Narcolepsy in the Older Adult
Epidemiology, Diagnosis and Management

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Abstract

Narcolepsy is a disorder of impaired expression of wakefulness and rapid-eye-movement (REM) sleep. This manifests as excessive daytime sleepiness and expression of individual physiological correlates of REM sleep that include cataplexy and sleep paralysis (REM sleep atonia intruding into wakefulness), impaired maintenance of REM sleep atonia (e.g. REM sleep behaviour disorder [RBD]), and dream imagery intruding into wakefulness (e.g. hypnagogic and hypnopompic hallucinations). Excessive sleepiness typically begins in the second or third decade followed by expression of auxiliary symptoms. Only cataplexy exhibits a high specificity for diagnosis of narcolepsy. While the natural history is poorly defined, narcolepsy appears to be lifelong but not progressive. Mild disease severity, misdiagnoses or long delays in cataplexy expression often cause long intervals between symptom onset, presentation and diagnosis. Only 15–30% of narcoleptic individuals are ever diagnosed or treated, and nearly half first present for diagnosis after the age of 40 years.

Attention to periodic leg movements (PLM), sleep apnoea and RBD is particularly important in the management of the older narcoleptic patient, in whom these conditions are more likely to occur. Diagnosis requires nocturnal polysomnography (NPSG) followed by multiple sleep latency testing (MSLT). The NPSG of...
a narcoleptic patient may be totally normal, or demonstrate the patient has a short nocturnal REM sleep latency, exhibits unexplained arousals or PLM. The MSLT diagnostic criteria for narcolepsy include short sleep latencies (<8 minutes) and at least two naps with sleep-onset REM sleep.

Treatment includes counselling as to the chronic nature of narcolepsy, the potential for developing further symptoms reflective of REM sleep dyscontrol, and the hazards associated with driving and operating machinery. Elderly narcoleptic patients, despite age-related decrements in sleep quality, are generally less sleepy and less likely to evidence REM sleep dyscontrol.

Nonpharmacological management also includes maintenance of a strict wake-sleep schedule, good sleep hygiene, the benefits of afternoon naps and a programme of regular exercise. Thereafter, treatment is highly individualised, depending on the severity of daytime sleepiness, cataplexy and sleep disruption.

Wake-promoting agents include the traditional psychostimulants. More recently, treatment with the ‘activating’ antidepressants and the novel wake-promoting agent modafinil has been advocated. Cataplexy is especially responsive to antidepressants which enhance synaptic levels of noradrenaline (norepinephrine) and/or serotonin. Obstructive sleep apnoea and PLMs are more common in narcolepsy and should be suspected when previously well controlled older narcolepsy patients exhibit a worsening of symptoms. The discovery that narcolepsy/cataplexy results from the absence of neuroexcitatory properties of the hypothalamic hypocretin-peptidergic system will significantly advance understanding and treatment of the symptom complex in the future.

The term narcolepsy was first coined by Gelineau in 1880[1] to describe a pathological condition characterised by irresistible brief sleep episodes, sometimes accompanied by falls, associated with emotional stimuli, later referred to as cataplexy.[2] It was not until the 1960s that the concept that narcolepsy/cataplexy reflected a primary disturbance in the expression of rapid-eye-movement (REM) sleep or its individual physiological components was established.[3-5]

1. Epidemiology

Narcolepsy is a disorder characterised by an impaired expression of wakefulness and REM sleep (behavioural states that share like conditions of increased thalamocortical arousal). In narcolepsy, sleep constitutes primarily of REM sleep and increases in the amount of sleep in a 24-hour period are minimal, emphasising that narcolepsy does not reflect an increased sleep drive.[6] Excessive sleepiness is usually first experienced in patients in their second or third decade. There is a smaller second peak of disease onset in patients in their early 40s which includes a slightly greater number of women.[7] Sleepiness is then followed by variable degrees of auxiliary symptoms, reflecting dyscontrol of individual physiological components of REM sleep, giving rise to the classic narcolepsy ‘tetrad’—cataplexy, sleep paralysis and hypnopompic hallucinations.[8-10] The natural history of narcolepsy is not accurately portrayed in text accounts, as it is a continuum of phenotypes with presentation often delayed because of mild severity, misdiagnoses or extreme delays in cataplexy expression.[11] Therefore, nearly half of patients with narcolepsy first present after the age of 40 years.

Population-based studies consistently reveal a prevalence rate of 1 per 2000 in North America and Europe.[12-14] Other prevalence rates include a low of 1 per 250 000 in Israel,[15] and a high of 1 per 600 in Japan,[16] but these studies have used less stringent designs and require confirmation. Prevalence data in the elderly are unavailable. First-degree relatives carry at least a 5-fold, and possibly as high as a 30–40-fold, increased risk of disease, suggesting an underlying genetic predisposition.[13] Environmental factors must also play a role, as monozygotic twins demonstrate only a 25–30% concordance for the disease (see detailed references in Mignot[13]). Despite a prevalence that approximates to those of multiple sclerosis and myasthenia gravis, in Finland it has been estimated that only 15–20% of narcolep-
tic patients are diagnosed while alive (based on the use of a standardised/validated questionnaire, with high sensitivity and specificity for detecting true narcolepsy/cataplexy, in a study of twins in Finland). Therefore, narcolepsy should always be included in the differential diagnosis of sleepiness or transient loss of muscle tone in any age group.

