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EFNS TASK FORCE/CME ARTICLE

EFNS guidelines on management of narcolepsy

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Management of narcolepsy with or without cataplexy relies on several classes of drugs, namely stimulants for excessive daytime sleepiness and irresistible episodes of sleep, antidepressants for cataplexy and hypnosedative drugs for disturbed nocturnal sleep. In addition, behavioral measures can be of notable value. Guidelines on the management of narcolepsy have already been published. However contemporary guidelines are necessary given the growing use of modafinil to treat excessive daytime sleepiness in Europe within the last 5–10 years, and the decreasing need for amphetamines and amphetamine-like stimulants; the extensive use of new antidepressants in the treatment of cataplexy, apart from consistent randomized placebo-controlled clinical trials; and the present re-emergence of gamma-hydroxybutyrate under the name sodium oxybate, as a treatment of all major symptoms of narcolepsy. A task force composed of the leading specialists of narcolepsy in Europe has been appointed. This task force conducted an extensive review of pharmacological and behavioral trials available in the literature. All trials were analyzed according to their class evidence. Recommendations concerning the treatment of each single symptom of narcolepsy as well as general recommendations were made. Modafinil is the first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep in association with behavioral measures. However, based on several large randomized controlled trials showing the activity of sodium oxybate, not only on cataplexy but also on excessive daytime sleepiness and irresistible episodes of sleep, there is a growing practice in the USA to use it for the later indications. Given the availability of modafinil and methylphenidate, and the forseen registration of sodium oxybate for narcolepsy (including excessive daytime sleepiness, cataplexy, disturbed nocturnal sleep) in Europe, the place of other compounds will become fairly limited. Since its recent registration cataplexy sodium oxybate has now become the first-line treatment of cataplexy. Second-line treatments are antidepressants, either tricyclics or newer antidepressants, the later being increasingly used these past years despite few or no randomized placebo-controlled clinical trials. As for disturbed nocturnal sleep the best option is still hypnotics until sodium oxybate is registered for narcolepsy. The treatments used for narcolepsy, either pharmacological or behavioral, are diverse. However the quality of the published clinical evidences supporting them varies widely and studies comparing the efficacy of different substances are lacking. Several treatments are used on an empirical basis, specially antidepressants for cataplexy, due to the fact that these medications are already used widely in depressed patients, leaving little motivation from the manufacturers to investigate efficacy in relatively rare indications. Others, in particular the more recently developed substances, such as modafinil or sodium oxybate, are evaluated in large randomized placebo-controlled trials. Our objective was to reinforce the use of those drugs evaluated in randomized placebo-controlled trials and to reach a consensus, as much as possible, on the use of other available medications.

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This is a Continuing Medical Education paper and can be found with corresponding questions on the Internet at: http://www.blackwellpublishing.com/products/journals/ene/mcqs. Certificates for correctly answering the questions will be issued by the EFNS.

Background

Narcolepsy is a disabling syndrome, first described by Westphal [1] and Gelineau [2]. Excessive daytime sleepiness is the main symptom of narcolepsy. It includes a feeling of sleepiness waxing and waning throughout the day and episodes of irresistible sleep recurring daily or almost daily. Cataplexy is the second commonest symptom of narcolepsy and the most specific one. It is defined as a sudden loss of voluntary muscle tone with preserved consciousness triggered by emotion. Its frequency is extremely variable from one or less per year to several per day. Other symptoms referred to as auxiliary symptoms are less specific and not essential for the diagnosis. They include hypnagogic and hypnopompic hallucinations, visual perceptual experiences occurring at sleep onset or on awakening, sleep paralysis, a transient generalized inability to move or to speak during the transition from wakefulness to sleep or vice-versa, and disturbed nocturnal sleep with frequent awakenings and parasomnias. Obesity, headache, memory/concentration difficulties, depressed mood, psychosocial problems and accidents are additional common features of narcolepsy. The prevalence of narcolepsy is estimated around 25 per 100 000 in Caucasian populations. It is often extremely incapacitating, interfering with every aspect of life, in work and social settings.

Excessive daytime sleepiness is lifelong although it diminishes with age as assessed by the multiple sleep latency test (MSLT), an objective test of sleepiness based on 20-min polygraphic recording sessions repeated every 2 h, 4 or 5 times a day. Cataplexy may vanish after a certain time spontaneously or with treatment. Hypnagogic hallucinations and sleep paralysis are most often temporary. Disturbed nocturnal sleep has no spontaneous tendency to improve with time. In the revised International Classification of Sleep Disorders [3], two forms of narcolepsy are distinguished: narcolepsy with cataplexy and narcolepsy without cataplexy.

The essential diagnostic criteria of narcolepsy with cataplexy are:

A. The patient has a complaint of excessive daytime sleepiness occurring almost delay for at least 3 months.

B. A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present.

C. The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT. The mean sleep latency on MSLT is ≤8 min and two or more sleep onset rapid eye movement periods (SOREMPs) are observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test. Alternatively, hypocretin-1 levels in the cerebrospinal fluid (CSF) are ≤110 pg/ml, or one-third of mean normal control values.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.

The diagnostic criteria of narcolepsy without cataplexy include criteria A and D, whilst criteria B and C are as follows:

B. Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported.

C. The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed by an MSLT. In narcolepsy without cataplexy, the mean sleep latency on MSLT is ≤8 min and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test.

Recent years have been characterized by several breakthroughs in the understanding of the pathophysiology of the condition. First, there have been the discoveries of a mutation of the hypocretin type 2 receptor in the autosomal recessive canine model of narcolepsy and of a narcoleptic phenotype in the orexin (hypocretin) knockout mice. Then came the observation of lowered or undetectable levels of hypocretin-1 in the CSF of most human narcoleptics and the finding that sporadic narcolepsy, in dogs and humans, may also be related to a deficiency in the production of hypocretin-1 ligands. The undetectable hypocretin-1 levels seem to be the consequence of a selective degeneration of hypocretin cells in the lateral hypothalamus. An autoimmune etiology is hypothesized. However direct evidence for such a mechanism is still lacking.

Compared with these advances there has been no revolutionary new treatments developed for excessive daytime sleepiness or cataplexy in the last few years, except for the recent trials with intravenous immunoglobulins (IVIg). However, there are several reasons for producing contemporary guidelines on the management of narcolepsy. First, modafinil has been used in Europe for over 10 years, decreasing the need to use amphetamine and amphetamine-like stimulants. Secondly, the newer antidepressants are now widely used in the treatment of cataplexy. Thirdly, sodium oxybate, a drug previously referred to as gamma-hydroxybutyrate (GHB) has been registered for use in cataplexy and is currently submitted for use in all symptoms of narcolepsy.

