penumbra. In the subacute setting of the recovering stroke patient, untreated OSA can also cause impaired cognitive function, decreased concentration and excessive daytime sleepiness, prolonging hospitalizations and compromising rehabilitation participation. (17,18,19)

Diagnosis of OSA after Stroke :

Randomized trials of CPAP after stroke suggest identifying OSA may be best accomplished with portable devices. The Sleep Apnea Treatment After Stroke (SATS) trial proposed screening with full polysomnography (PSG), but switched to portable monitoring early in the study sue to intolerance and logistical challenges of coordinating an in-laboratory PSG during the acute stroke period.

Treatment of OSA after Stroke :

Treatment with CPAP has the unique potential to improve the recovery from stroke and to reduce the risk of recurrent stroke both indirectly through better control of multiple modifiable risk factors and directly through a variety of proposed mechanisms. It is an effective treatment for OSA, reducing OSA-associated hypertension, atrial fibrillation, cardiovascular morbidity and mortality, exclusive of stroke, and reducing daytime somnolence. CPAP provides a constant, positive pressure to the airway throughout the respiratory cycle, serving to open the upper airways to prevent narrowing or collapse. The impact of early treatment of OSA with CPAP on neurologic recovery after stroke is just beginning to be studied. Preliminary randomized trials of CPAP therapy after ischemic stroke have shown an improvement in stroke impairment scales, depressive symptoms, motor recovery, sleepiness, and the time until the appearance of cardiovascular events. Other randomized trials have shown no difference. Although results across the studies appear inconsistent, a few conclusions may guide neurologists to initiate CPAP in a stroke patient with OSA. The studies that have shown increased CPAP adherence have demonstrated greater improvements in stroke symptom recovery, while those limited by poor recruitment or adherence have been underpowered to show any significant CPAP benefit (17,18,19).

Treatment with CPAP may also reduce the risk of recurrent stroke in patients with OSA directly. An observational study suggested that treating stroke patients with CPAP prevented recurrent stroke. Stroke patients with moderate to severe sleep apnea (AHI> 20 events/hour) who did not tolerate CPAP showed an increased adjusted incidence of nonfatal cardiovascular events, especially for new ischemic stroke, during a 7-year follow-up period (hazard ratio 2.897; 95% CI 1.11-7.71) compared to those who tolerated CPAP and compared to patients with mild disease (AHI 10-19 events/hour) or without OSA (AHI< 10 events/hour).

Conclusions :

1. Evidence that sleep apnea is a risk factor for stroke is strong and its prevalence among stroke survivors is high. After stroke, OSA may be an underappreciated risk factor for both poor functional outcome and stroke recurrence.
2. Until better evidence accumulates, providers are left having to decide how aggressively to pursue a diagnosis of OSA and treatment with CPAP in patients who have had a stroke.
3. Current studies suggest that treatment with CPAP may be beneficial in patients after stroke.

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Sleep and Endocrinology:
Hypothalamic-pituitary- adrenal axis and growth hormone

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ABSTRACT

The supra-chiasmatic nucleus (SCN) is the primarily biological clock determining the circadian rhythm. The neurons of the nucleus making this clock have inherent rhythm and set in biological day and night. These periods usually corresponds to day/night, and indirectly to sleep-wakefulness cycle, in most individuals. Retino-hypothalamic tract carrying photic information from the retina provides the most important input to maintain the inherent rhythm of the SCN. The rhythmic discharges from the SCN to various neurons of the central nervous system, including pineal gland and hypothalamus, translate into circadian rhythm characteristic of several hormones and metabolites such as glucose. As a result there is a pattern of hormonal changes occurring during cycle of sleep wakefulness. Most characteristic of these changes are surge of melatonin with biological night, surge of growth hormone-releasing hormone (GHRH) at onset of sleep and surge of corticotropin- releasing hormone (CRH) during late part of the sleep. The cause and effect relationship of the hypothalamic releasing hormones and their target hormones on various phases of sleep including initial non rapid eye movement (NREM) phase at onset of sleep, and rapid eye movement (REM) phase near awakening, is an upcoming research area. Sleep electroencephalogram (EEG) determining the onset of NREM and REM sleep is an important tool complimenting the studies assessing relationship between various hormones and phases of sleep. The slow wave activity (SWA) corresponds to the intensity of sleep at its onset during the biological night of an individual. Besides, GHRH and CRH, several other peptide and steroid hormones such as growth hormone (GH), its secretagogues, ghrelin, neuropeptide Y, estrogen and dehydroepiandrosterone sulfate are associated or have the potential to change phases of sleep including initial slow wave-NREM sleep.