2. Pathophysiology

Insights into the pathophysiology of narcolepsy have blossomed with the recent discovery of two novel, hypothalamus-derived, excitatory neuropeptides – hypocretin (Hcrt)1 and Hcrt2 (see Silber and Rye [18] for a brief review). Conspicuous among Hcrt pathways is innervation to all of the sleep/wake state-related monoaminergic (dopamine, histamine, serotonin and noradrenaline [norepinephrine]) and cholinergic nuclei that together make up the ascending reticular activating system (ARAS). [19] Hcrt point mutation. [22] Screens of more than 100 narcoleptic patients have failed to reveal any pathogenic mutations in the genes for Hcrt or its receptors. [22,28] Vascular or mass lesions involving Hcrt-synthesising neurons or their projection sites [29,30] are likely to account for many cases of ‘secondary’ narcolepsy previously noted to arise from lesions involving the diencephalon and hypothalamus. [31]

Clues to a biological basis for narcolepsy focused originally on the fact that virtually all Japanese narcoleptic patients carried the specific class II MHC antigens HLA DR2 and DQw1. [32] Evidence that narcolepsy is a classic autoimmune disorder, however, has been lacking. The HLA DR2 and DQw1 may represent only markers, possibly susceptibility loci, for the illness.

Caucasians and Japanese carry the DRB1*1501 gene (new nosology), whereas Black narcoleptic patients are DR2 negative, [33] carrying antigens such as DRB1*1503. This led to subsequent observations that narcolepsy is most strongly associated with DQw1 (DQB1*0602). [34] Homozygotes for the DQB1*0602 gene are at a 2–4 times increased risk for developing narcolepsy compared with DQB1*0602 heterozygotes. [35]

While DQB1*0602 remains a sensitive marker (e.g. present in about 95% of narcoleptic patients), it is nonspecific (e.g. present in 25–40% of the general population). [13,24,36] Therefore, in clinical practice we reserve polymerase chain reaction-based methods using sequence-specific primers for patients in whom a diagnosis of narcolepsy is ambiguous. The potential utility of analysing levels of the Hcrt orexin in the cerebrospinal fluid (CSF) for the detection of human narcolepsy has recently been confirmed. [38,39] Low or undetectable levels of CSF Hcrt are quite sensitive and specific for narcolepsy/cataplexy and are a useful diagnostic adjunct for patients lacking cataplexy. [40] The vast majority of ‘monosymptomatic’ narcoleptic patients exhibit normal...
CSF Hcrt levels, thereby justifying a distinction from true idiopathic narcolepsy/cataplexy (see section 3).

3. Clinical Features

3.1 Clinical Diagnosis

Clinical criteria for diagnosis of narcolepsy include complaints of excessive daytime sleepiness. Many patients also exhibit symptoms reflecting the pathological expression of individual physiological correlates of REM sleep that include cataplexy and sleep paralysis (REM sleep atonia persisting into wakefulness), impaired maintenance of REM sleep atonia (e.g. RBD) and dream imagery intruding into wakefulness (e.g. hypnagogic and hypnopompic hallucinations). Each of these symptoms exhibit variable degrees of sensitivity and specificity for a diagnosis of narcolepsy.

Cataplexy, for example, is a specific, but insensitive marker for narcolepsy. This reflects an extreme variability in its expression and common idioms of our language (e.g. ‘knees buckling with laughter’, ‘jaw dropped with surprise’) that obscure its substantiation with confidence. A history of cataplexy is best elicited by inquiring as to whether diminution of muscle tone can be triggered by one of three situations: when hearing and telling a joke, while laughing, or when angry. While most narcoleptic patients who develop cataplexy do so within 4–5 years of onset of sleepiness, delays of 40–50 years in cataplexy expression are not unheard of (see section 3.2.1), and can be an unusual cause of falls in the elderly. Cataplexy is interpreted by many patients and physicians as a seizure or fainting spell or stroke, although the lack of a prodrome and the maintenance of consciousness with observance of fine phasic muscle twitches characteristic of phasic components of REM sleep allow for its distinction.

The diagnosis of narcolepsy is universally accepted to be certain in patients with sleepiness and cataplexy. The International Classification of Sleep Disorders (ICSD) criteria for narcolepsy, however, does not require the presence of cataplexy. Thus, many previous patient series describe a large number of narcoleptic patients lacking cataplexy, or ‘monosymptomatic’ narcolepsy, which may represent as many as 50% of all diagnosed patients. Such cases are more likely to present in the third or fourth decade of life and may exhibit a slight predilection for affecting women. The fact that narcolepsy/cataplexy can be distinguished from most monosymptomatic cases via ancillary testing for low CSF Hcrt (orexin) levels argues that the ICSD criteria are too broad and require revisiting.

The symptoms of sleep paralysis and hypnagogic hallucinations are neither sensitive nor specific for narcolepsy. Sleep paralysis is exceedingly common in the normal population. It is so common in some ethnic groups, in fact, that colloquialisms have been attached to the phenomenon of REM sleep atonia persisting into wakefulness: ‘being hagged’ (Newfoundland), ‘the witch be riding you’ (West Indies and southern US) and ‘Kanashibari’ (Japan).