The first effort in standardizing the treatment of narcolepsy was the 'Practice parameters for the use of stimulants in the treatment of narcolepsy' [4]. Seven years later an update of these practice parameters for

the treatment of narcolepsy grading the evidence available and modifying the 1994 practice parameters was published [5]. Finally guidelines on the diagnostic and management of narcolepsy in adults and children were prepared for the UK [6].

Methods and search strategy

The best available evidence to address each question was sought, with the classification scheme by type of study design according to the EFNS Guidance document [7]. If the highest level of evidence was not sufficient or required updating the literature search was extended to the lower adjacent level of evidence. Several databases were used including Cochrane library, MEDLINE, EMBASE, Clinical Trials until September 2005. Previous guidelines for treatment were sought. Each member of the Task force was assigned a special task, primarily based on symptoms of narcolepsy (excessive daytime sleepiness and irresistible episodes of sleep, cataplexy, hallucinations and sleep paralysis, disturbed nocturnal sleep, parasomnias) and also on associated features (obstructive sleep apnea, adult periodic limb movements in sleep (PLMS), neuropsychiatric symptoms) and special treatments (behavioral and experimental).

Methods for reaching consensus

Each member of the Task force was first invited to send his own contribution to the chairman. Then a meeting gathering seven of the nine members of the Task force was scheduled during the Vth International Symposium on Narcolepsy in Ascona, Switzerland, October 10–15, 2004. A draft of the Guidelines was then prepared by the chairman and circulated amongst all members of the task force for comments. On receipt of these comments the chairman prepared the final version which was circulated again amongst members for endorsement.

Results

Excessive daytime sleepiness and irresistible episodes of sleep

Modafinil and methylphenidate have the indication narcolepsy. Sodium oxybate is currently submitted for all symptoms of narcolepsy. All other drugs are 'off-label'.

*Modafinil (N06BA05)**

Modafinil is a (2-[(diphenylmethyl) sulfinyl] acetamide) chemically unrelated to central nervous system (CNS) stimulants such as amphetamine and methylphenidate. Involvement of adrenergic alpha-1 stimulation [8], indirect and direct interactions of dopamine systems [9–12] and involvement of serotonergic/GABAergic mechanisms [10] have been suggested as possible mechanisms of action. Elimination half-life is 10–12 h.

Four major class I evidence studies ([13], 50 patients; [14], 70 patients; [15,16], 285 and 273 patients) have shown the efficacy of modafinil on excessive daytime sleepiness at doses, 300, 200 and 400 mg/day. The key points of these studies were a reduction of daytime sleepiness, an overall benefit noted by physicians as well as by patients, and a significant improvement in maintaining wakefulness measured by the Maintenance of Wakefulness Test (MWT), with the 300 mg/day dose [13]; a significant decrease of the likelihood of falling asleep measured by the Epworth Sleepiness Scale (ESS), a reduction of irresistible episodes of sleep and of severe somnolence as assessed by the sleep log and a significant improvement in maintaining wakefulness measured with the MWT, with both 200 and 400 mg/day doses [14]); consistent improvements in subjective measures of sleepiness (ESS) and in clinician-assessed change in the patient's condition (Clinical Global Impression or CGI), significant improvement in maintaining wakefulness (MWT) and in decreasing sleepiness judged on the MSLT with both the 200 and the 400 mg/day doses [15,16].

Three further studies have dealt with open label extension data. Beusterien *et al.* [17] reported significantly high scores on 10 of 17 health-related quality of life scales in 558 narcoleptic patients on modafinil 400 mg/day dose, with positive treatment effects sustained over the 40-week extension period. Moldofsky *et al.* [18] reported on 69 patients who entered a 16-week open label extension, followed by a randomized placebo-controlled 2-week period of assessment. Mean sleep latencies on the MWT were 70% longer in the modafinil group compared with placebo. The latency to sleep decreased from 15.3 to 9.7 min in the group switched from modafinil to placebo, and the ESS score increased from 12.9 to 14.4. Mitler *et al.* [19] reported on 478 patients who were enrolled in two 40-week open label extension studies. The majority of patients (75%) received modafinil 400 mg daily. Disease severity improved in $>80\%$ of patients throughout the 40-week study.

According to a class I evidence study [20] in which the efficacy of modafinil 400 mg once daily, 400 mg given in a split dose, or 200 mg once daily was compared, the 400 mg split-dose regimen improved wakefulness significantly in the evening compared with the 200 and 400 mg once daily regimen (both $P < 0.05$).

Although co-administration of drugs is very common in the treatment of narcolepsy with cataplexy, there is

*Anatomical Therapeutic Chemical (ATC) nomenclature

little systematic evidence to support particular combinations. In volunteers there appears to be no pharmacokinetic interactions between modafinil and D-amphetamine or methylphenidate

In the randomized trials adverse effects were minimal. In the Broughton *et al.* [14], the modafinil 400 mg group had more nauseas and nervousness than the modafinil 200 mg and placebo groups. In the US Modafinil in Narcolepsy Multicenter Study Group [15] trial, headache was reported in the treatment groups with a frequency of 52% in the modafinil 200 mg/day, 51% in the modafinil 400 mg/day and 36% in the placebo groups, respectively. However it is our experience that headache usually disappears after several weeks. In the US Modafinil in Narcolepsy Multicenter Study Group [16] trial, modafinil was associated with nausea and rhinitis in 11–13% of the subjects compared with 2–3% in the placebo group.

There is no reported evidence that tolerance develops to the effects of modafinil on excessive daytime sleepiness, although some clinicians have observed it. Similarly, it is generally accepted that modafinil has a low abuse potential. On rare occasions worsening of cataplexy with modafinil has been observed.

The possibility of induction of human hepatic cytochrome P450 enzymes by modafinil should be borne in mind. For example modafinil increases the metabolism of the oral contraceptives [21] and a product containing 50 μg or higher ethinyloestradiol should be prescribed.

Teratology studies performed in animals did not provide any evidence of harm to the fetus (FDA B-category). However modafinil is not recommended in narcoleptic pregnant women as clinical studies are still insufficient.