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The sleep disturbances with aging and depression are common and reflected as impaired SWA in the EEG and early morning awakening. Recognition of sleep associated endocrine changes has resulted into a number of studies assessing sleep promoting effect of compounds such as melatonin and CRH antagonists. These studies have potential implications for patients with sleep disturbances associated with depression, aging and those having frequent night shifts.

The misalignment of normal circadian rhythm and sleep wake cycle, as observed during night shift work, has been recognized to have important adverse consequences. These include difficulty in maintaining sleep during day time, and metabolic derangement such as obesity, impaired insulin secretion and associated glucose intolerance. Understanding of sleep-endocrine physiology is clinically important to deal with these adverse consequences.

OVERVIEW

On an average, humans spend one-third of their life in sleep. The adverse effects of misaligned sleep wake cycle, as in night shift worker, has given an impetus to the research related to the physiology of sleep and associated endocrine disturbances. The inherent aspects of this research are the factors determining normal sleep wake cycle and changes secondary to this. The hormone system coupled with nervous system control virtually all the major activities of the body. It is therefore natural to expect these two to have effect on sleep wake cycle. The purpose of this review is to present salient aspects of sleep physiology in relation to endocrine system. The information in this review was presented in the annual meeting of the National Academy of Medical Sciences held at Jodhpur, AIIMS, in 2013, and is based on two excellent reviews by Morris *et al.* (1) and Steiger (2) and other published data.

Sleep wake cycle and its integration with endocrine system :

The normal sleep wake cycle is influenced by circadian rhythm, hormonal changes and pressure for sleep after long working hours. Its architecture includes repeated phases of NREM and REM sleep. It begins with NREM sleep, which is reflected in the EEG as SWA.

The circadian system is primarily governed by the SCN located in the anterior hypothalamus with projections to the various parts of the brain. Inherent rhythmicity of the neurons in this nucleus with its downstream effect on hormones and autonomic nervous system determines the biological day and night. The biological day and night reflect phases of activity and inactivity respectively. The SCN entrained by solar day and night is responsible for biological day and night. Retino-hypothalamic tract helps in the integration of internal circadian system with external environment. This tract conveys the important information from external world through photic stimuli on the ganglion cell of retina to the SCN. Thus,

the pulsatility of SCN can be entrained by external environment. Other factors, which can entrain SCN, are body temperature and metabolites.

The circadian rhythm leads to a predictable form of change in hormone system. Some of these hormones themselves can have overriding effect on sleep wake cycle. The salient example of this is melatonin hormone, which is released during biological night but can be used to reset alteration in sleep wake cycle induced through jet lag or night shift. Another example related to use of information regarding endocrine changes during sleep is in the treatment of sleep disturbance observed in depressed and aged individuals. Attempts are on in various laboratories assessing the use of sleep associated hormones or their antagonists in modulating sleep disturbances.

Sleep and hormones

(A) Hypothalamic pituitary somatotroph axis

GHRH, somatostatin, GH, ghrelin and other GH secretagogues are important sleep modulating hormones (1,2). Normally, there is a surge of GH at the onset of sleep. In males there is only a single peak, but females have additional peaks of GH in the middle of the night. The sleep has a greater influence on GH than the circadian rhythm, which is indicated by the occurrence of GH surges irrespective of the onset of sleep during day or night. Its occurrence at multiple points during night, coinciding with SWA, further support the less important role of circadian system in explaining the association of GH surge with sleep (1,2). GHRH is the chief regulator of the GH surge and its slow wave sleep (SWS) promoting effect has been confirmed both by central and intravenous/intranasal administration of GHRH peptide in experimental animals as well as in human volunteers respectively (2-6). Though the hormone had no effect in the early morning in young subjects, it had a sleep promoting effect in normal elderly with prolongation of first NREM and decrease in the number of awakenings (2). Interestingly, a sexual dimorphism was observed in patients with depression. In males, GHRH inhibited cortisol during the second half of the night (7). However, in females where cortisol levels increased during second half, along with sleep impairing effect (2). This indicated antagonist action of GHRH on CRH-cortisol during sleep wake cycle in males but it has synergistic effect in females. In contrast to GHRH, no consistent pattern of change in sleep architecture has been reported on GH administration. This indicates the primary role of GHRH, rather than GH, in normal sleep architecture (8).

