

# Approach to a patient with Excessive Daytime Sleepiness

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## Case vignette

A 21 year old girl, college student, was referred to our Sleep Clinic for evaluation of her excessive drowsiness during the day hours.

Her symptoms started at the age of 17 years, when her family noticed that she seemed to need more sleep than her siblings and peers. This would often hinder her daytime functioning as she would be fatigued and “worn out” all the time and needed regular naps to refresh herself. When she avoided the naps, she would have an irresistible urge to sleep which she succumbed to and would doze off anywhere at any time. Recently, she had even burnt herself in one such “attack” where she had “dozed off” while cooking. At 19, she had her first spell of a sudden inability to move that was triggered by laughter. Her speech was slurred and her “knees became weak” for a few seconds, but she did not fall down. Events were unassociated with any alteration in consciousness, headaches, sensory disturbances, cardiopulmonary symptoms, visual disturbances or seizure activity. She also experienced a few incidents where she was unable to move her limbs, talk and “became stiff” for several minutes after waking up from sleep, which were suggestive of sleep paralysis. She attends college regularly but reports struggling academically though she had no history of any learning disorder.

Her sleeping habits indicated an altered sleep-wake pattern. She would usually stay awake until 2 or 3 am watching television or surfing the net and awakened

several times a night by terrifying dreams. On weekdays, she woke up at 8 am for college while on weekends, she preferred to sleep till 10 am. She took 2-3 half hour naps after college i.e between 2 pm to 11pm. These naps were refreshing for her and she remained active for 3-4 hours after each nap. She had 2-3 cups of coffee at college, which did help her to keep her awake and attentive.

She lives with her parents. She was socially not very active but spent time working out in the gymnasium. She drove a car for short distances on a daily basis and reported no motor vehicle accidents.

Her past medical history was unremarkable except for history of tonsillectomy at 14 years of age. Prior to the tonsillectomy, she regularly used anti-histaminics for rhinitis. Thereafter, she had not been on any drugs for any illness.

Her mother was diagnosed with narcolepsy without cataplexy at the age of 17.

She had an overnight polysomnogram 2 years back, which her parents reported gave no explanation for her symptoms. The records of that previous sleep study were unavailable for review.

On examination, she appeared well, with a normal blood pressure. Oropharyngeal examination revealed a Mallampati Score of 1. Findings from her general medical examination, including her cardiopulmonary examination, were unremarkable, with normal heart sounds and no carotid bruits. Neurologic examination showed normal motor strength throughout, with normal reflexes.

A mental status examination showed her to be alert and able to make good eye contact. Her speech and language skills were normal, though she was slightly anxious. Her thought form was unremarkable and thought content lacked any delusional thinking or

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hallucinations. A Mini Mental State Examination revealed no abnormality.

Her PSG findings revealed a reduced sleep latency, increase REM sleep, decreased REM sleep latency (< 20 minutes), increased frequency of awakenings in the form of microarousals and wake time after sleep onset (WASO). A Multiple sleep latency test (MSLT) was done the following morning, and revealed reduced REM sleep latency (3 sleep onset REM periods).

## Hypersomnia

Hypersomnia is characterized by difficulty maintaining alertness during waking hours. The 2nd edition of the International Classification of Sleep Disorders classifies hypersomnias. Narcolepsy due to medical conditions, menstruation-related hypersomnia, behaviorally induced insufficient sleep syndrome, hypersomnia due to medical condition, drug, or substance and secondary to another disorders<sup>1</sup>.

### Insufficient sleep:

A night sleep of 7-8 hours is mandatory for optimal functioning. Insufficient sleep can be due to many reasons, some common ones being poor sleep hygiene, sleep deprivation, shift work, jet lag etc.