Amphetamines and amphetamine-like CNS stimulants

Amphetamine (N06BA01)

At low doses the main effect of amphetamine is to release dopamine and to a lesser extent norepinephrine and serotonine. At higher doses monoaminergic depletion and inhibition of reuptake occurs. The D-isomer of amphetamine is more specific for dopaminergic transmission and is a better stimulant compound. Methamphetamine is more lipophilic than D-amphetamine and therefore has more central and fewer peripheral effects than D-amphetamine. The elimination half-life of these drugs is between 10 and 30 h.

Five reports concerned the use of amphetamines. Three class II evidence studies [22–24] showed that D-amphetamine and methamphetamine are effective treatments of excessive daytime sleepiness in short-term use (up to 4 weeks) at starting doses of 15–20 mg increasing up to 60 mg/day. One class IV evidence study [25] showed that long-term drug treatment would result in only minor reduction in irresistible sleep episode propensity.

The main adverse effects are minor irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia and insomnia [26]. Doses of amphetamine >60–100 mg daily often cause serious toxic effects including 'very fast thinking', 'difficulty controlling burst of thoughts', 'bursts of verbal aggressiveness'. Psychotic reactions occur in $<1\%$ of subjects [27]. There are conflicting views on the risk of developing hypertension under chronic administration.

Tolerance to amphetamine effect may develop in up to one-third of patients [27]. There is little or no evidence of abuse and addiction in narcoleptic patients [28].

The FDA classifies drugs as A (controlled studies in humans have shown no risk), B (controlled studies in animals have shown no risk), C (controlled studies in animals have shown risk), D (controlled studies in humans have shown risk) according to their embryotoxic and teratogenic effects). Dextro-amphetamine, with an FDA D-classification and methamphetamine, with an FDA C-classification, are contraindicated during conception and pregnancy. Amphetamines are controlled drugs.

Methylphenidate (N06BA04)

Similar to the action of amphetamine methylphenidate induces dopamine release, but in contrast, it does not have any major effect on monoamine storage. The clinical effect of methylphenidate is supposed to be similar to that of amphetamines. However clinical experience would argue for a slight superiority of amphetamines. In comparison with amphetamine, methylphenidate has a much shorter elimination half-life (2–7 h) and the daily dose may be divided in 2–3 parts. A sustained release form is available and can be useful for some patients.

There were five reports on the use of methylphenidate. There was only one class II evidence study showing significant improvement in all dosages (10, 30, and 60 mg/day) compared with baseline [29]. According to a class IV evidence study [30] methylphenidate conveyed good to excellent response in 68% of cases and according to another one [31] methylphenidate produced marked to moderate improvement in 90% of cases. On the MWT the sleep latencies were increased to 80% of controls with a 60 mg daily dose [23].

Adverse effects are the same as with amphetamines. However methylphenidate probably has a better therapeutic index than D-amphetamine with less reduction of appetite or increase in blood pressure [32].

Tolerance may develop. Abuse potential is low in narcoleptic patients. Methyphenidate has no FDA classification because no adequate animal or human studies have been performed. It is contraindicated in pregnant women.

Gamma-hydroxybutyrate (GHB), Sodium oxybate (in its most recent designation) (N07XX04)

Gamma-hydroxybutyrate is a natural neurotransmitter/neuromodulator that may act through its own receptors and via stimulation of GABA-B receptors. A major effect may be silencing of dopaminergic neurons. Its elimination half-life is 90–120 min.

Broughton and Mamelak [33] were the first to suggest that GHB was useful to control cataplexy, enhance daytime alertness and improve night sleep in narcoleptic patients. Scrima *et al.* [34] published the first reports of a class II evidence study showing no effect of GHB at a dose of 25–50 mg/kg, twice a night, on subjective estimates of sleep latency at night and on the Stanford Sleepiness Scale (SSS). Later on an evidence class 1 study [35] found a substantial improvement of all parameters of subjective daytime sleepiness with two nocturnal doses of 30 mg/kg, although MSLT results were not significantly different from placebo. The main potential problem with GHB is abuse potential. GHB is misused in athletes for its metabolic effects (growth hormone releasing effect) and it has been used as a 'date rape' drug because of its rapid sedating effects. However the monitored prescription program in the US revealed that this is very low risk in narcoleptic patients. Cases of overdose or severe withdrawal symptoms are occasionally observed in emergency rooms. Adverse effects, in particular when using high doses, may be enuresis and somnambulism. Waking up whilst the drug is still centrally active may result in dizziness and gait problems.

Gamma-hydroxybutyrate has recently re-emerged as a major treatment for narcolepsy with cataplexy under the name sodium oxybate (the terms 'GHB', '4-hydroxybutyric acid, sodium salt', and 'sodium oxybate' are completely synonymous). Four class I evidence studies [36–39] have shown reduced excessive daytime sleepiness, increased level of alertness and ability to concentrate and a recent class I evidence study [40] has shown sodium oxybate and modafinil to be equally efficacious for the treatment of excessive daytime sleepiness, producing addictive effects when used together [40]. Starting dose is 4.5 g/night, divided into two equal doses of 2.25 g/night. Full therapeutic benefit generally occurs at the 6–9 g/night doses. This drug is only available in liquid form and must be taken twice a night. Most commonly reported adverse effects are nausea, which usually goes away after a few days, nocturnal enuresis which may persist intermittently, confusional arousals and headache. Of concern is the above-mentioned abuse potential of GHB. Whilst there is no clear evidence of emergence of dependence in patients taking sodium oxybate at therapeutic doses, this possibility cannot be excluded. Animal studies have shown no evidence of teratogenicity (FDA B-category). However the potential risk for humans is unknown, and sodium oxybate is not recommended during pregnancy.

Pemoline (N06BA05)

Pemoline, an oxazolidine derivative with long half-life (12 h) and mild action, selectively blocks dopamine reuptake and only weakly stimulates dopamine release. There were two reports on the use of pemoline in narcoleptic patients. According to a class II evidence study [29] using three dosages (18.75, 56.25 and 112.50 mg/day) pemoline did not improve wakefulness but it did improve ability to perform Wilkinson Addition and Digit-Symbol Substitution tests on a 112.50 mg daily dose. According to a class IV evidence study [41] there was a moderate to marked improvement in sleepiness in 65% of narcoleptic subjects. Pemoline is usually better tolerated than D-amphetamine or methamphetamine in terms of adverse effects (minimal sympathomimetic effects) and tolerance [41]. Due to potential lethal hepatotoxicity, the medication has been withdrawn in several countries. Pemoline is classified as FDA B-category (no risk in animal studies), but there have been no controlled studies in humans, so that the drug is not recommended during pregnancy.