Eliciting a history of hypnagogic or hypnopompic hallucinations specific for narcolepsy can be quite difficult, since they can occur in severely sleep-deprived individuals with another disorder. Vivid REM sleep-related hallucinations, on the other hand, not uncommonly lead to a misdiagnosis of schizophrenia. A history of recent or remote head trauma, meningitis or encephalitis may predate the onset of symptoms; therefore, a detailed past medical history should also be obtained, as many medical and psychiatric conditions affect sleep and vice versa.

There is little evidence that narcolepsy is relentlessly progressive. Elderly narcoleptic patients, in fact, despite age-related decrements in sleep quality, are generally less sleepy and less likely to evidence REM sleep dyscontrol. Other investigators have failed to identify age-related improvements in alertness and REM sleep intrusion into daytime naps. A review of medication status is critical in older patients, as many agents interfere with sleep continuity or exacerbate pre-existing sleep disorders. For example, α1-adrenoreceptor antagonists such as prazosin and dopamine D2 agonists should be avoided because they exacerbate cataplexy. Concurrent medical conditions in elderly narcoleptic patients may precipitate/aggravate cataplexy (see section 3.2.2) and can even draw attention to their illness for the first time.

3.2 Case Histories

Several case histories of patients evaluated and treated by the authors have been chosen as illustrative of the expression of narcolepsy/cataplexy in elderly adults. They emphasise the complex interactions of narcolepsy/cataplexy with comorbid condi-
tions such as sleep-disordered breathing and periodic leg movements of sleep which seem to be more commonly encountered in this patient population, as well as in the elderly. Additional confounding variables that might influence the expression of sleepiness and cataplexy such as aging and other common medical conditions are also evidenced in these examples.

3.2.1 Case 1: Late-Life Presentation of Cataplexy

An 82-year-old retired, but previously self-employed, electrician presented with a several-year history of ‘falling out’ spells several times daily. A recent spell was precipitated upon hearing a joke from a friend and resulted in him falling from a couch and remaining relatively motionless, but aware of his surroundings, for at least 5 minutes. He was admitted to a local hospital and underwent an extensive evaluation that included brain imaging, 4-vessel cerebral angiography, and 24-hour cardiac monitoring. A 24-hour video-electroencephalogram recording session on an epilepsy unit revealed: “...a spell while the patient was standing in the doorway of his hospital room. Although no definite changes in background activity were noted initially, there was some attenuation of muscle activity recorded on the electromyogram lead. Near the end of the episode there was some attenuation and disorganisation of background activities, with evidence of REMs, and at the time the event button was pushed, almost complete abolition of muscle activity.”

Upon referral, a lifelong history of excessive daytime sleepiness was obtained. This was so severe that when stationed in Europe during World War II, he needed to pay colleagues to cover his guard duties and slept intermittently through the whole of the Battle of the Bulge. He denied sleep paralysis or hypnagogic hallucinations.

A diagnostic polysomnogram was performed that revealed a reduced sleep efficiency (68%), PLMs (25 per hour), and obstructive sleep apnoea (35 apnoea/hypopnoeas per hour of sleep). Multiple sleep latency testing (MSLT) revealed a mean sleep latency of 4 minutes with 2 of 4 naps exhibiting sleep-onset REM sleep. He was treated successfully with protriptyline 10mg each morning, daily naps and continuous positive airway pressure during sleep.

Comment

This case illustrates several important points about the natural history and treatment of narcolepsy. First, narcoleptic patients adapt via lifestyle adjustments such as self-employment to their sleepiness. Second, late-life presentation can be precipitated by delayed expression of cataplexy. Third, significant morbidity can be associated with cataplectic falls themselves,[42] or their work-up if not recognised as such. Fourth, PLMs and obstructive sleep apnoea are common in elderly narcoleptic patients and need to be treated.

3.2.2 Case 2: Exacerbation of Narcolepsy/ Cataplexy Due to Concurrent Medical Conditions

A 38-year-old woman undiagnosed as narcoleptic retired from teaching because of embarrassing cataplectic attacks. She was told that she was schizophrenic after giving birth to her second child, presumably because of the presence of vivid hypnagogic hallucinations. Presentation was delayed until the age of 59 years, when mild cataplexy increased to several times daily during hospital admission for pylephritis. A diagnostic polysomnogram revealed REM sleep onset in 30 seconds (normal 60–90 minutes) and a PLM arousal index of 56 per hour of sleep. Mean sleep latency was 40 seconds, with three of five naps displaying REM sleep. At that time she was treated with imipramine 100mg at bedtime and pameline 37.5mg each morning. Subsequently, she was switched to fluoxetine 20–40mg each morning and either methylphenidate or dexamfetamine to enhance wakefulness. Clonazepam (0.5–1.0mg) or temazepam (15–30mg) one hour before bedtime, together with levodopa-carbidopa (25/100) were used to alleviate her PLM and consolidate her sleep.

The drug regimen proved relatively successful for several years before she began experiencing recurrent cataplexy and discontinued her psychostimulants, as they made her feel worse. She injured herself frequently, even falling down a flight of stairs, at her rural home. She reported a 6.8kg weight loss, as well as polydipsia and polyuria. When examined in the clinic, she had nearly continuous cataplectic attacks affecting her lower extremities and bulbar musculature, remaining recumbent for an entire 30-minute interview, unable to rise. She was admitted to hospital, where laboratory testing revealed an elevated blood glucose level. She was diagnosed with adult-onset, type 2 diabetes mellitus. Her biochemical parameters returned to normal after institution of insulin therapy, and coincidentally the frequency and severity of cataplectic events de-
creased dramatically. She has since remained well for 3 years taking fluoxetine (40mg every morning), dexamfetamine (15mg twice daily) and temazepam (15–30mg one hour before bedtime).