Ghrelin is hunger stimulating hormone produced from cells lining the fundus of the stomach. Besides, it is an endogenous GH secretagogue stimulating GH release. Weikel *et al* showed SWS promoting effect of intravenous administration of ghrelin in young males (9). However, in contrast to GHRH,

cortisol level increased after Ghrelin. The effect of synthetic GH secretagogues like GH-releasing peptide-6 and hexarelin are also under investigation. Similarly, galanin peptide, which is wildly distributed in brain, and which stimulated GH, can also have SWS promoting effect in normal males (10). Ghrelin, synthetic GH secretagogues and galanin deserve further investigation for their possible role in altering sleep.

Somatostatin and octreotide lead to impairment in NREM/SWS sleep (11). The effect of somatostatin is more marked in the elderly than the young subjects. Steiger *et al.,* suggested that somatostatin antagonist may be of help in the modulation of sleep disturbances in elderly males (2). The fact that somatostatin antagonist arginine increased SWS in elderly male indicated that the balance of GHRH/somatostatin in favour of GHRH would help sleep promotion in elderly.

(B) Hypothalamic pituitary adrenal axis

CRH, ACTH and cortisol are hormones, which are associated with sleep, especially at the termination of biological night or near awakening (1,2). It is well known that circadian system has strong influence on serum cortisol levels in human with level peaking in the biological morning and low in the early part of the biological night. These circadian rhythms are produced through hormonal and neuronal pathways. Projections from SCN and paraventricular nucleus are important for release of CRH. Neuronal signals to the intermediate lateral column of the spinal cord, and then to the adrenal cortex, result in increase in serum cortisol. CRH seems to be the prime regulator of sleep architecture, followed by corticosteroids (1,2). The effect of CRH seems to be reciprocal of GHRH, because in animal and experimental studies CRH administration reduced SWS, prolonged sleep latency and increased REM sleep (12,13). Besides, CRH administration in young volunteers also decreased GH surge along with increase cortisol after the sleep onset. The disturbing effect of CRH on sleep increases with aging (14). The importance of CRH in sleep disturbance is also indicated by the fact that patients with depression and elderly subjects have increased cortisol activity in the late half of the night, especially before wakening. It is interesting to recall the sexual dimorphism in the action of GHRH in females. Unlike males, GHRH in females had synergistic effect on CRH. The increased CRH/cortisol activity in the females, elderly and patients with Cushing's disease could explain the high prevalence of depression and sleep disturbances in these subjects. Interestingly, apart from decreasing SWS, CRH administration in human led to decrease in REM sleep also (2).

Theoretically, the effect of increased CRH described above could also be due to increases in the ACTH and cortisol activities. All the three hormones i.e., CRH, ACTH, GH lead to suppression of REM sleep. However, pulsatile

administration of synthetic ACTH analogue had no effect on cortisol and REM activity (2). Steiger *et al* suggested that CRH induced decrease in REM sleep in human could reflect a direct effect of cortisol (2). In fact, cortisol administration led to reduced REM sleep in young normal males (2). The effect of acute and chronic cortisol administration were found to be different (2). The acute administration of steroids resulted in increase SWS and GH release in elderly and young controls as well as in patients with depression (2,15,16). On the other hand, chronic glucocorticoid therapy resulted in decreased REM sleep latency, increase REM sleep density (17). As serum cortisol levels were maximum in the early morning hours, when the arousal from sleep also occurred, it is highly unlikely that cortisol determined the circadian rhythm of sleep.

Realizing the importance of CRH in sleep disturbances, research is ongoing on various CRH antagonist molecules in sleep disorders (2). CRH antagonist like alpha helical CRH and astressin could decrease the stress induced changes in sleep in experimental animals (2). Similarly, a four weeks trial with CRH receptor 1 antagonist (NBI-30775) led to increase in the SWS and decrease number of awakenings. Paradoxically REM was shown to be increased in these studies (2,18).