Mazindol (A08AA06)

Mazindol is an imidazolidine derivative with similar pharmacological effects to the amphetamines. It is a weak releasing agent for dopamine, but it also blocks dopamine and norepinephrine reuptake with high affinity. Its elimination half-life is around 10 h. There were five reports on the use of mazindol in treating excessive daytime sleepiness in narcoleptic patients. According to a class II evidence study [22] mazindol was effective on reducing sleepiness at a dose of 2 + 2 mg/day (during 4 weeks) in 53–60% of subjects. In addition several class IV evidence studies [42–45] have shown significant improvement of sleepiness in 50–75% of patients. Clinical experience suggests to start treatment at a low dosage of 1 mg/day which may be effective in individual patients. Adverse effects include dry mouth, nervousness, constipation, and less frequently nauseas, vomiting, headache, dizziness, tachycardia, excessive sweating. Rare cases of pulmonary hypotension and valvular abnormalities have

been reported. For this reason it has been withdrawn from the market in several countries. The use in narcolepsy is still warranted according to most experts, but as third-line treatment and with close monitoring. Tolerance is uncommon and abuse potential may be low [44]. Mazindol is also classified as FDA B-category, without controlled studies in humans. It is not recommended in pregnant women.

Phenelzine (N06AF03)

Phenelzine is a non-selective monoamine oxidase inhibitor which can cause hypertensive crises if tyramine or dopamine-containing food or sympathomimetic agents are ingested concurrently. Wyatt *et al.* [46] administered phenelzine (60–90 mg/day) for 1 year to seven narcoleptic patients who previously had unsatisfactory responses to more conventional forms of therapy. All patients noted improvement in cataplexy and irresistible episodes of sleep, although three continued to experience some drowsiness. However there is the above-mentioned risk of hypertensive crisis and the necessity to avoid some drugs and to adhere to certain dietary restriction which makes this medication unsuitable for long-term treatment.

Selegiline (N04B0D1)

Selegiline is a potent irreversible MAO-B selective inhibitor. It is metabolically converted to desmethyl selegiline, amphetamine and methamphetamine. The elimination half-life of the main metabolites is variable, 2.5 h for desmethyl selegiline, 18 h for amphetamine and 21 h for methamphetamine. According to one class I evidence study [47] selegiline, 10–40 mg daily, reduced irresistible episodes of sleep and sleepiness up to 45%, and according to another one [48] selegiline at a dose of at least 20 mg/day caused a significant improvement of daytime sleepiness and a reduction of irresistible episodes of sleep, as well as a dose-dependent REM suppression during nighttime sleep and naps. The results were similar in a class IV evidence study [49] showing improvement in 73% of patients. Use of selegiline is limited by potentially sympathomimetic adverse effects and interaction with other drugs. Co-administration of triptans and serotonin specific reuptake inhibitors is contraindicated. Abuse potential is low [47,48]. Selegiline is another FDA B-category drug without controlled studies in humans. It is not recommended in pregnant women.

Behavioral treatments

Although non-pharmacological treatments of narcolepsy have more or less always been part of an integrative treatment concept, very little systematic studies have been performed investigating the impact of such approaches on the symptomatology of narcoleptic patients. Five class II evidence studies and three class III evidence studies investigated the effects of various sleep–wake schedules on excessive daytime sleepiness and sleep in narcoleptic patients. However most of these studies were extremely heterogeneous and only two studies [50,51] looked at the effects of a behavioral regime in a clinically meaningful time range (2–4 weeks). All other studies considered only acute (1–2 days) manipulations. Amongst those, a study by Mullington and Broughton [52] tested two napping strategies, a single long nap placed 180° out of phase with the nocturnal midsleep time (that is with the midnap point positioned 12 h after the nocturnal midsleep time) and five naps positioned equidistantly throughout the day, with the midnap time of the third nap set at 180° out of phase with the nocturnal midsleep and the others equidistant between the hours of morning awakening and evening sleep onset. The two protocols tested resulted in a reaction time improvement, but no difference between long and multiple naps was disclosed. Most experts agree that patients should live a regular life: go to bed at the same hour each night and rise at the same time each day.

Recommendations

First-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep should rely on modafinil, 100–400 mg/day, given in two doses, one in the morning and one early in the afternoon (level A). In a few cases dosage should be increased up to 300 mg twice a day. Increase of the daily dosage above 600 mg is in general not advisable. Second line pharmacological treatment is methylphenidate at a daily dosage of 10–60 mg. Of note a growing practice in the USA, based on level A evidence, of using sodium oxybate as a first line treatment of excessive daytime sleepiness. This could be the case in Europe as well, if sodium oxybate is registered for narcolepsy (including cataplexy, excessive daytime sleepiness and disturbed noctural sleep). In severe cases the combination of modafinil and sodium oxybate appears to be beneficial. Given these various possibilities the role of other compounds becomes fairly limited, unless recommended treatments have failed. Behavioral treatment measures are always advisable. Essentially the studies available support on a B level the recommendation to take planned naps during the day, as naps decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.

Cataplexy

Only Sodium oxybate, and the monoamine non specific uptake inhibitor clomipramine in a few European countries, have the indication 'cataplexy'. All other medications are 'off-label'

Gamma-hydroxybutyrate (GHB), Sodium oxyate (in its most recent designation) (N07XX04)

According to a class II evidence study [34] GHB at a dose of 25–50 mg/kg, twice at night, reduced cataplexy in 50% of 20 subjects. Later on a class I evidence study [35] showed a significant reduction in the number of cataplectic attacks per day with GHB two daily doses of 30 mg/kg at night in 24 subjects. Adverse effects were rather limited with one patient reporting a single period of protracted sleep paralysis in combination with hypnagogic hallucination in the first week of treatment and another patient reporting loss of weight in the first 2 weeks of treatment with GHB.

US Xyrem Multicenter Study Groups [36,37] (class I evidence) have shown a significant dose-dependent reduction of the number of cataplectic attacks in large samples of patients (136 in the first one and 118 in the second) in doses of sodium oxybate, 3–9 g nightly in two doses, which were significant at 4 weeks and maximal after 8 weeks. In addition the US Xyrem Multicenter Study Group [53] was conducted to demonstrate the long-term efficacy of sodium oxybate for the treatment of cataplexy. Fifty-five narcoleptic patients with cataplexy who had received continuous treatment with sodium oxybate for 7–44 months (mean: 21 months) were enrolled in a double-blind treatment withdrawal paradigm. During the 2-week double-blind phase, the abrupt cessation of sodium oxybate therapy in the placebo group resulted in a significant increase in the number of cataplexies compared with the patients who remained on sodium oxybate. Ultimately the Xyrem International Study Group [54] conducted a study with 228 adult narcolepsy with cataplexy patients randomized to receive 4.5, 6, or 9 g of sodium oxybate nightly or placebo for 8 weeks. Compared with placebo, doses of 4.5, 6, and 9 g sodium oxybate for 8 weeks resulted in statistically significant median decreases in weekly cataplexy attacks of 57.0, 65.0 and 84.7% respectively.