Comment
This case illustrates several important points about the natural history and treatment of narcolepsy. First, narcoleptic patients are not commonly diagnosed as having schizophrenia. Second, late-life presentation can be precipitated by delayed expression, or worsening, of cataplexy by concurrent illnesses. Third, PLMs are more common in narcolepsy and may require treatment when previously well controlled older narcoleptic patients exhibit a worsening of symptoms. Worsening of symptoms with diabetes mellitus in this instance probably reflects the fact that psychostimulant-induced catecholamine excess accentuated the hyperglycaemia and glycosuria owing in part to direct actions, but also because of promoted glucagon secretion and inhibited insulin secretion. Alternatively, a narcolepsy phenotype may have been exacerbated by hyperkalaemia through unknown mechanisms or by hyperglycaemia/hyperinsulinaemia-mediated down-regulation of Hcrt expression in any surviving Hcrt neurons.

3.2.3 Case 3: Late-Life Presentation of Narcolepsy and Worsening Secondary to Coexistent Sleep Apnoea
A 54-year-old commercial airline pilot related a history of sleepiness dating back to his early 20s when he was an air-force pilot in Vietnam. He compensated for this by ingestion of 14–22 cups of caffeinated coffee each day and frequent daytime naps between flights. He stated that he never experienced symptoms while on the job and found flying to be ‘fun’ and ‘stimulating’. During an intense 72-hour pilot training certification he was witnessed to ‘fall out’ while on a flight simulator. Cardiopulmonary resuscitation was initiated and he ‘came to’ within minutes and was hurried to a cardiologist for further evaluation. Similar cataplectic episodes occurred only 2–3 times per year, only under stressful conditions. His cardiac status was normal and he eventually underwent diagnostic polysomnography. This revealed a normal nocturnal REM latency, as well as normal total sleep time and sleep efficiency. There was no apnoea and 165 periodic limb movements were seen, only 13 of which were associated with cortical arousals (PLM index = 23, PLM arous-

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to sleepiness, thereby aiding in interpretation of the MSLT.

MSLT is a standardised test in which the patient is asked to close their eyes and go to sleep.[63] It measures the latency to sleep in 4–5 nap opportunities at 2-hour intervals during the day to quantify/objectify sleepiness and to reveal the sleep stage that is entered. A mean sleep latency of 5 minutes indicates a ‘pathological’ level of sleepiness. A mean sleep latency of more than 10 minutes is considered normal, with values of 5–10 minutes falling in a diagnostic grey zone. In the pre-teen population, evidence of sleep on any two naps is considered unusual. Normative values for late teens and early 20s are less well established, partly because of the physiological tendency for this population to be phase delayed.[64]

REM sleep (i.e. dream sleep) on at least two naps in the setting of a normal NPSG is suggestive of a diagnosis of narcolepsy.[65] Two or more daytime sleep-onset REM sleep periods may alternatively reflect REM sleep rebound secondary to obstructive sleep apnoea or drug-related (e.g. antidepressant, psychostimulant, alcohol or cocaine) REM sleep deprivation. Thus, ideally, medications should be withdrawn several weeks before testing, a careful history of drug ingestion should be documented, and a urine drug screen performed during the MSLT.

Compared with measuring a tendency to fall asleep with the MSLT, the maintenance of wakefulness test (MWT) answers a more practical question, namely, what is the ability of someone to maintain alertness? The MWT is performed in a standardised soporific setting on four occasions throughout the day and following an NPSG. Maintaining alertness for 18–20 minutes in the MWT is considered adequate, although normative values are less well established than for the MSLT. As many as 2–15% of narcoleptic patients, for example, appear to have an unimpaired ability to remain awake as compared with controls.[66]

In narcolepsy, the NPSG may be essentially normal (~25%), demonstrating a short (<60 minutes) nocturnal REM sleep latency (~75%) and is frequently punctuated by unexplained arousals or arousals associated with nocturnal movements.[4,49,56,57,67-69] Enhanced nocturnal movement manifested as PLM and even RBD are observed in a smaller proportion of narcoleptic patients (~10–20%), particularly those exhibiting severe cataplexy.[7,11,70] The MSLT criteria for narcolepsy include short sleep latencies with a mean sleep latency typically of less than 8 minutes[71] and at least two naps consisting of sleep-onset REM sleep. The sensitivity but not the specificity of these criteria is quite high, with test-retest reliability of more than two sleep-onset REMs approaching 95%.[72] Nonetheless, the MSLT criteria for narcolepsy are still highly controversial and vary significantly between laboratories.[73] In part, this reflects personal experience and an increasing number of neurological disorders in which sleepiness and sleep-onset REMs have been described (e.g. hyperkalaemic periodic paralysis, Parkinson’s disease and myotonic dystrophy). The MWT, in which patients are asked to remain awake rather than fall asleep, is increasingly being used in the evaluation of treatment interventions for narcolepsy, as for this indication it appears more sensitive than the MSLT.