### Fragmented sleep:

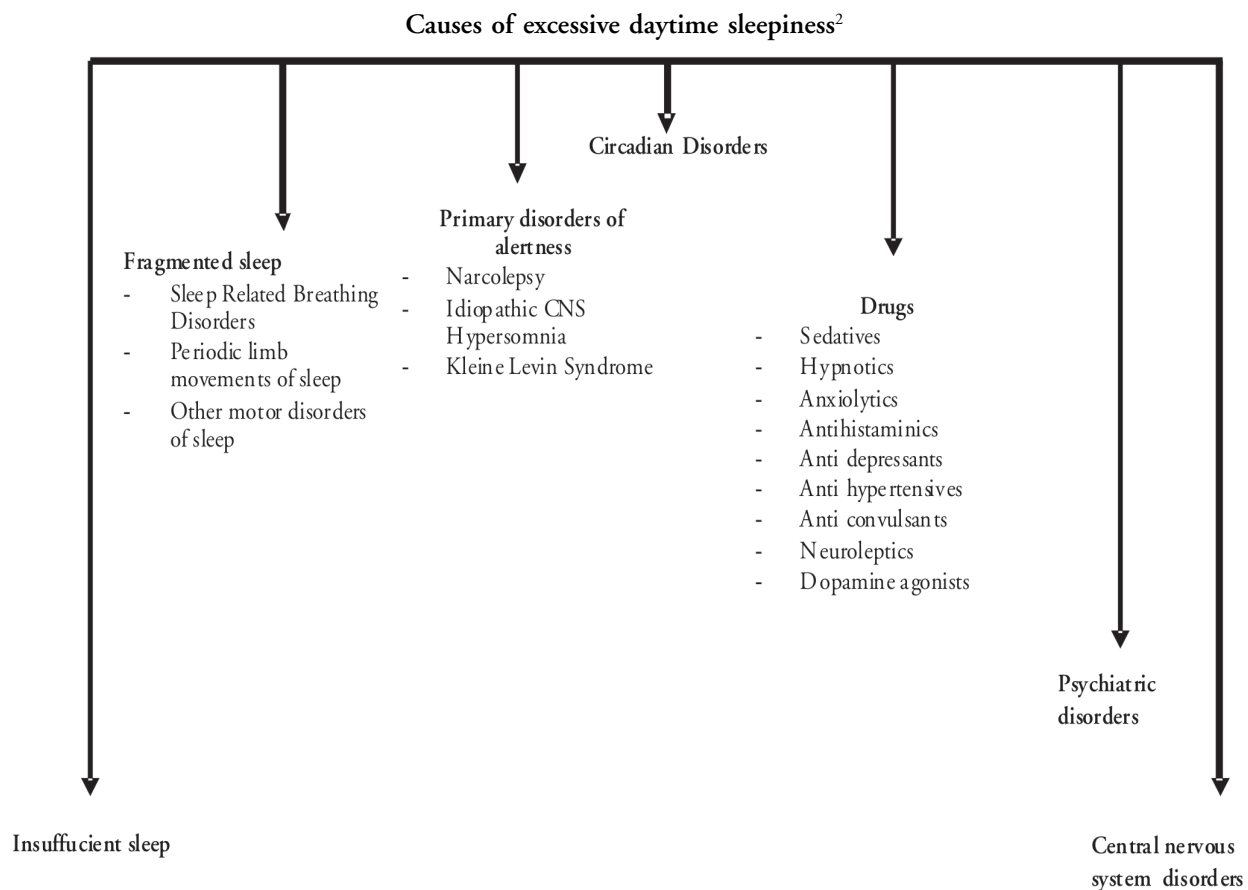
Sleep quality is equally important for a refreshing sleep. Disruption of sleep due to sleep maybe due to various reasons; common ones are discussed below:

#### 1. Sleep Disordered Breathing (SDB):

This category is the most important cause of sleep fragmentation, though underplayed and less known in the general population due to lack of awareness.

Sleep disordered breathing may be from one end of the spectrum representing the mildest form i.e Upper airway resistance syndrome (UARS) to the other end of the spectrum representing severe obstructive sleep apnea.

SDB may be due to the abnormal anatomy, in the



form of crowded oral cavity due to any reason- most common being obesity, crowding of upper airway, collapsibility of the upper airways worsened by the physiological changes during sleep (decreased muscle tone) etc<sup>1,3</sup>. Obstructive sleep apnea can be successfully managed by PAP therapy<sup>1</sup>.