Adverse effects, nausea, vomiting, headache, dizziness, sleepiness, paresthesia, tremor, enuresis were generally mild, and only dizziness occurred at a significant level ($P < 0.5$). Patients showed no evidence of tolerance.

Monoamine non-specific uptake inhibitors (N06AA)

The first use of tricyclics for treating cataplexy dates back to 1960 with imipramine [55]. It was followed by desmethylimipramine [56], clomipramine [57] and protryptiline [58].

Clomipramine, a drug which is principally a serotoninergic reuptake inhibitor, but metabolizes rapidly into desmethyl clomipramine, an active metabolite with principally adrenergic reuptake inhibitory properties, has been the most widely evaluated for cataplexy, with one class III evidence study [59] and four class IV evidence studies [25,57,60,61]. All these studies have shown a complete abolition or decrease in severity and frequency of cataplexy at doses of 25–75 mg daily. However low doses of 10–20 mg daily are often very effective and it is always advisable to start with them.

Reported adverse effects consist of anticholinergic effects including dry mouth, sweating, constipation, tachycardia, weight increase, hypotension, difficulty in urinating and impotence. One trial [61] mentioned the development of tolerance after 4.5 months. Patients may experience with tricyclics a worsening or 'de novo' onset of REM sleep behavior disorder (RBD). Moreover, there is a risk, if the tricyclics are suddenly withdrawn, of a marked increase in number and severity of cataplectic attacks, a situation referred to as 'rebound cataplexy', or even 'status cataplecticus'. Tolerance to the effects of tricyclics may develop.

Animal studies have not shown teratogenic properties and epidemiological studies performed in a limited number of women have not shown any risk of malformation in the fetus (FDA B-category). However newborns of mothers submitted to long-standing treatment with high doses of antidepressants may show symptoms of atropine intoxication. Thus, if cataplexy is mild, it is advisable to cease the anti-cataplectic drug before conception. When cataplexy is severe the risk of injury during pregnancy may be greater than the risks caused to the infant by the drug.

Newer antidepressants

Selective serotonin re-uptake inhibitors (SSRIs) (N06AB)

These compounds are much more selective than tricyclic antidepressants toward the serotoninergic transporter, although most of them have affinities for other monoamine transporters at 10 to 100 times higher concentrations. In comparison with tricyclics higher doses are required and effects less pronounced [62].

According to a class I evidence study [63] femoxetine, 600 mg/day, reduced cataplexy. In addition two class III evidence studies [64,65] have shown fluoxetine (20–60 mg/day) [59] and fluvoxamine (25–200 mg/day) to be mildly active on cataplexy. In a class IV evidence study [66] citalopram proved active in three cases of intractable cataplexy.

Adverse effects are less pronounced than with tricyclics. They include CNS excitation, gastrointestinal upset, movement disorders and sexual difficulties. The risk of marked increase in number and severity of cataplectic attacks has been documented after discontinuation of SSRIs [67]. Tolerance to SSRIs does not develop.

Studies performed in animals did not provide any evidence of malformation (FDA B-category). However clinical studies are not sufficient to assess a possible risk for the human fœtus. Thus the use of SSRIs is not recommended in narcoleptic pregnant women.

Norepinephrine uptake inhibitors

In a class III evidence study [68], viloxazine (N06AX09) at a 100 mg dose daily significantly reduced cataplexy. The main advantage of this compound rests on its limited adverse effects (nausea and headache in one subject only out of 22). In a class IV evidence study [69], reboxetine (N06AX18) at a daily dose of 2–10 mg, significantly reduced cataplexy. Treatment was generally well tolerated, with only minor adverse effects being reported (dry mouth, hyperhydrosis, constipation, restlessness). Atomoxetine (N06BA09) (36–100 mg/day) has been used anecdotally with success on cataplexy. Of note however, atomoxetine has been shown to slightly but significantly increase heart rate and blood pressure in large samples. Thus caution is needed.

Norepinephrine/serotoninergic uptake inhibitor

Venlafaxine (N06AX16) (150–375 mg/day), was given to four subjects, for periods 2–7 months [70]. Initial improvement in both excessive daytime sleepiness and cataplexy was reported by all subjects. No subjective adverse effects were observed apart from slight insomnia in two subjects. Increased heart rate and blood pressure are potential adverse effects. Tolerance was reported in one subject. Venlafaxine is not recommended in pregnant narcoleptic women.

Other Compounds

Mazindol (A08AA06)

Mazindol has an anticataplectic property in addition to its alerting effect. According to a class II evidence study [22] mazindol at a dose of 2 + 2 mg/day (during 4 weeks) did not alter the frequency of cataplexy. On the other hand, in one class IV evidence study [42] the 'percentage of efficacy' was 50% and in another class IV evidence study [44] 85% of subjects reported significant improvement on cataplexy. Potential adverse effects have been reviewed above.

Phenelzine (N06AF03)

As already pointed out, Wyatt *et al.* [46] administered phenelzine (60–90 mg/day) for 1 year, to seven narcoleptic patients who previously had insatisfactory response to more conventional forms of therapy (class IV evidence study). All patients noted improvement in cataplexy.

Selegiline (N04B0D1)

Selegiline has a potent anticataplectic effect in addition to its relatively good alerting effect. According to one class 1 evidence study selegiline reduced cataplexy up to 89% at a dose of 10–40 mg [47] and, according to a second one, reduced cataplexy significantly at a dose of 10 mg × 2 [48]. Adverse effects and interaction with other drugs have been referred to above.

Amphetamine (N06BA01)

As previously indicated, the main effect of amphetamines is to release dopamine and to a lesser extent norepinephrine and serotonine. The effect of amphetamine on norepinephrine neurons, in particular, may help to control cataplexy. This may be an important factor in patients who switch from amphetamine to modafinil and find that mild cataplexy is no longer controlled.