4. Pharmacological Management/Neuropharmacological Basis of Treatment

The treatment of narcolepsy should first include counselling as to its chronic nature, the potential for developing further symptoms reflective of REM sleep dyscontrol, and the hazards associated with driving and operating machinery. Driving restrictions may be appropriate. For example, in the US narcoleptic patients must be reported to the Secretary of State’s Office in several jurisdictions. Initial nonpharmacological management should include instruction on avoiding shifts in the sleep-wake schedule, maintaining a regular timing of nocturnal sleep, the positive benefits of several long daytime naps,[74,75] and a programme of regular, intense exercise. Smoking should be strongly discouraged, since nicotine worsens narcolepsy/cataplexy as a result of cholinergic hypersensitivity that accompanies the disease.[76,77] Alcohol and caffeine intake in the late afternoon and evening should similarly be discouraged because of their detrimental effects on any coincident PLMs and interference with sleep continuity. Impairments in wakefulness in narcoleptic patients using nicotine and caffeine have been recently confirmed.[86] Thereafter, treatment is highly individualised and directed by the degree of daytime sleepiness, the presence/absence of cataplexy and the severity of sleep disruption (figure 1).
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Psychostimulants such as amphetamines (dextroamphetamine, methamphetamine), as well as methylphenidate, mazindol and pemoline, have been the mainstays of treatment until quite recently. They compensate for the lack of excitatory Hcrt influences on monoaminergic neurons in the ARAS. These agents promote presynaptic release of monoamines (e.g. dopamine, serotonin and noradrenaline) and/or inhibit their reuptake. This being said, the preponderance of recent evidence implicates the dopamine transporter and the mesocorticolimbic dopamine system as the principal site of action for the wake-promoting effects of the traditional psychostimulants.

Psychostimulant use has been controversial for numerous reasons. First, the tolerance and potential abuse of these agents is high, leading, in the US, to drug agency surveillance of prescription patterns. Second, real and potentially serious central and peripheral sympathomimetic adverse effects of these agents can occur. Third, therapeutic endpoints are poorly defined. Fourth, few controlled trials have established their efficacy in treating narcolepsy, and those that have included small numbers of patients. Each of these points holds that much more weight when considering that the majority of patients, each of these points holds that much more weight when considering that the majority of patients, who as a group tend to be less sleepy with lower REM sleep propensity. In this patient subgroup, we therefore tend to favour the use of alternative wake-promoting agents or lower doses of psychostimulants (see sections 4.1.1, 4.1.2 and 4.1.3). Differences in baseline sleep latencies between studies involving small numbers of patients make it quite difficult to compare relative efficacies of different agents, especially among an elderly subpopulation. The tendency of a particular drug to produce adverse effects also varies between patients and therefore demands highly individualised treatment plans and frequent medication adjustments. However, the treatment of sleepiness in narcolepsy has been revolutionised with the introduction of the novel wake-promoting agent modafinil.

The treatment of cataplexy is even less standardised than the treatment of sleepiness, because of the lack of controlled trials. Insights into the pathophysiology and treatment of cataplexy have been

If standard treatments are ineffective, one needs to reconsider the presence of coincident disorders that have gone untreated. Obstructive sleep apnoea and PLMs, for example, are more common in narcolepsy and should be suspected when previously well controlled older narcoleptic patients exhibit a worsening of symptoms (see section 3.1.3). Many patients (30–50%) also experience depressive symptomatology that appears intimately related to disease pathophysiology rather than a response to a chronic disease state.

The majority of narcoleptic patients reaching medical attention require medications for symptomatic relief of daytime sleepiness and for cataplexy, if frequent and severe. The practice parameters of the American Sleep Disorders Association published in 1994 advocate the aggressive use of traditional psychostimulants in the treatment of excessive daytime sleepiness. A recent 2001 update to these parameters has been published. Data specifically related to the treatment of elderly narcoleptic patients are lacking. The greatest amount of experience comes from the 40–49-year-old age group, which represents the majority of patients in treatment studies.

### Table: How likely are you to doze off or fall asleep in the following situations in contrast to just feeling tired?

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing</th>
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<tbody>
<tr>
<td>1 Sitting and reading</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>2 Watching TV</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>3 Sitting inactive in a public place (e.g. a theatre or a meeting)</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>4 As a passenger in a car for an hour without a break</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>5 Lying down to rest in the afternoon when circumstances permit</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>6 Sitting and talking to someone</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>7 Sitting quietly after a lunch without alcohol</td>
<td>□ □ □ □</td>
</tr>
<tr>
<td>8 In a car, while stopped for a few minutes in traffic</td>
<td>□ □ □ □</td>
</tr>
</tbody>
</table>

Scale: 0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing

Fig. 1. Epworth sleepiness scale.

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derived principally from investigations in canine narcolepsy/cataplexy and extrapolation of these findings to the human condition.\textsuperscript{[91,92]} Pharmacological studies in canine cataplexy have implicated the $\alpha_1\beta$-adrenoreceptor in cataplexy expression. Inhibition of noradrenergic uptake is therefore critical to the therapeutic efficacy of antidepressant compounds which are used to treat human cataplexy. Noradrenergic neurons of the locus coeruleus completely cease firing during REM and during cataplectic attacks in narcoleptic dogs.\textsuperscript{[93]} In treating cataplexy, therefore, noradrenaline reuptake blockers function presumably to counteract loss of noradrenergic transmission, which occurs secondary to loss of the excitatory drive of Hcrt to the locus coeruleus.