Misalignment of sleep with circadian rhythm and endocrine influences

One of the important functions of the circadian system is to maintain homeostasis of essential parameters such as body weight, appetite and balance of autonomic nervous system activity at various points of the day according to the requirement of activity. The system works in close association with biological day and night in most individuals. Long term deviation in the close harmony between circadian rhythm and sleep wake cycle has recently been recognized to result in several adverse consequences. A typical example of misalignment is seen in night shift workers like health professionals. Figueiro and White recently reviewed data on the effect of rotating night shift (19). Circadian disruption resulting from rotating shift work was associated with increased risk for metabolic syndrome, diabetes, cardiovascular disease and cancer (19). Marquezea *et al* investigated the relationship between night shift and body weight in 446 nursing staff (20). Logistic regression analysis showed that more time spent during night shift was associated with development of overweight/obesity (20). The increased risk of obesity associated with night shift work might translate into glycemic dysregulation. Monk *et al*., reported higher risk of diabetes among 1111 retired night shift workers aged > 65 years, with odd ratio of two which remained significant even after adjusting for BMI and gender (21). Pan *et al.,* followed 69269 women aged 42-67 years in Nurses' Health Study I (NHS I, 1988-2008), and 107915 women aged 25-42 in NHS II (1989-2007) without diabetes, cardiovascular disease, and cancer at baseline (22). The results showed that an

extended period of rotating night shift work was associated with increased risk of type 2 diabetes in women which was partly mediated through body weight (22). Caciari *et al.,* studied 163 health workers exposed to night work and compared with 252 similar controls who were not exposed for alteration of some cardiovascular risk parameters (23). Night workers had clinically significant changes in serum total cholesterol, HDL cholesterol and triglycerides. Puttonen *et al.,* studied associations between shift work with the metabolic syndrome in employees of an airline company (24). Findings of the cross-sectional study suggest that metabolic syndrome diagnosed by International Diabetes Federation (IDF) criteria and the National Institute of Health Adult Treatment Panel III (NCEP) guidelines was more prevalent among former male shift workers than current day workers who had never worked in shifts with Odds ratio of approximately 2.0. Currently, the pathophysiology of the disturbances in cardio metabolic system and glycemic dysregulation in misalignment of sleep with circadian rhythm is not very clear. However, alteration in GH, cortisol and their influence on insulin-glucose system would be a subject of further study.

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Determination of Satisfaction Index as a tool in evaluation of CME Program

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ABSTRACT

Continuing Medical Education is an indispensable part of physician's learning. Well designed program based on andragogy principles can enhance learning by motivating the learner and providing platform to encourage self directed learning. The present study aimed to explore the impact of program "NAMS-AIIMS Regional Symposium on Sleep Medicine" in changing the behavior and attitude of participants using "Satisfaction Index" and descriptive analysis of responses as evaluation tools for program effectiveness. This descriptive cross sectional study captured the response of participants through a pre-tested and validated questionnaire administered at the end of symposium. The result showed almost equal sex distribution (M: F- 27: 34) with majority being UG students (86%). Reliability of data showed Cronbach's Alpha of 0.98 indicating high reliability. Satisfaction index (SI) calculated as per WHO Educational Handbook for Health Personnel showed highest satisfaction for conducive environment of symposium (87.87 %) followed by provision for time to seek clarifications (87.21%), provision of appropriate Learning Resource material (85.90 %) and handling of critical comments by organizers (85.57%). Descriptive analysis showed majority responses as highly positive to our questionnaire with suggestions for more such activity, inclusion of clinical cases and other aspects of practical relevance.

Key words : evaluation, program, satisfaction index, Kirkpatrick Model, student satisfaction, adult learning, Knowles Theory.

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INTRODUCTION

Education is a purposeful activity to bring about desired behavioural changes in knowledge, attitudes and skills among the learner with an aim to benefit the society of which learners are an integral part. Medical education is the systematic process to bring about these changes enabling the learner to practice medicine efficiently and provide need based health care to the society.

Continuing Medical Education (CME) is an integral part of a health professional's training and aims to keep him updated with newer technology and knowledge for effective and efficient clinical practice. Since these activities are a systematic way of imparting knowledge and skills, it becomes imperative that preceptor(s) are able to evaluate the program for its outcome and impact on learner.