Behavioral therapy

The single non-pharmacological approach known to specifically reduce the frequency and severity of cataplexy, which however has not been empirically studied, is to avoid precipitating factors. Because cataplexy is tightly linked to strong, particularly positive, emotions, the most important precipitating factor is social contact. Indeed, social withdrawal is frequently seen in narcolepsy and helpful in reducing cataplexy, but it can hardly be considered as a recommendation or 'treatment'.

Recommendations

Based on class I evidence (level A rating) studies, first-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum dosage of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g. Most patients will start to feel better within the first few days, but optimal response at any given dose may take as long as 8 to 12 weeks. For this reason adjustment should typically occur at least 2-week intervals. Second-line pharmacological treatments are antidepressants. Tricyclic antidepressants, particularly clomipramine (10–75 mg), are the most potent anticataplectic drugs. However they have the drawback of anticholinergic adverse effects. Starting dosage should be as low as possible. SSRIs are slightly less active but have less adverse effects. The norepinephrine/serotonine

reuptake inhibitor venlafaxine is widely used today but lacks any published clinical evidence of efficacy. Norepinephrine reuptake inhibitors, such as reboxetine and atomotexine, also lack published clinical evidence. Given the availability of sodium oxybate and the activity of antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy. However, advice to some subjects should include the avoidance of known triggers, whenever possible.

Hallucinations and sleep paralysis

Treatment of hallucinations and sleep paralysis is considered as a treatment of REM-associated phenomena. Most studies have focused much more on the treatment of cataplexy. Improvement of cataplexy is most often associated with reduction of hallucinations and sleep paralysis. One class I evidence study [35] focused on the effects of GHB on irresistible sleep episodes, awakenings at night, cataplexy, hallucinations and sleep paralysis. There was a reduction of the daily number of hallucinations, whilst the effect on sleep paralysis could not be assessed due to the low incidence of this item during the baseline period. There are no reports on attempts to modify the occurrence of these symptoms by behavioral techniques

Recommendations
As for cataplexy but lack of studies with these outcome parameters.

Poor sleep

Benzodiazepines (N05CD) and non-benzodiazepines (N05CF)
A single class III evidence study [71] has shown an improvement of sleep efficiency and overall sleep quality with triazolam 0.25 mg given for two nights only. Adverse effects were not recorded. No effect of improved sleep on excessive daytime sleepiness was recorded. No study has been performed with either zopiclone or zolpidem or zaleplon.

Gamma-hydroxybutyrate (GHB), Sodium oxybate (in its most recent designation) (N07XX04)
Studies performed with GHB 25–30 mg/kg at night have shown either a decrease of subjective arousals [34], or a decrease of the number of awakenings [35], or a decrease of sleep fragmentation [72]. The US Xyrem studies have shown a significant decrease of the number of nighttime awakenings, significant with sodium oxybate 9 g [36] and a significant improvement of nocturnal sleep quality ($P = 0.001$) with sodium oxybate 3–9 g, due to increased slow wave sleep [37]. Adverse effects are the same as already listed.

Modafinil (N06BA07)
In the US Modafinil in Narcolepsy Multicenter Study Group [16] a small improvement in sleep consolidation was evidenced through an increased sleep efficiency. Thus it is always advisable to wait for the effects of modafinil before prescribing a special treatment for disturbed nocturnal sleep.

Behavioral therapy
No study has been conducted to investigate the effects of behavioral treatments on night sleep in narcoleptic patients in clinically relevant settings.

Recommendations
Benzodiazepines or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (level C). Objective evidence is lacking over intermediate or long-term follow-up. The improvement reported by some patients once established on modafinil is noteworthy. According to level A studies with gamma-hydroybutyrate and sodium oxybate, sodium oxybate might become the most appropriate option.

Parasomnias

Narcoleptic patients often display vivid and frightening dreams and RBD. Given the beneficial effects of sodium oxybate on disturbed nocturnal sleep, this medication might be of interest in the case of disturbed dreams. However no systematic study of sodium oxybate on dreams of narcoleptics has ever been conducted.

In the case of RBD its occurrence in narcoleptic patients is remarkable for two aspects: first, the mean age of onset of RBD in narcoleptic patients is young (between 25 and 30 years of age) and RBD may precede narcolepsy in one-third of patients; secondly, RBD events are usually less violent in narcoleptic patients than in other patients.

There is no available report of any prospective, double-blind, placebo-controlled trial of any drug specific for RBD in narcoleptic subjects, but only a few case reports. Use of clonazepam was reported as successful in two cases [73,74]. In one case [73]) clonazepam led to the development of obstructive sleep apnea syndrome. An alternative treatment is needed when patients affected with RBD do not respond or are intolerant to clonazepam. In a recent study involving 14 patients, two of whom had narcolepsy, melatonin was used successfully

in 57% of cases at a dose of 3–12 mg/night [75]. Adverse effects such as sleepiness, hallucination and headache were recorded in one-third of patients

Recommendations
Based on available information it is difficult to provide guidance for prescribing in parasomnias associated with narcolepsy other than to recommend conventional medications.

Associated features

Obstructive sleep apnea/adult (OSA)
According to several publications [76,77] the prevalence of OSA is larger in narcoleptic patients than in the general population. One potential explanation is the frequency of obesity in narcolepsy, which could predispose to OSA. There is no documented effect of OSA treatments in narcoleptic patients.

Periodic limb movements in sleep
Periodic limb movements in sleep (PLMS) are more prevalent in narcolepsy than in the general population [77,78]. This applies particularly to young narcoleptic patients. L-dopa [79], GHB [80], bromocriptine [81] are effective treatments. However there is no documented effect on excessive daytime sleepiness.

Neuropsychiatric symptoms
No higher rate of psychotic manifestations has been evidenced in narcoleptic patients. On the other hand, depression is more frequent in narcoleptic patients than in the general population [82–84]. Antidepressant drugs and psychotherapy are indicated. However there is no systematic study of these therapeutic procedures in depressed narcoleptic patients.

Recommendations
OSA should be treated no differently to the general population, although some experts have the experience that the majority of patients refuse to continue continuous positive airway pressure (CPAP) therapy because of a lack of clinical improvement. There is usually no need to treat PLMS in narcoleptic patients. Antidepressants and/or psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.

Psychosocial support and counseling

Patients' groups
Interaction with those who have narcolepsy is often of great benefit to the patient and his (or her) spouse regarding the recognition of symptoms and possible counter measures. The website addresses of four important patient support groups are:
- France: http://perso.wanadoo.fr/anc.paradoxal/
- Germany: http://dng-ev.org
- The Netherlands: http://www.narcolepsie.nl
- United Kingdom: http://www.narcolepsy.org.uk

Social workers
Social workers can provide support and counseling in various important areas such as career selection, adjustments at school or at work, and when financial or marital problems exist.