## 2. Periodic Limb Movements of Sleep

Earlier known as nocturnal myoclonus, these repetitive movements in sleep are predominantly seen in the initial part NREM sleep<sup>3</sup>. PLMs are known to be associated with Restless leg syndrome, both are seen in conditions like deficiencies of iron and folate, renal disease, peripheral neuropathy, Parkinsonism and spinal disorders. Caffeine, anti depressants, neuroleptics etc. exacerbate these movements. Dopaminergic agonists are the drugs of choice in these patients. Benzodiazepines, opioids, anti-convulsants and beta blockers may also be used in these patients .

## 3. Other medical conditions

Medical conditions causing pain of any nature such as arthritis, fibromyalgia, spondylosis, cardiac conditions such as nocturnal angina, paroxysmal nocturnal dyspnea, respiratory conditions like COPD, restrictive pulmonary disease, asthma, GI disorders like gastroesophageal reflux disorder (GERD), irritable bowel syndrome (IBS), alcoholism, urinary dysfunction etc are also important causes of fragmentation of sleep. Appropriate management of the medical conditions is beneficial to manage these causes of EDS<sup>4</sup>.

## Primary disorders of alertness

### 1. Idiopathic Hypersomnia

Patients with idiopathic hypersomnia have EDS regardless of the amount of sleep obtained. The nocturnal sleep is normal, and none of the associated features of narcolepsy are present. Naps are generally not refreshing. ICSD-2 Criteria for hypersomnia with long sleep time include EDS almost daily for 3 months, prolonged nocturnal sleep time (more than 10 hours), waking up from nocturnal sleep or naps is difficult, and no other disorder better explains this<sup>1</sup>. The polysomnogram shows short sleep latency (time to sleep onset) and greater than 10 hours of sleep. The MSLT shows a mean sleep latency of less than 8 minutes, and less than 2 episodes of REM.

### 2. Narcolepsy

EDS is the first and most disabling symptom of

Narcolepsy, which is defined as a neurologic disorder characterized by excessive sleepiness in the form of sleep attacks with manifestations of rapid eye movement (REM) sleep physiology during wakefulness (eg: cataplexy, sleep paralysis and hypnagogic hallucinations). Automatic behavior, nocturnal sleep disturbance, visual changes (blurred vision, diplopia, ptosis), memory lapses, associated sleep disorders, obstructive sleep apnea, REM sleep behavior disorder, periodic limb movement disorder etc. may be associated with narcolepsy<sup>5,6</sup>.

### Clinical subtypes of Narcolepsy<sup>7</sup>:

SN	Subtype	Characteristics
1	Narcolepsy with cataplexy with normal hypocretin-1 levels in the CSF.	Normal hypocretin-1 levels are seen in upto 10% of patients
2	Narcolepsy without cataplexy with low hypocretin-1 levels in the CSF.	Low CSF hypocretin-1 levels (< 110 pg/mL) are present in up to 10% to 20% of cases of HLA DQB1*0602-positive narcolepsy without cataplexy <i>HLA DQB1*0602-negative narcolepsy without cataplexy</i> <i>patients generally have normal CSF hypocretin-1 levels</i>
3	Narcolepsy with cataplexy-like or atypical episodes	Low CSF hypocretin-1 levels (< 110 pg/ml) are present in up to 20% of cases
4	Isolated cataplexy	Rare familial cases with early onset
5	Hypocretin gene mutations	Early-onset (6 month of age) narcolepsy with cataplexy due to preprohypocretin mutation has been described

Narcolepsy can be secondary to several causes

### 1. Narcolepsy with cataplexy

- Brainstem lesions
- Immune
- Degenerative
- Infectious
- Inflammatory
- Neoplastic (craniopharyngioma, gliomas, pituitary, and hypothalamic tumors)
- Vascular (stroke or arteriovenous malformations)
- Cerebellar ataxia
- Coffin-Lowry syndrome (possible)
- Hydrocephalus secondary to space-occupying lesions
- Multiple sclerosis (hypothalamic)
- Neiman-Pick type C disease
- Norrie's disease
- Paraneoplastic syndrome (associated with anti-Ma2

antibodies)