### 4.1 Wake-Promoting Agents

#### 4.1.1 Traditional Psychostimulants

Traditional psychostimulants have been the pharmacological mainstay of treatment of sleepiness.\textsuperscript{[94]} Commonly prescribed stimulants include methylphenidate, dexamfetamine and pemoline. Others, which are taken by fewer than 5% of patients, include methamphetamine, mazindol, phenmetrazine and amfepramone. These drugs increase wakefulness, vigilance and performance on certain tasks and decrease fatigue. Traditional psychostimulants improve daytime somnolence in 65–85% of patients; however, few large, well controlled studies have evaluated their efficacy in alleviating sleepiness in narcolepsy. A discussion of some of the seminal studies follows.

Mitler et al.\textsuperscript{[95]} studied methamphetamine in eight narcoleptic patients with age-matched controls. Patients received 0, 20, 40 or 60mg of drug, whereas controls were given the drug in 0, 5 or 10mg strengths (total daily doses given 2–3 times daily). All participants underwent MSLT, and daytime mean sleep latency improved from 4.29 minutes during placebo treatment to 9.27 minutes with high-dose treatment ($p < 0.0005$). Although adverse effects including nervousness, insomnia, akathisia, headache, nausea, abdominal pain and loss of appetite were noted, this did not limit treatment.

Honda et al.\textsuperscript{[96]} reported the effects of long-term treatment with methylphenidate (30–60mg average total daily dose given 2–3 times daily) in 106 narcoleptic patients. Of these, 50 patients had been treated for 5 years or more, and 92% showed marked amelioration of sleep tendency and this improvement was dose related. The most common adverse effects were headache, dry mouth, stomach upset, sweating and impaired micturition. Many patients were receiving concomitant tricyclic antidepressants or hypnotics. In a further study by Mitler et al., methylphenidate 60mg/day improved the ability to stay awake (measured by the MWT see section 3.2) and perform several cognitive tasks in six narcoleptic patients compared with nine control subjects.\textsuperscript{[97]}

Pemoline has a pharmacological profile similar to methylphenidate, although it appears to be less potent.\textsuperscript{[98]} In the previous study by Mitler et al.,\textsuperscript{[97]} seven narcoleptic patients given pemoline (up to 112.5 mg/day) demonstrated no significant improvement in ability to remain awake, yet performed better on cognitive tasks compared with baseline. In a long-term open-label study of pemoline, 60 narcoleptic patients were followed for up to 8 years. Medication dosage varied from 60 to 200mg daily. Two-thirds of patients reported marked to moderate reduction in sleep attacks and sleepiness. Observed adverse effects included reduced appetite, headache, dry mouth and stomach discomfort.\textsuperscript{[99]} Treatment should be initiated only in patients without liver disease or laboratory evidence of elevations in liver enzymes, given recent realisation that pemoline may contribute to irreversible, acute hepatic failure.\textsuperscript{[100,101]} This has led to its removal from the market in several countries.

Each of these traditional psychostimulants is rapidly absorbed, with peak plasma concentrations occurring between 0.5 and 2 hours after ingestion, and they exhibit varying degrees of rebound hypersomnolence, which can be clinically significant. The prototypical psychostimulants methamphetamine and dexamfetamine (including methylphenidate), for example, produce rebound hypersomnolence in animals, while pemoline does not.\textsuperscript{[102]} This quality may necessitate prescribing sustained or slow-release formulations to produce more stable steady-state levels of psychostimulant that peak roughly between 8 and 10 hours after ingestion.

#### 4.1.2 Modafinil

Modafinil is a novel wake-promoting agent with unknown mechanism of action. Because it does not significantly alter the release of dopamine or noradrenaline, its mode of action appears distinct from the traditional psychostimulants.\textsuperscript{[103]} Of particular significance is its ability to enhance wakefu-
ness without increasing or intensifying motor activity or producing rebound hypersomnolence in animals.\[102\] The wake-promoting effects may be related to its low affinity for the dopamine transporter\[104\] or the activation of hypothalamic arousal regions such as the Hcrt and histamine cell groups.\[105\] Modafinil does not promote release of extracellular striatal dopamine as do traditional psychostimulants, yet its wake-promoting actions appear to require the presence of the dopamine transporter.\[86\]

The subjective effects of modafinil are markedly different from those of amphetamine, suggesting that at clinically useful doses (usual range 200–400 mg/day) it does not have the same abuse potential or adverse effect profile as traditional psychostimulants. In contrast to traditional psychostimulants, modafinil does not appear to adversely affect sleep or early morning behaviour, particularly in the elderly.\[106,107\] Significant improvements in global clinical improvement, as well as subjective and objective sleepiness compared with placebo/baseline, have been consistently observed independently of age.\[106-114\] Modafinil was first evaluated in clinical trials in Europe, including one randomised, controlled trial\[108\] and two open-label studies,\[109,110\] and demonstrated significantly improved sleepiness in narcoleptics. In two further early trials modafinil was generally well tolerated, with some patients exposed to the drug for longer than 7 years.\[111,112\]

Modafinil has also been studied extensively in North America. Broughton et al.\[113\] evaluated the clinical efficacy of modafinil in 75 patients with narcolepsy in a 6-week randomised, crossover, placebo-controlled trial. Patients received placebo or modafinil 200mg in the morning or 400mg in divided doses (morning and noon). Modafinil increased mean sleep latency on the MSLT by 40% and on the MWT by 54%, both being highly significant. There were no effects on nocturnal sleep initiation, maintenance, wakefulness or architecture, nor were effects noted on sleep apnoea or PLM. Voluntary daytime naps and quantity and quality of nocturnal sleep were not affected. The drug did not produce any blood pressure changes or alter heart rate. The only significant adverse effects were nausea (p = 0.039) and nervousness (p = 0.007), which were seen with the 400mg dose more frequently than with 200mg or placebo. No significant differences were found between placebo and 200mg of modafinil for any adverse events.