Recommendations
Interaction with narcoleptic patients and counseling from trained social workers are recommended (level C).

Good practice points

A prerequisite before implementing a potentially life long treatment is to establish an accurate diagnosis of narcolepsy with or without cataplexy, and to check for possible comorbidity. Following a complete interview the patient should undergo an all-night polysomnography followed immediately by an MSLT. Human leucocyte antigen (HLA) typing is rarely helpful. CSF hypocretin-1 measurement may be of help and is added as diagnostic test in the revised International Classification of Sleep Disorders [3], particularly if the MSLT cannot be used or provides conflicting information. Levels of CSF hypocretin are only significantly reduced or absent in cases of narcolepsy with cataplexy. In the absence of cataplexy, the value of measuring hypocretin is debatable.

Once diagnosed, patients must be given as much information as possible about their condition (nature of the disorder, genetic implication, medications available and their potential adverse effects) to help them cope with a potentially debilitating condition.

Regular follow-up is essential to monitor response to treatment, adapt the treatment in case of insufficient response or adverse effects, and above all encourage the patient to stand on an efficacious therapy. Another polysomnographic evaluation of patients should be considered in case of worsening of symptoms or development of other symptoms, but not for evaluating treatment in general.

Future treatments

Current treatments for human narcolepsy are symptomatically based. However given the major developments in understanding the neurobiological basis of the condition, new therapies are likely to emerge. It is

imperative that neurologists remain aware of future developments, not only out of interest but also because of the implications for treating a relatively common and debilitating disease.

There are three focuses for future therapy:

- Symptomatic endocrine/transmitter modulating therapies: selective histamine agonists (H3-antagonists), growth hormone-releasing hormone (GHRH) antagonists, GHB agonists and GABA-B agonists, most of which have been tried in narcoleptic mice or canines [85].
- Hypocretin-based therapies: hypocretin agonists and cell transplantation [86,87].
- Immune-based therapies including steroid therapy, IVIg and plasmaphoresis.

The latter are of special interest as several attempts have been made so far in man, the most promising being an association of prednisone and IVIg near the onset of narcolepsy in a 10-year-old boy [88] and IVIg alone in four subjects [89] and in another four sujects [90] with positive subjective effects mainly on cataplexy.

Conclusion

The recommendations expressed in these guidelines are based on the best currently available knowledge. However developments in the field of narcolepsy are rapidly advancing and the use of agents such as sodium oxybate may become widespread, largely depending on regulation issues. In addition treatments directed at replacing hypocretin or even preventing the loss of neurons containing the neuropeptide may become a reality in the near future.

Statement of the likely time when the guidelines will need to be updated

An update of the guidelines will need to be considered if sodium oxybate is registered for 'narcolepsy' (including excessive daytime sleepiness and disturbed nocturnal sleep in addition to cataplexy) and once sodium oxybate has been used for cataplexy, for two years or so. The introduction on the market of one of the future experimental therapies listed at the end of the Guidelines may well have a profound impact on subsequent recommendations.

Conflicts of interest

Dr Billiard received honoraria from Orphan Drugs for invited talks and is a member of the Xyrem (UCB Pharma) advisory board. Dr Bassetti received honoraria from Orphan Drugs for invited talks and is a member of the Xyrem (UCB Pharma) advisory board. He was involved in clinical trials with Cephalon and Orphan. Dr Dauvilliers was involved in a clinical trial with Cephalon and another one with Orphan. Dr Lammers is a member of the Narcolepsy advisory group for Organon Nederland BV (license holder for modafinil in the Netherlands) and a member of the Xyrem (UCB Pharma) advisory board. Dr Mayer received honoraria from Cephalon and UCB Pharma for invited talks. He was involved in one trial with Cephalon and two trials with Orphan Drugs. He is a member of the Xyrem advisory board. Dr Reading received honoraria from Cephalon for invited talks. Dr Sonka was involved in two trials with Orphan and is currently involved in a trial with Cephalon. Dr Sonka is also a member of the Xyrem advisory board.

References

1. Westphal C. Eigentümliche mit Einschlafen verbundene Anfälle. *Arch Psychiatr Nervenkr* 1877; **7:** 631–635.
2. Gelineau J. De la narcolepsie. *Gaz des Hôp (Paris)* 1880; **55:** 635–637.
3. American Academy of Sleep Medicine. *ICSD-2-International Classification of Sleep Disorders*, 2nd edn. Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine, 2005.
4. Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of stimulants in the treatment of narcolepsy. *Sleep* 1994; **17:** 348–351.
5. Standards of Practice Committee. Practice parameters for the treatment of narcolepsy: an update for 2000. *Sleep* 2001; **24:** 451–466.
6. Britton T, Hansen A, Hicks J, *et al*. *Guidelines on the Diagnosis and Management of Narcolepsy in Adults and Children. Evidence-Based Guidelines for the UK with Graded Recommendations*. Ashtead, UK: Taylor Patten Communications Ltd, 2002.
7. Brainin M, Barnes M, Baron JC, *et al*. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces-revised recommendations 2004. *European Journal of Neurology* 2004; **11:** 577–581.
8. Lin JS, Roussel B, Akaoka H, Fort P, de Billy G, Jouvet M. Role of catecholamines in modafinil and amphetamine induced wakefulness, a comparative pharmacological study. *Brain Research* 1992; **591:** 319–326.
9. Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. *Sleep* 1994; **17:** 436–437.
10. Ferraro L, Tanganelli S, O'Connor WT, Antonelli T, Rambert F, Fuxe K. The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local GABAergic mechanism. *European Journal of Pharmacology* 1996; **306:** 33–39.
11. Dauvilliers Y, Neidhart E, Lecendreux M, Billiard M, Tafti M. MAO-A and COMT polymorphisms and gene effects in narcolepsy. *Molecular Psychiatry* 2001; **6:** 367–372.
12. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. *Journal of Neuroscience* 2001; **21:** 1787–1794.