- Sarcoidosis (hypothalamic)
- Tumors (hypothalamic)
- Viral illness (unspecified)

## 2. Narcolepsy without cataplexy

- Head trauma
- Multiple sclerosis
- Multiple system atrophy
- Myotonic dystrophy
- Parkinson disease
- Prader-Willi syndrome

## 3. Narcolepsy and sleep apnea (*Sleep onset REM periods and excessive sleepiness persist after adequate therapy of sleep apnea*)

- Myotonic dystrophy
- Prader-Willi syndrome

Several medicines and substances used in day to day clinical practice may cause drowsiness and are listed in the table below.

**Medications and substances commonly associated with sleepiness**

Medications	Substances of Use/Abuse	Withdrawal of substances
Alpha1-adrenergic blockers	Alcohol	Amphetamine withdrawal
Alpha2 agonists	Cannabis	Caffeine withdrawal
Anticholinergic medications	Narcotics	Cocaine withdrawal
Anti-epileptic medications		Abrupt discontinuation of Modafinil
Anti-psychotics		Abrupt discontinuation of stimulants
Antihistamines		
Anxiolytics		
Beta-adrenergic blockers		
Benzodiazepines		
Dopaminergic agents		
Hypnotics		
Opiates or narcotics		
Selective serotonin reuptake inhibitors		
Tricyclic antidepressants		Source: <sup>2</sup>

## Evaluation of a patient with EDS:

A thorough clinical history differentiating tiredness and fatigue from sleepiness, followed by a detailed examination is the first step in the evaluation.

## Tools for measuring EDS

1. **The Stanford Sleepiness Scale** (Glenville M; 1978): This Likert scale measures sleepiness over time. It is particularly useful to study sleep deprivation, sleep fragmentation and circadian rhythms. Scores on SSS requires standardization to remove the discrepancy among subject ratings<sup>9</sup>.
2. **The Karolinska Sleepiness Scale** (Kaida K, 2006): This is a 9 point is also a Likert Scale (1= very alert to 9= very sleepy) which measures the level of drowsiness subjectively in a patient complaining of EDS <sup>10</sup>.
3. **The Epworth Sleepiness Scale** (Johns, 1991): This eight item questionnaire measuring subjective sleepiness has scores from 0 (not sleepy) to 24 (excessive sleepiness). A score of >10 is suggestive of sleepiness and >15 suggests excessive daytime sleepiness. ESS has a high sensitivity (93.5% - 97%) and specificity (100%) <sup>11</sup>.
4. **Visual Analogue Scale (VAS)**: is a horizontal line 100mm long that represents the two extremes from "very alert" to "very sleepy". The VAS is the distance between the patients mark on the line and the extreme end. The VAS requires standardization of scores <sup>13,14</sup>.
5. **Sleep -Wake Activity Inventory**: is a 35 item scale that has subscales enquiring about sleep habits and disorders. It can assess several aspects of the sleep. The patient is tested at random intervals of a few seconds. A "lapse" in the performance is said to occur when the reaction time is greater than 500 msecs. Currently, there are no studies to prove a standardized measure of sleepiness based on the reaction time.
6. **Infrared Reflectance Oculography during a Vigilance test-** This test based on infrared oculography, is a relatively newer computer based test that takes 10-15 minutes to administer. A frame with the prescription glasses also includes tiny infrared transducers with a microprocessor. Though it has not been widely used, studies suggest it to be a promising test<sup>12,15</sup>.
7. **Video Camera Methods for detecting Eyelid Closure- PERCLOS**: This technique measures eyelid closures,

which are stronger and longer than average blinks and more prolonged eyelid closures. Position of the eyelids and pupil size can also be measured by this technique. This was mainly developed to detect sleepiness or drowsiness in drivers<sup>12</sup>.

