

INTRINSIC SLEEP DISORDERS

Introduction

Excessive daytime sleepiness (EDS) is a common complaint. Causes of EDS are numerous and include:

- Intrinsic sleep disorders (e.g. narcolepsy, obstructive sleep apnoea/hypopnea syndrome (OSAHS) and idiopathic hypersomnia);
- Extrinsic sleep disorders due to external factors (e.g. inadequate sleep hygiene, insufficient sleep syndrome, toxin-induced sleep disorder);
- Circadian rhythm sleep disorders (e.g. time-zone change “jet lag” syndrome, shift work sleep disorder);
- Sleep disorders associated with medical disorders (e.g. dementia, Parkinsonism); and
- Sleep disorders associated with mental disorders (e.g. psychoses, mood disorders, anxiety disorders).

A detailed clinical history, examination and appropriate investigations will assist in determining the cause.

The treatment of EDS is best achieved by treating the underlying condition.

Intrinsic sleep disorders, specifically narcolepsy and idiopathic hypersomnia, may warrant consideration of treatment with sympathomimetic psychostimulants such as methylphenidate and dexamphetamine and/or wakefulness agents such as modafinil. The use of sympathomimetic agents should only be considered in severe cases of sleep apnoea where other treatments have failed.

The diagnosis of intrinsic sleep disorders requires input from a physician experienced in the diagnosis and management of sleep disorders.

A. NARCOLEPSY

1. Medical Condition

Narcolepsy is characterised by uncontrolled daytime sleepiness and the initiation of REM sleep during times when a person would normally be awake.

The other major symptom of narcolepsy is cataplexy. Cataplexy is the sudden loss of voluntary muscle tone that is triggered by the experience of an intense emotion, one of the most common being laughter.

Other symptoms can include sleep paralysis (which consists of transient episodes of complete paralysis while falling asleep or during waking) and/or vivid auditory or visual hallucinations while falling asleep (hypnagogic hallucinations), night time sleep is almost always described as disturbed. Narcolepsy is a lifelong illness without a cure, typically symptoms first become noticeable between the ages of 10 and 30; diagnosis can be difficult as the symptoms can develop slowly over many years before they become severe enough to effect daily life

2. Diagnosis criteria

Diagnostic criteria (based on the American Academy of Sleep Medicine criteria):

- a. Complaint of severe excessive daytime sleepiness occurring daily for at least 3 months; typically, patients sleep for a short time and feel somewhat refreshed afterwards for short periods of time;
- b. Definite history of cataplexy, i.e. sudden loss of muscle tone triggered by strong emotions (fear, surprise, or, most reliably, positive items, such as joking or laughing); this is transient (less than 2 minutes) and can affect the knees, neck, or face. There is no loss of consciousness as occurs in “drop attacks” or fainting or other sudden losses of muscle tone;
- c. Exclusion of any medical or psychiatric conditions that could account for hypersomnia. This should involve a neurological and psychiatric examination and a negative drug screen. Brain imaging is not mandatory;
- d. Exclusion of respiratory and other causes of sleep disturbance by night time polysomnography in a centre experienced in sleep disorder diagnosis;
- e. Demonstration of at least 2 sleep onsets in REM (SOREMs) during a Multiple Sleep Latency Test (MSLT), with a mean sleep latency of less than 8 minutes (typically less than 5 minutes) for the 4 sessions of the test. The MSLT must be preceded by nocturnal polysomnography. Sleep prior to the MSLT must be at least 6 hours in duration.

N.B: It is important to note that SOREMs, on their own, are not diagnostic of narcolepsy and may be a normal phenomenon. Supportive history and short sleep latency on the MSLT should accompany SOREMs.

B. NARCOLEPSY WITHOUT CATAPLEXY (IDIOPATHIC HYPERSOMNIA)

1. Medical Condition

Narcolepsy without cataplexy can be considered a form of idiopathic hypersomnolence.

2. Diagnosis criteria

This diagnosis, in the context of a TUE application, may only be accepted with the greatest caution. There must be objective evidence of excessive daytime sleepiness with extrinsic causes excluded.

The following diagnostic criteria should be met:

- a. Excessive daytime sleepiness with refreshing naps and no clear cataplexy. (Cataplexy may however appear several years after the onset of sleepiness and result in a diagnosis of true narcolepsy.);
- b. Absence of respiratory disturbance on night time polysomnography. (in the case of repeated awakenings, upper airway resistance syndrome i.e. multiple respiratory events related arousals, must be ruled out through oesophageal pressure monitoring, and periodic limb movements through tibialis anterior EMG recording);
- c. Demonstration of at least 2 SOREMs during the MSLT, with a mean sleep latency of less than 8 minutes. (The preceding night time sleep duration should be more than 6 hours, in order to rule out “sleep rebound.” Recent use of antidepressants should be eliminated by drug screening, since there may be a rebound of REM-sleep in the days following cessation of these compounds. Ideally, monitoring of sleep time for one week previously should be performed to exclude behaviourally induced insufficient sleep as a cause of excessive sleepiness);
- d. Exclusion of causes of extrinsic sleep disorders by a full history and examination focusing on neurological and psychiatric cause.

C. SLEEP APNOEA/HYPOPNEA SYNDROME (OSAS)

1. Medical Condition

Sleep Apnoea is a sleep disorder characterised by abnormal pauses in breathing or instances of abnormally reduced breathing during sleep. Each pause in breathing, called an apnoea, can last from a few seconds to minutes and may occur 5 to 30 times or more an hour. The most common type of sleep apnoea is obstructive sleep apnoea (OSA). The individual with sleep apnoea is rarely aware of having difficulty breathing, even upon awakening. Sleep apnoea is recognised as a problem by others witnessing the individual during episodes (usually loud snoring and breathing pauses) or due to daytime sleepiness secondary to significant levels of sleep disturbance.

