



1. Medical Condition

NARCOLEPSY – CATAPLEXY

Introduction

The most common cause of excessive daytime somnolence is sleep respiratory disturbance, best treated with nasal continuous positive airway pressure ventilation. However, in younger, non-snoring, non obese subjects, narcolepsy is not an uncommon disease (prevalence ca. 0.03-0.06%) which may warrant treatment by modafinil.

Its clinical picture is well delineated, with two major symptoms (irresistible sleepiness and cataplexy), and two minor symptoms (sleep paralysis and hypnagogic/hypnopompic hallucinations). Diagnostic criteria are outlined in the following section and require input from a physician experienced in sleep medicine, often this may be a neurologist or a psychiatrist.

2. Diagnosis

- A. Medical history

A familial history of narcolepsy is only found in a small subset of patients (5-10%). A documented history suggestive of excessive daytime somnolence deserves investigation.

- B. Diagnostic criteria

Adapted from the AASM criteria (American Academy of Sleep Medicine)

1. Complaint of excessive daytime sleepiness occurring daily for at least 3 months; typically, patients sleep for a short time and feel refreshed afterwards.
2. 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, usually much briefer); symptoms may involve the entire body, or only the knees, neck, or face.

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3. Normal neurological and psychiatric examination. Negative drug screen. Brain imaging is not mandatory.
4. Exclusion of respiratory or other causes of sleep disturbance by night time polysomnography in an accredited Sleep-Wake Disorders Center.
5. 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 5 sessions of the test.
6. HLA genotyping is almost constantly DQB1*0602 across all ethnic groups in sporadic cases. Its absence strongly argues against the diagnosis, unless cataplexy is ascertained, and SOREMs are repeatedly demonstrated. Conversely, DQB1*0602 presence in itself is clearly insufficient.
7. Hypocretin-1 level in CSF should be obtained in dubious cases (disputable cataplexy, unclear MSLT results). Levels below 110 pg/ml, or a third of reference value, confirm the hypocretinergic alteration, pathognomonic of the disease.

Clinical variant: Narcolepsy without cataplexy

This diagnosis, in the context of a TUE application, may only be accepted with the greatest caution, if the following items are present:

1. Excessive daytime sleepiness with refreshing naps, and no clear cataplexy (which may however appear several years after the onset of sleepiness).
2. 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 esophageal pressure monitoring, and periodic limb movements through tibialis anterior EMG recording.
3. 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.
4. CSF hypocretin-1 measurement is advisable: it is normal in 90% of cases, but if the level is significantly low, the diagnosis will be firmly established.

Note: HLA genotyping has only limited value in narcolepsy without cataplexy, the DQB1*0602 association being much lower than in full-blown narcolepsy.

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- C. Relevant medical information

None

3. Medical best practice treatment

- A. Name of prohibited substances

Modafinil (Provigil®, Modiodal®)

- B. Route

Oral

- C. Frequency

The mean dosage is 300 mg in one or two doses (morning & noon; not later than 4 pm to avoid sleep onset insomnia, the half-life being 10-12 hours).

- D. Recommended duration of treatment

Indefinite but an annual 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

Scheduled or *ad libitum* naps

Caffeine

SSRI, SNRI or tricyclic antidepressants in small dosages are often necessary for controlling cataplexy.

5. Consequences to health if treatment is withheld

Impairment of daytime functioning through sleepiness could be minor or significant, depending on the professional or leisure activity.

6. Treatment monitoring

Although there is no commonly available drug monitoring, its implementation is feasible in selected laboratories. It may be used to verify compliance with the recommended dosage.

7. TUE validity and recommended review process

Patients must always be referred to a sleep specialist on a yearly basis, in order to monitor the clinical efficacy of the therapeutic regime. A new TUE request must be submitted.

If the response to modafinil is not satisfactory, methylphenidate (or dexamphetamine) is usually tried. In such case, a new TUE application must be initiated. If the above medications are not successful, sodium oxybate (gamma-hydroxybutyrate) at bedtime is another alternative. These compounds are obviously not compatible with competitive sport. Treatment with stimulants may be tapered or stopped after retirement from sport, or where a vocational change demands less vigilance.

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 sport activity.

9. References

1. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed.: Diagnostic and coding manual. Westchester, Illinois: American academy of Sleep Medicine, 2005).