#### 8. Other Oculometric Tests <sup>12</sup>

- **Pupillary Unrest Index:** Is a sensitive test as it varies with the time of the day and increases with sleep deprivation.
  - **Saccadic Eye Movements:** The velocity of the saccades reduces with sleep deprivation.
  - **Pupillary reflex:** Increased latency of the light reflex and the consensual light reflex is seen in sleep deprived patients.
9. **Actigraphy:** An actigraph is an ambulatory activity monitoring device that is placed on the wrist of the patient, like a watch. It is used for sleep assessment in clinical sleep research, and as a diagnostic tool in sleep medicine, especially in patients with insomnia and hypersomnia <sup>14, 15, 16</sup>.
10. **Sleep Diary/ Log:** During clinical evaluation, a sleep log enables the physician to see the sleeping patterns and sleep habits of the patients<sup>17</sup>.
11. **Screening Blood Tests:** Screening for anemia, drug intoxication and other medical causes of EDS can be ruled out.
12. **Psychiatric Evaluation and Psychological Testing:** In patients where mood disorders, psychosis, conversion

disorders or malingering is suspected ancillary evaluation is required.

### Polysomnographic Evaluation:

13. **Overnight Polysomnogram:** An overnight polysomnogram is indicated in patients with excessive daytime sleepiness to rule out conditions like sleep disordered breathing, periodic limb movements of sleep etc. which may be causing the daytime somnolence.
14. **Multiple Sleep Latency Test (MSLT):** is a test designed to check on a patient's propensity to fall asleep at regular intervals. This test is diagnostic of narcolepsy, which is a major cause of EDS, where a mean sleep latency of 8 minutes or less is observed with 2 or more sleep onset REM periods (SOREMP's)<sup>18,19</sup>.
15. **Maintenance of Wakefulness Test (MWT):** This test measures the propensity of a person to stay awake. The 40 minute protocol comprising of 4 trials separated by 2 hours. The latency of sleep onset is recorded during this test. Healthy or alert individuals will not fall asleep during this test <sup>12, 18, 19</sup>.
16. **Osler's Test:** This alternative to the MWT was proposed in 1997 as a simpler and cheaper modification. The patient sits semi reclined in a chair and is supposed to push a button following a flash of light that appears at a regular interval of 3 seconds. Failure to push the button for 7 consecutive stimuli is said to be diagnostic for the patient being asleep<sup>12,18</sup>.