2. Diagnosis criteria

Sleep apnoea is diagnosed with an overnight sleep study (polysomnography). There is no absolute cut-off level but most specialists would consider patients with more than 10 apnoeas or hypopneas per hour of sleep as having OSA. The presence of moderate to severe sleepiness in addition to sleep study features of OSA is often denoted as obstructive sleep apnoea syndrome.

3. Medical Best Practice Treatment

Both sympathomimetic psychostimulants (e.g. methylphenidate and amphetamine derivatives) and wakefulness agents (e.g. modafinil) are considered to be appropriate treatment options for the EDS component of narcolepsy and narcolepsy without cataplexy. They have no effect on the cataplexy component of narcolepsy.

Different countries around the world have differing preferences for which group of drugs they consider first line, however, methylphenidate is often preferred to dexamphetamine as it has a more rapid action and is considered to have fewer adverse effects.

The use of sympathomimetic agents or modafinil should only be considered in severe cases of sleep apnoea when there has been demonstrable failure of CPAP (continuous positive airway pressure) to improve the sleep apnoea. The initial treatment of sleep apnoea is to institute behavioural change, including weight loss and reduced alcohol intake, however the mainstay of treatment for moderate to severe sleep apnoea is the use of CPAP. Evidence of failed CPAP is required, in particular in the form of objective investigations such as polysomnography, prior to the commencement of sympathomimetic agents or modafinil.

Name of Prohibited Substances	Route	Dose/Frequency	Recommended duration of treatment
Modafinil	Oral	The mean dosage is 200-400 mg in two divided doses (morning & noon; not later than 4 pm to avoid sleep onset insomnia, the half-life being 10-12 hours); or as a single dose in the morning.	Indefinite but regular review by a sleep specialist is considered to be the accepted practice to regulate medication and observe clinical progress.
Dexamphetamine, methylphenidate	Oral	<p>Dexamphetamine: 5-60mg in divided doses. The usual initial dose is 5 to 10 mg daily in divided doses, increased if necessary by 5 to 10 mg at weekly intervals to a maximum of 60 mg daily.</p> <p>Methylphenidate: 10-60mg The usual oral dose is 20 to 30 mg daily in divided doses, normally 30 to 45 minutes before meals, but the effective dose may range from 10 to 60 mg daily.</p>	Indefinite but regular review by a sleep specialist is considered to be the accepted practice to regulate medication and observe clinical progress.

4. Other Non-Prohibited Alternative Treatments

A. Narcolepsy and idiopathic hypersomnia

- Scheduled or ad libitum naps (short naps may be helpful to some people, regular sleep hours and avoidance of sleep deprivation are very important, large meals should also be avoided during the day)
- Caffeine
- SSRI, SNRI or tricyclic antidepressants in small dosages are the primary treatment necessary for cataplexy and sleep paralysis. (Patients requiring both central stimulants and tricyclic antidepressants require careful monitoring as the combination may produce serious adverse effects such as cardiac arrhythmias or hypertension).

B. Sleep apnoea

- CPAP (must have demonstrable failure of this to be able to trial stimulant medication)
- Behavioural change including reduced alcohol intake and weight loss

5. Consequences to Health If Treatment Is Withheld

Impairment of daytime functioning through excessive sleepiness can range from minor to significant, depending on the activity. Sports involving speed and significant risk of injury from falls (e.g. motor racing, equestrian, downhill skiing) pose significant risks to athletes with intrinsic sleep disorders, and their fellow competitors.

6. Treatment Monitoring

Although there is no commonly available drug monitoring, response to treatment can be monitored by “Maintenance of Wakefulness” test.

7. TUE Duration and Recommended Review Process

The recommended duration of a TUE for Intrinsic Sleep Disorders is 4 years with an annual review by a specialist physician.

8. Any Appropriate Cautionary Matters

Treatment is only symptomatic and is not mandatory every day, many patients preferring to take it only on working days, or before a given task (e.g. long trip). In the particular case of a TUE, one should question the absolute necessity of alleviating sleepiness, which may vary according to the type of sporting activity.

References

1. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. American Academy of Sleep Medicine, 2005.
2. Banerjee D, Vitiella M, Grunstein R. Pharmacotherapy for excessive daytime sleepiness. *Sleep Medicine Reviews.* 2004; 8:339-354.
3. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology.* 2000; 54: 1166–75.
4. Kingshott RN, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine.* 2001; 163: 918–23.
5. Nishino S, Mignot E. Drug treatment of patients with insomnia and excessive daytime sleepiness. *Clin Pharmacokinet.* 1999; 37: 305–30.
6. Mitler MM, Hayduk R. Benefits and risks of pharmacotherapy for narcolepsy. *Drug Safety.* 2002; 25: 791–809.
7. Morgenthaler TI, et al. Standards of Practice Committee of the American Academy of Sleep Medicine: Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep.* 2007; 30: 1705–11.
8. Nishino S, Mignot E. Narcolepsy and cataplexy. *Handbook of Clinical Neurology.* 2011; 99:783-814.
9. Pack AI, Pien GW. Update on sleep and its disorders. *Annual Review of Medicine.* 2011; 62: 447-60.
10. Roth T, Bogan RK, Culpepper L, et al. Excessive sleepiness: under-recognised and essential marker for sleep/wake disorder management. *Current Medical Research and Opinion.* 2010; 26 Suppl 2: S3-24.