In a separate 18-centre, randomised, placebo-controlled, parallel-group study of 285 narcoleptic patients,\[114,115\] modafinil 200 and 400mg daily significantly reduced subjective sleepiness and increased mean scores on the MWT and MSLT. The only significant adverse effect noted was mild to moderate headache, which has subsequently been attributed to rapid institution of treatment. In clinical practice we therefore advocate starting with 50–100mg each morning and escalating the dose each 4–5 days by 50mg to reach a maximum of 200mg twice daily. Maximum plasma drug concentrations are somewhat delayed (e.g. 2–4 hours after ingestion) which may necessitate concomitant morning administration of a small dose of a traditional psychostimulant. The plasma elimination half-life is approximately 10–12 hours. In patients with renal failure, the maximum plasma drug concentration and elimination half-life are nearly twice as high compared with those in patients with normal renal function.\[116\]

Influence of age on modafinil pharmacokinetics was also assessed in an open-label evaluation of a single 200mg oral dose of modafinil.\[117\] Plasma concentrations were 2-fold higher in older patients than in historically matched younger individuals, suggesting a reduced capacity to eliminate modafinil. Since most of these patients were treated with multiple concomitant medications, changes in pharmacokinetic parameters of modafinil may not be solely attributable to the effects of aging. On the basis of these observations, elderly patients may benefit from lower doses of modafinil. The long-term effectiveness of modafinil is under evaluation. It is a useful addition to the clinician’s therapeutic armamentarium in the management of narcolepsy.

### 4.1.3 Alternative Agents

Realisation that narcolepsy is associated with secondary alterations in dopamine neurotransmission and that wakefulness is enhanced with dopaminergic compounds has prompted investigations of alternative means of enhancing synaptic dopamine levels in narcoleptic patients. Levodopa, a precursor of dopamine, is also a potent REM sleep suppressant when administered intravenously to humans.\[118\] In two small open-label studies in narcolepsy, however, levodopa (0.25–2.4g daily) failed to improve MSLT-documented sleep latency or daytime REM sleep propensity.\[119,120\] Nevertheless, patients experienced subjective improvement and en-
Enhancement of vigilance as assessed by an analogue vigilance scale and reaction time testing.

Synaptic dopamine can also be enhanced by interfering with enzymes that participate in its catabolism, such as monoamine-oxidase B (MAO-B). The efficacy of the MAO-B inhibitor selegiline (deprenyl) has been established in two separate studies. In one randomised, double-blind, placebo-controlled trial in 30 narcoleptic patients, selegiline 5–10 mg twice daily demonstrated dose-dependent suppression of nocturnal and daytime REM sleep as well as lengthening of sleep latencies. A placebo-controlled, double-blind, crossover study in 17 narcoleptic patients given selegiline 10, 20, 30 and 40 mg/day dose confirmed dose-dependent improvements in subjective and objective measures of disordered arousal in patients given selegiline. Surprisingly, cataplexy frequency was also reduced by 80–90%.

At doses greater than 20 mg/day, selegiline loses its selectivity for MAO-B, requiring institution of a tyramine-free diet to avoid hypertensive reactions. Mild adverse effects do not typically contribute to discontinuation of treatment. Adverse events are similar in character and frequency to those encountered with traditional psychostimulants.

Synaptic dopamine can also be enhanced by interfering with dopamine reuptake via presynaptic blockade of the dopamine transporter. In this regard, a single report has demonstrated normalisation of subjective and objective symptoms of narcolepsy with bupropion 100 mg three times daily (also see section 3.2.3). The most troublesome adverse effect with bupropion is seizure (0.4% risk at 450 mg/day in divided dosage). One advantage to prescribing this agent in the US is that it is not a controlled substance, i.e. it is not considered to have abuse potential and therefore has no limit on prescription refills as do the traditional psychostimulants. Given the large interindividual differences in narcolepsy severity, it is not surprising that in our practice we have not found bupropion to be universally effective. Yet we find it particularly useful in the elderly population in whom sleepiness is less severe, in narcoleptic patients requiring smoking cessation (e.g. see section 3.2.3), or as an adjunct to traditional psychostimulants and modafinil.

Several other agents have been investigated with respect to their potential benefit in alleviating narcoleptic symptoms. The mechanisms underlying the purported benefits of protriptyline and codeine or like agents in alleviating sleepiness in narcolepsy are unclear. Treatment with the non-sedating tricyclic antidepressant protriptyline in divided doses of 20–60 mg/day has been advocated. Yet this agent, despite improving vigilance in the hands of some investigators, has not been found to exhibit similar results in the hands of others and does not positively affect the objective MSLT or MWT findings. Anticholinergic adverse effects, particularly urinary retention, argue against the use of protriptyline in the elderly. Treatment of narcolepsy with codeine has also been advocated on the basis of reports of fewer daytime sleep episodes and subjective improvement in 18 of 27 narcoleptic patients. Objective studies in two subgroups of five and eight failed to confirm these subjective reports.