### Differential Diagnosis

#### Common and important causes of excessive daytime sleepiness (EDS) <sup>5,8,12</sup>

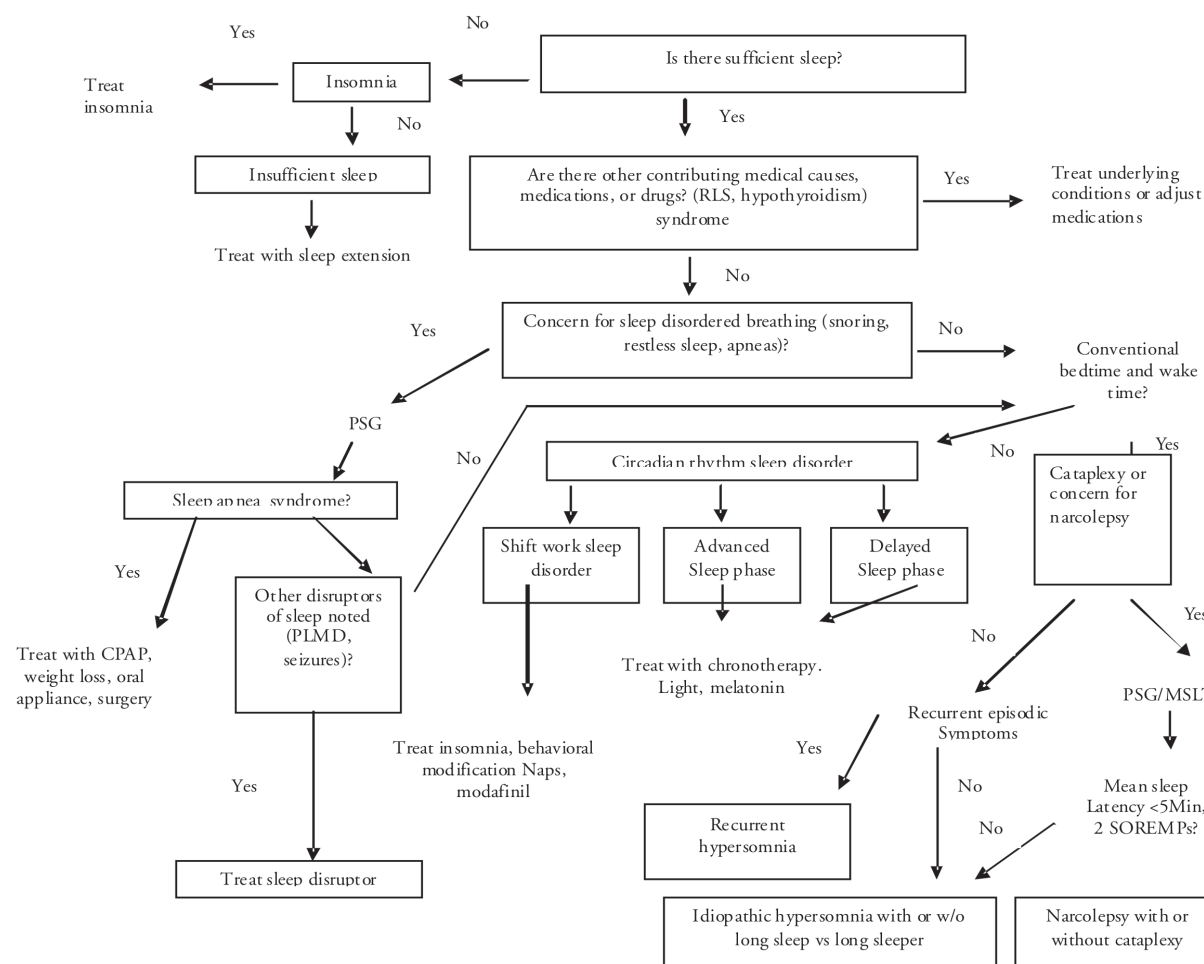
Case of EDS	Clinical history	Treatment
Insufficient sleep time	<ul style="list-style-type: none"> <li>▪ Inadequate amount of sleep</li> <li>▪ Poor sleep "hygiene", such as irregular sleep and wake times</li> <li>▪ Many forms of insomnia can impair night sleep and have daytime consequences</li> </ul>	<ul style="list-style-type: none"> <li>▪ Increase sleep time</li> <li>▪ Improve sleep hygiene / educations about appropriate sleep behaviors</li> <li>▪ Specific therapies based on the type of insomnia may be used e.g. relaxation techniques etc.</li> </ul>
Sleep apnea	<ul style="list-style-type: none"> <li>▪ Loud snoring, gasping or cessations of breathing (apnea) during sleep</li> <li>▪ Upper airway abnormalities</li> <li>▪ Use of sedatives / alcohol</li> </ul>	<ul style="list-style-type: none"> <li>▪ Weight loss, avoiding sedatives</li> <li>▪ Positional therapy (i.e. avoid sleeping supine)</li> <li>▪ Continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BIPAP)</li> <li>▪ Dental appliance</li> <li>▪ Surgery (less commonly)</li> <li>▪ After these treatments are implemented, modafinil may be useful adjunct</li> </ul>
Narcolepsy	<ul style="list-style-type: none"> <li>▪ Must have daytime sleepiness</li> </ul>	<ul style="list-style-type: none"> <li>▪ Scheduled naps</li> </ul>