Donald Kirkpatrick, Professor Emeritus at the University of Wisconsin, US and past president of the American Society for Training and Development (ASTD), first published his Four-Level Training Evaluation Model in 1959, in the US Training and Development Journal. Since then Kirkpatrick model has become the most common tool for evaluating a training program or educational activity (1).

The model was subsequently updated in 1975, and again in 1994, when Kirkpatrick published his best-known work, "Evaluating Training Programs." The desired levels are- Reaction, Learning, Behavior and Results (Outcomes). While reactions can be evaluated by survey questionnaire and learning can be assessed using pre-post intervention test or a similar retrospective questionnaire, behaviour and results (outcomes) are long term levels and can only be evaluated over an extended period of time. Out of these, results (outcomes) evaluation is complex, time consuming and challenging. It essentially depends on identifying outcomes, benefits, or final results which are most closely linked to the learning objectives of the training, and designing an effective way to measure these outcomes over an extended period of time. The CME program can be evaluated realistically upto level 1 with the help of a well designed survey.

As part of 53rd Annual Conference of National Academy of Medical Sciences, NAMSCON 2013, a Regional symposium on Sleep Medicine was organized on 25th October 2013. Through this paper we wish to share our experience of the Kirkpatrick's first level of evaluation through measurement of an objective index termed as Satisfaction index.

Aims of the study :

To find out the impact of program "NAMS-AIIMS Regional Symposium on Sleep Medicine" in terms of *reaction* of participants using "Satisfaction Index" and descriptive analysis of responses as evaluation tools for program effectiveness.

Methods :

This descriptive cross sectional study carried out during Regional Symposium on Sleep Medicine as part of the 53rd Annual Conference of National Academy of Medical Sciences consisted of a planned educational activity with well defined learning objectives stated below:

At the end of symposium, participants will be able to :

1. demonstrate awareness of magnitude of problems of sleep in Indian scenario, and the association with the increasing prevalence of Obesity in adults and children.
2. comprehend the importance of changes in normal sleep physiology leading to diverse medical disorders in both young and old.
3. demonstrate a thorough understanding of specific disease states associated with sleep disorders.
4. interact with multi specialty biomedical scientists in elucidating causation and consequences of sleep disordered breathing.
5. describe screening approaches and test procedures for the diagnosis of sleep disorders and associated clinical conditions.
6. rationalize and plan the management of OSA.
7. explain the need and emerging roles of sleep labs and comprehensive sleep centers in India.

The educational programme was delivered with the help of live presentations by renowned experts in the field of sleep medicine and was further augmented by distribution of pre-symposium Learning Resource Material (LRM), content-based well planned interactive sessions, problem triggers and facilitating participants' involvement through interaction in non-threatening environment.

Following tools were used for *program evaluation*:

Program Evaluation Questionnaire

a. CME committee of National Academy of Medical Sciences provided a prepared and pre tested questionnaire based on Likert scale.

b. This included following:

i. Demographic details

ii. Part A about symposium planning, utility of working method(s), academic content, and format of symposium

iii. Part B concerned with Gain in knowledge, skills and some additional information needed for further improvement of such activities

c. Satisfaction Index based on data from Part A questionnaire

Formula used for calculating Satisfaction Index is stated below (2):

$$SI = \frac{\{(a \times 1) + (b \times 2) + (c \times 4) + (d \times 5)\} \times 20}{N}$$

Where,

SI is Satisfaction Index : a,b,c,d are number of total responses for the Co-efficient 1, 2, 4 and 5

N= number of total participants

d. Qualitative evaluation based on individual responses of data from Part B. The participants were explained about the aim of the research. They were assured that all information solicited and collated was confidential and self identification entirely optional. The willingness of the participants to answer the questions was obtained. SPSS 17.0 was used for data analysis.

Results

At the start of Symposium, 103 participants registered for the program. ***Sixty one*** participants returned the pre-assessment form, attended all the sessions and were present throughout the academic programme*. They also gave consent to fill the evaluation questionnaire after being briefed about the objective of the survey, confidentiality of the data, and the protected identity of the participants, if willingly provided.