4.2 Anticataplectic Agents

Pharmacological studies in canine narcolepsy emphasise the critical role of normal noradrenergic ‘tone’ in reversing cataplexy. This is consistent with the experience that protriptyline, desipramine and venlafaxine, three adrenergic reuptake blockers with lesser effect on serotonergic transmission, are effective and potent anticataplectic agents in humans. As a first-line agent in treating cataplexy, we advocate the use of venlafaxine which inhibits both noradrenaline and serotonin reuptake at doses of 25–50 mg twice daily.

Unfortunately, most available adrenergic uptake blockers exhibit some anticholinergic or antihistaminergic properties. Novel compounds without anticholinergic effects such as reboxetine are available in Europe and are undergoing trials in the US for the treatment of depression. One open-label pilot trial in 12 patients in Europe demonstrated reboxetine 10 mg daily had stimulant and anticataplectic effects. When more widely available, similar agents will be useful adjuncts in the management of cataplexy.

Selective serotonin receptor inhibitors (SSRIs), such as fluoxetine, are also effective at relatively high doses in reducing cataplexy in apparent contradiction to findings in narcoleptic canines. This discrepancy reflects the significant noradrenergic reuptake inhibition exhibited by the desmethyl me-
4.3 Sleep-Consolidating Agents

Sleep can be significantly fragmented in narcoleptic patients, partly because of the increased likelihood of enhanced nocturnal movement in the form of PLMs, parasomnic behaviour such as RBD or treatments directed at alleviating cataplexy. These are more commonly encountered in patients who exhibit severe cataplexy. Sodium oxybate, a naturally occurring metabolite of the human nervous system that has been increasingly advocated in patients with cataplexy and disturbed nocturnal sleep, has several years of clinical experience in Canada and elsewhere and has recently been approved by the US FDA. Sodium oxybate improves nocturnal sleep and reduces the frequency of cataplectic events in narcolepsy. Daytime alertness is also improved when sodium oxybate is used in conjunction with typical doses of daytime wake-promoting agents. Sodium oxybate is characterised by a rapid onset and short pharmacological effect (elimination half-life of about 1 hour) and therefore requires administration at bedtime and again 3–4 hours later.

An alternative means of improving nocturnal sleep via alleviation of nocturnal movements is with dopaminomimetics, but this strategy, unlike that with sodium oxybate, has little positive benefit upon daytime symptoms. We do, however, advocate consolidation of sleep because, as noted above, this promotes proper sleep hygiene, which itself is advantageous in treatment (see section 3.2.2). Suspected aggravators such as caffeine, nicotine, alcohol, sleep deprivation and traditional antidopaminergic compounds (e.g. metoclopramide) should be avoided. Clonazepam (0.5–2.0mg at bedtime) has been considered the mainstay of treatment for RBD, as it is reported effective in 80% of cases of idopathic RBD. Unfortunately, the long half-life of this agent precludes its use in the elderly, in whom it can induce daytime confusion and somnolence. Therefore, in the elderly we commonly use the shorter half-life agent temazepam (15–30mg 1–2 hours before bedtime) as an alternative (3.2.2). Inadequate treatment response may necessitate adjunctive treatment with low doses of carbidopa/levodopa (25/100mg at bedtime).

5. Conclusions

Narcolepsy is a life-long disease characterised by excessive daytime sleepiness. It is differentiated from other disorders of daytime sleepiness by the presence of accessory symptoms reflecting dysfunctional expression of REM-sleep (e.g. cataplexy, sleep paralysis and hypnagogic hallucinations). Onset of symptoms in the majority of cases occurs before the age of 30, yet because of its insidious nature, diagnosis is frequently delayed. Age at onset for these various symptoms is an important variable affecting when the diagnosis is made. Cataplexy, for example, while pathognomonic for diagnosis, is difficult to substantiate and may present overtly 20 or more years after the onset of sleepiness. Diagnosis is primarily clinical with confirmation by polysomnography and characterisation of daytime sleepiness by MSLT. Through increasing recognition, more routine application of diagnostic studies, and discovery of Hcrt pathophysiology underlying narcolepsy/cataplexy, delay in diagnoses have been significantly shortened. Nonetheless, delays are still common and most patients elude diagnosis for many years and may never be diagnosed.

Insights into the natural history of the disease and further improvements in recognition and diagnosis are areas requiring future investigation. Significant advances have been made in identifying pharmacological interventions that alleviate the principal symptoms of sleepiness and cataplexy. More knowledge is needed on the dosing, pharmacokinetics and efficacies of these pharmacological agents in the elderly narcoleptic.

Age-related nocturnal sleep disturbances including PLM and sleep apnoea are likely more commonly encountered in narcolepsy. These and other common medical disorders likely account for the unexpected worsening of narcolepsy/cataplexy in previously well controlled narcoleptics. Optimising management of the older narcoleptic will also neces-
sitate more knowledge of how these factors interact with the primary pathophysiology underlying narcolepsy/cataplexy.

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