	<ul style="list-style-type: none"> <li>▪ Cataplexy (loss of muscle tone with emotional stimuli) is pathognomonic</li> <li>▪ Sleep paralysis</li> <li>▪ Hypnagogic hallucinations</li> <li>▪ Fragmented nocturnal sleep</li> </ul>	<ul style="list-style-type: none"> <li>▪ For excessive daytime sleepiness (EDS) : modafinil, stimulants</li> <li>▪ For cataplexy : sodium oxybate, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine</li> </ul>
Idiopathic hypersomnia (IH)	<ul style="list-style-type: none"> <li>▪ Despite adequate sleep time, prominent sleepiness without other rapid eye movement (REM) sleep related features of narcolepsy</li> <li>▪ Occasionally associated with Raynaud's phenomenon</li> <li>▪ Sleep "drunkenness" is a common feature</li> </ul>	<ul style="list-style-type: none"> <li>▪ Stimulants and modafinil may be helpful</li> </ul>
Recurrent hypersomnia (Kleine-Levin Syndrome)	<ul style="list-style-type: none"> <li>▪ More commonly seen in young males</li> <li>▪ Episodes of severe somnolence that lasts day to weeks, and recurs weeks or months apart</li> <li>▪ Cognitive and behavioural disturbances, including confusion, binge eating, hypersexuality</li> </ul>	<ul style="list-style-type: none"> <li>▪ Lithium may be helpful in reducing attacks</li> <li>▪ Stimulants and modafinil may be useful in symptomatic management</li> </ul>
Circadian Rhythm Disorders	<ul style="list-style-type: none"> <li>▪ Shift work</li> </ul>	<ul style="list-style-type: none"> <li>▪ Sensible scheduling practices</li> <li>▪ Light therapy</li> <li>▪ Modafinil</li> <li>▪ Melatonin may be useful in the blind</li> </ul>
Restless legs Syndrome (RLS) & Periodic Limb Movement Disorders (PLMD)	<ul style="list-style-type: none"> <li>▪ Restless feeling in legs that occurs at rest at night and resolves with movement</li> <li>▪ Leg jerks or kicking during sleep associated with fragmented sleep</li> <li>▪ RLS is often associated with increased arousal but higher doses of dopaminergic agonists have been associated with sleepiness particularly in Parkinson disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Address reversible causes e.g. iron deficiency</li> <li>▪ Minimize high dose dopaminergic agonists</li> <li>▪ Ensure upper airway resistance is not contributing to arousals</li> </ul>
Neurological conditions	<p>Commonly associated with sleepiness:</p> <ul style="list-style-type: none"> <li>▪ Parkinson's disease</li> <li>▪ Other neurodegenerative disorders</li> <li>▪ Multiple sclerosis</li> <li>▪ Stroke</li> <li>▪ Epilepsy</li> <li>▪ Neuromuscular disorders</li> <li>▪ Structural brain disorders e.g affecting midline projecting systems, bithalamic, or bi cortical</li> </ul>	<ul style="list-style-type: none"> <li>▪ Management of underlying neurological condition</li> <li>▪ Stimulants and modafinil may be helpful</li> <li>▪ Treatment of apnea may be particularly important as there is an increased incidence in many of these conditions</li> </ul>
Medical conditions	<p>Commonly associated with sleepiness :</p> <ul style="list-style-type: none"> <li>▪ Respiratory disorders e.g chronic obstructive pulmonary disease (COPD), asthma</li> <li>▪ cardiac: congestive heart failure</li> <li>▪ renal : chronic renal failure</li> <li>▪ rheumatologic : arthritis, inflammatory disorders e.g. lupus</li> <li>▪ malignancy hepatic : liver failure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Management of underlying medical condition</li> <li>▪ Avoid use of sedating therapies where possible</li> </ul>



Psychiatric Disorders	<ul style="list-style-type: none"> <li>▪ Mood disorders</li> <li>▪ Anxiety disorders</li> <li>▪ Schizophrenia and other psychotic disorders</li> </ul>	<ul style="list-style-type: none"> <li>▪ Management of underlying psychiatric condition</li> <li>▪ Choice of psychoactive medications that minimize sedation or preferentially enhances alertness where possible</li> </ul>
Medication-induced somnolence	<ul style="list-style-type: none"> <li>▪ Benzodiazepines</li> <li>▪ Barbiturates</li> <li>▪ Other "sleeping pills"</li> <li>▪ Antidepressants</li> <li>▪ Antipsychotics</li> <li>▪ Over the counter agents such as antihistamines</li> </ul>	<ul style="list-style-type: none"> <li>▪ Minimize or stop the offending medication where possible</li> <li>▪ Appropriately time medications</li> <li>▪ Institute specific therapies for underlying sleep disorders</li> </ul>