Salient data outcome includes :

1. **Demographics**

   Majority of participants were UG students (n=53; 86 %). Males- 27, females 34

2. **Response rate (relevant to participants*) : 53/61 (86.88 %)**

3. **Satisfaction index: (Table 1)**

Mean score of satisfaction index was 82.47 ± 5.09. Reliability analysis with Cronbach's Alpha was 0.98 showing reliability of all variables.

The participants were requested to rate each statement in a four point rating scale : 1- strongly disagree; 2 – disagree; 4 – agree; 5 – strongly agree. A satisfaction index (SI), having a maximum possible score of 100 was calculated for each statement rated, considering the value assigned to each point in the scale and the number of participants rating the statement under reference. A total of twenty-one statements were analysed.

It is gratifying to note that none of the twenty-one statements was rated with a satisfaction index of less than 60%, the internationally accepted norm for an unsatisfactory outcome. Therefore, arbitratory cut-off points (SI above 85% and SI below 80%) were used for further analysis.

There were four statements with SI more than 85%. These included :

Statement	*Satisfaction Index*
i) I found the documents provided of acceptable quality	85.90
ii) Time was provided to seek clarification on issues included in the background documentation	87.21
iii) The general atmosphere of the symposium was conducive to serious work	87.87
iv) The organizers made use of any critical comments I made during the symposium	85.57

Table 1: Program evaluation using satisfaction Index

Sl No	Parameter	Response				Total (A)	Number participated/ responded (B)	Satisfaction Index (A X 20)/B
		1	2	4	5			
1	I received precise information in advance on the aims of the Symposium.	0	2	172	85	259	61	84.91
2	The goals of the symposium appeared to me to be of immediate interest for my academic activities.	0	4	160	95	259	61	84.91
3	The content of the symposium dealt with issues I generally encounter in my academic assignments	0	32	152	35	219	61	71.80
4	Considering my other professional commitments, the symposium Scheduling was appropriate.	2	22	136	70	230	61	75.40
5	I found the documents provided of acceptable quality.	0	2	160	100	262	61	85.90
6	Time was provided to seek clarification on issues included in the background documentation	0	8	108	150	266	61	87.21
7	The working methods used during the symposium encouraged me to take an active interest in the session themes.	0	6	128	120	254	61	83.27
8	The pace of presentation of the subject content was appropriate.	0	20	124	100	244	61	80.00
9	The general atmosphere of the symposium was conducive to serious work.	0	2	136	130	268	61	87.87
10	The organisers gave me opportunity for critical comment.	2	12	156	75	245	61	80.33
11	The organizers made use of any critical comments I made during the symposium	2	32	192	35	261	61	85.57

These four statements reflected the quality and content of learning resource material provided to the participants; time provided to seek clarification on issues included in the background document; ambience of the symposium considered conducive to serious work; and use of any critical comments made during the symposium.

Overall, these four statements reflect the planning, conduct, and content of the workshop.

The statements with SI below 80% were :

Statement	***Satisfaction Index***
i) The content of the symposium dealt with issues I generally encounter in my academic assignments	71.80
ii) Considering my other professional commitments, the symposium scheduling was appropriate	75.40

Least satisfaction was shown for the programme content which dealt with issues related to their academic assignments (71.80 %) followed by symposium scheduling considering other professional commitments (75.4). Indeed this is obviously due to the fact that 86% of participants are under-graduate students, a fact not known at the time of designing the questionnaire.

Friedman's test did not show significant difference between parameter ($\chi 2$ of 3.487 p= 0.968)

Descriptive analysis of Part B is shown in Table 2 :

The table showed **highly positive** responses for *gain in knowledge*, *attainment of new skills, improvement in competencies and a desire for more such symposia on the theme of Sleep Medicine*. Non-responders ranged from 11% for attainment of new skills and 14 % for desire for future workshop to 73% for question pertained to post-graduates preparing for examinations. This reinforces earlier observations pertaining to '*least satisfaction*' under Para A.