### Approach to Management of EDS <sup>2</sup>



### Consequences of excessive sleepiness

Consequences of excessive sleepiness include a greater risk of accidents, both due to the disorder itself and the drug effects (vehicular, industrial, or household), increased absenteeism, reduced work productivity, poor academic performance, mood disorder (depression or

irritability), and impaired interpersonal relationships. All these ultimately lead to a poor quality of life <sup>3</sup>.

### Treatment modalities

#### Behavioural therapy

Patient, caregiver and family counseling is a must on the

importance of sleep, sleep hygiene practices, behaviors affecting sleep and risks associated with the daytime somnolence. Patient should be introduced to relaxation techniques for sleep induction. The importance of pharmacotherapy should be emphasized and treatment seeking behavior should be promoted. For underlying psychiatric conditions, psychotherapy and counseling sessions should be promoted as an adjuvant to the pharmacotherapy. Dietary habits and physical exercise should also be discussed.

### Scheduled naps

Though sleeping during the day is not promoted. However, if the patient cannot resist sleeping, he/she may take 1-2 scheduled naps a day, each not exceeding 15-20 minutes. This is not the primary line of treatment but may be an adjuvant to pharmacotherapy in patients of narcolepsy.

### Role of surgery in OSA

Various surgical procedures have been used to treat OSA. None other than tracheotomy have been shown to be consistently effective. The most common surgery for OSA is uvulopalatopharyngoplasty (UPPP); other surgical modalities are : Laser-assisted uvulopalatoplasty, Palatal implants, Radiofrequency tissue ablation, Nasal surgery and Trans-nasal insufflation. These surgeries have little role in the treatment of OSA.

### Pharmacotherapy:

1. **OSA:** No drug has shown efficacy better than nasal PAP therapy. Mirtazapine and Donepezil have been tried in OSA though with little success.

2. **Narcolepsy:**

**Caffeine:** in the form of sodas and coffee may provide temporary relief in sleepiness.

**CNS stimulants:** are the mainstay of treatment. These increase wakefulness, vigilance and performance.

The table below lists these medications with their side effects.<sup>6,2</sup>

### Nasal PAP therapy for OSA

Although there is clearly a significant impact of CPAP on excessive daytime sleepiness (EDS), it may still persist in a significant proportion of patients. Other treatment modalities which contribute are: weight loss, positional therapy, oral appliances (mandibular advancement) and upper airway surgery (UPPP), treatment of ENT conditions like congestion, sinusitis etc.<sup>22</sup>

Table showing medication used in narcolepsy

Medication	Dose (mg)	Maintenance Dose (mg/day)	Regimen	Side effects
Modafinil	100-200	100-400	QID, BD	Headache, GI irritability, Nausea
Methylphenidate	5, 10, 20	20-60	QID, BD	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse
Methylphenidate extended release	10, 20, 30 SR, 10,	20-60	QID, BD	Headache, tachycardia, arrhythmia, anorexia, weight loss, dependence and abuse
Amphetamine	5, 7.5, 10, 12.5, 15, 20, 30	10-60	QID, BD	Headache, tachycardia, arrhythmia, anorexia, weight loss, hypertension, dependence and abuse
Dextroamphetamine	5, 10, 15 SR	10-60	QID, BD	Anorexia, Weight loss, headache, tachycardia, behavioural change, seizures
Sodium Oxybate	2.25-4.5 in 4.5-9 ml fluid	2.25-4.5	HS	Confusion, impaired walking, exacerbation of sleep walking, hallucination, psychosis, respiratory depression, abuse.

### Conclusion

EDS impacts significantly all spheres of functioning it can result in jeopardizing employment, lifestyle, safety and relationships. It is necessary that a meticulous history and management of these be done to improve the individuals functioning. At all stages basic measures of sleep hygiene and sleep practice must be advised. Realistic part by part goal setting and improvement are required.

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