Discussion :

Evaluating any educational intervention for its effectiveness on learner is not only desirable but mandatory. The information not only provides feedback about the program but also brings forth the essential pre-requisite to continuously monitor and modify the design of the academic content and process of educational programme. Curran et al have used a retrospective, pre-post evaluation study design comparing identical satisfaction, knowledge and confidence outcome measures for their internet based CME delivery format (3). While these investigators used the mean of the Likert scale score, present study was based on satisfaction index. Moreover, present study was a post symposium evaluation with descriptive responses

Table 2: Descriptive analysis of participant's response Part B

Parameter	Positive	Negative	No response	Salient descriptive comments
Gain in knowledge in respect of clinical management	45	3	13 (21%)	Being a 1st year student, I gained a lot and will read more on OSA Realised the seriousness of Sleep disorders
Attainment of new skills and will you be able to utilize in your practice	44	10	7 (11%)	Developed correlations between various sleep conditions. Acquired valuable information for my future use
Improving in competencies in managing such problems	44	2	15 (24%)	Because of knowledge, broader view of pathophysiology, identifying co -morbidities. I gained foundation of sleep medicine I am new to this topic and hence can't comment
If you are a PG student, has this helped you in preparation for your exams?	10	1	45 (73%)	I am a UG student and hence can't say I am UG student but I think such sessions would help in my exam I am Asst professor but will help me in preparing for teaching UG and PGs
What additional topic areas should be included in a symposium in future?	6	5	31 (50%	Practical aspects and case based approach - it was only a theoretical discussion. Elaboration of medical terms beforehand Inclusion of Indian scenarios. More prevalent disorders with scope of research
What topics/subjects to be deleted or under-emphasized if this symposium is to be repeated in future	24	5	32 (50%)	Pharmacology and Bio-molecular portion Topic which were of very high level No deletion required – all are relevant
Is one workshop on this subject sufficient?	21 (yes)	29 (No)	11	At least for motivation otherwise update always required More is required as the topic is very vast and some other sleep conditions not covered
Would you like more workshops in future on this theme	46	6	9 (14%)	Yes, but with new ideas/topics/modifications With more details and new development More workshop on different themes would be appreciated
Suggest any improvement	23	15	23	Interaction, more videos It should be 2-3 day workshop
Deficiencies in planning, conduct or any other academic/organizational aspect of workshop	24	9	28 (45%)	Everything was good Workshop was properly conducted, there were no deficiencies to draw my attention. More experts from the field should have been invited for better quality discussion

about gain in knowledge, skills and competencies. Participants showed highly positive responses in these areas. They also showned their eagerness to participate in such educational activities in future.

Karaman evaluated the perception of nurses toward distance CME using survey method in a quantitative study and found positive response with significant difference among nurses who used computer frequently (5). The present study showed that goals which are of immediate interest, provision of conducive environment, and time provided for the clarifications, were the parameters considered highly satisfying by the participants. Arminia also found that clarity of educational objectives and advantage of the program format yield higher score for satisfaction (6). Observations in the present study also conform to the principles of adult learning that states : 'Adults need to know *why* they need to learn something : Adults need to learn *experientially* : Adults approach learning as *problem-solving*, and Adults learn best when the topic is of *immediate value*' (7). These basic tenets of adult learning are generally endorsed by medical educationists who have elaborated these as follows :

- New facts must relate to the pre-existing knowledge-base so that these get *contextually integrated.*
- Learning is greatly facilitated if the cohesion between new information and its integration with already existing knowledge is *purposeful and meaningful*.
- Learning must be directed to, and applied for, *problem solving*.
- Learners are *motivated* to achieve a higher level of performance if they feel involved and challenged.

It is essential that feedback must be immediate and should be positive to reinforce learning, with suggestions for improving performance and for taking remedial measures to avoid or minimize errors.

A limitation of the present study was lack of comparative analysis between diverse academic status of participants since majority of participants were undergraduates students. It may be argued that further sub-classification of undergraduate students could have been made accordingly to their scholastic level. However, a small sample size of 56 students could not permit further sub-classification to provide any meaningful statistical data. Another limitation is the fact that data reflects only immediate learning as *reaction* and needs long term follow-up for evaluation of *change in behaviour* and *skills* over an extended period of time.

Conclusions:

The study shows that a well planned educational activity with defined learning objectives delivered through experts under favourable environment provides high satisfaction to participants in gaining knowledge, and in imparting skills and competencies. Such well-designed activities motivate participants and encourage them to seek additional academic assignments for their self development, in addition to self-directed learning through internet and other electronic media.

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