13. Billiard M, Besset A, Montplaisir J, *et al*. Modafinil: a double-blind multicenter study. *Sleep* 1994; **17** (Suppl.)**:** 107–112.
14. Broughton RJ, Fleming JAE, George CFP, *et al*. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; **49:** 444–451.
15. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Annals of Neurology* 1998; **43:** 88–97.
16. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000; **54:** 1166–1175.
17. Beusterien KM, Rogers AE, Walsleben JA, *et al*. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep* 1999; **22:** 757–765.
18. Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. *Sleep Medicine* 2000; **1:** 109–116.
19. Mitler MM, Hirsh J, Hirshkowitz M, Guilleminault C, for the US Modafinil in Narcolepsy Multicenter Study Group. Long-term efficacy and safety of modafinil (PROVIGIL®) for the treatment of excessive daytime sleepiness associated with narcolepsy. *Sleep Medicine* 2000; **1:** 231–243.
20. Schwartz JR, Feldman NT, Bogan RK, Nelson MT, Hughes RJ. Dosing regimen of modafinil for improving daytime wakefulness in patients with narcolepsy. *Clinical Neuropharmacology* 2003; **26:** 252–257.
21. Palovaara S, Kivisto KT, Tapanainen P, Manninen P, Neuvonen PJ, Laine K. Effect of an oral contraceptive preparation containing ethinylestradiol and gestodene on CYP3A4 activity as measured by midazolam l-hydroxylation. *British Journal of Clinical Pharmacology* 2000; **50:** 333–337.
22. Shindler J, Schachter M, Brincat S, Parkes JD. Amphetamine, mazindol, and fencamfamin in narcolepsy. *BMJ* 1985; **290:** 1167–1170.
23. Mitler MM, Hajdukovic R, Erman M, Koziol JA. Narcolepsy. *Journal of Clinical Neurophysiology* 1990; **7:** 93–118.
24. Mitler MM, Hajdukovic R, Erman M. Treatment of narcolepsy with methamphetamine. *Sleep* 1993; **16:** 306–317.
25. Chen SY, Cloift SJ, Dahlitz MJ, Dunn G, Parkes JD. Treatment in the narcoleptic syndrome: self assessment of the action of dexamphetamine and clomipramine. *Journal of Sleep Research* 1995; **4:** 113–118.
26. Mitler MM, Aldrich MS, Koob GF, Zarcone V. Narcolepsy and its treatment with stimulants (ASDA standards of practice). *Sleep* 1994; **17:** 352–371.
27. Guilleminault C. Amphetamines and narcolepsy: use of the Stanford database. *Sleep* 1993; **16:** 199–201.
28. Parkes JD, Dahlitz M. Amphetamine prescription. *Sleep* 1993; **16:** 201–203.
29. Mitler MM, Shafor R, Hajdukovik R, Timms RM, Browman CP. Treatment of narcolepsy: objective studies on methylphenidate, pemoline, and protriptyline. *Sleep* 1986; **9:** 260–264.
30. Yoss RE, Daly D. Treatment of narcolepsy with Ritalin. *Neurology* 1959; **9:** 171–173.
31. Honda Y, Hishikawa Y, Takahashi Y. Long-term treatment of narcolepsy with methylphenidate (Ritalin®). *Current Therapeutic Research* 1979; **25:** 288–298.
32. Guilleminault C, Carskadon MA, Dement WC. On the treatment of rapid eye movement narcolepsy. *Archives of Neurology* 1974; **30:** 90–93.
33. Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gammahydroxybutyrate. *Canadian Journal of Neurological Sciences* 1979; **6:** 16.
34. Scrima L, Hartman PG, Johnson FH, Jr, Hiller FC. Efficacy of gamma-hydroxybutyrate versus placebo in treating narcolepsy-cataplexy: double-blind subjective measures. *Biological Psychology* 1989; **26:** 331–343.
35. Lammers GJ, Arends J, Declerck AC, Ferrari MD, Schouwink G, Troost J. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep* 1993; **16:** 216–220.
36. US Xyrem Multicenter Study Group. A randomized, double-blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep* 2002; **25:** 42–49.
37. US Xyrem Multicenter Study Group. A 12-month, open-label multi-center extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003; **26:** 31–35.
38. Mamelak M, Black J, Montplasir J. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. *Sleep* 2004; **27:** 1327–1334.
39. The Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *Journal of Clinical Sleep Medicine* 2005; **1:** 391–397.
40. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep* 2006; **29:** 939–946.
41. Honda Y, Hishikawa Y. A long-term treatment of narcolepsy and excessive daytime sleepiness with pemoline (Bentanamin®). *Current Therapeutic Research* 1980; **27:** 429–441.
42. Iijima S, Sugita Y, Teshima Y, Hishikawa Y. Therapeutic effects of mazindol on narcolepsy. *Sleep* 1986; **9:** 265–268.
43. Parkes JD, Schachter M. Mazindol in the treatment of narcolepsy. *Acta Neurologica Scandinavica* 1979; **60:** 250–254.
44. Vespignani H, Barroche G, Escaillas JP, Weber M. Importance of mazindol in the treatment of narcolepsy. *Sleep* 1984; **7:** 274–275.
45. Alvarez B, Dahlitz M, Grimshaw J, Parkes JD. Mazindol in long-term treatment of narcolepsy. *Lancet* 1991; **337:** 1293–1294.
46. Wyatt R, Fram D, Buchbinder R, Snyder F. Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *New England Journal of Medicine* 1971; **285:** 987–999.
47. Hublin C, Partinen M, Heinonen E, Puuka P, Salmi T. Selegiline in the treatment of narcolepsy. *Neurology* 1994; **44:** 2095–2101.
48. Mayer G, Meier-Ewert K. Selegiline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. *Clinical Neuropharmacology* 1995; **18:** 306–319.

49. Reinish LW, MacFarlane JG, Sandor P, Shapiro CM. REM changes in narcolepsy with selegiline. *Sleep* 1995; **18:** 362–367.
50. Rogers AE, Aldrich MS. The effect of regularly scheduled naps on sleep attacks and excessive daytime sleepiness associated with narcolepsy. *Nursing Research* 1993; **42:** 111–117.
51. Rogers AE, Aldrich MS, Lin X. Comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. *Sleep* 2001; **24:** 385–391.
52. Mullington J, Broughton R. Scheduled naps in the management of daytime sleepiness in narcolepsy-cataplexy. *Sleep* 1993; **16:** 444–456.
53. US Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. *Sleep Medicine* 2004; **5:** 119–123.
54. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Medicine* 2005; **6:** 415–421.
55. Akimoto H, Honda Y, Takahashi Y. Pharmacotherapy in narcolepsy. *Diseases of the Nervous System* 1960; **21:** 1–3.
56. Hishikawa Y, Ida H, Nakai K, Kaneko Z. Treatment of narcolepsy with imipramine (tofranil) and desmethylimipramine (pertofran). *Journal of the Neurological Sciences* 1965; **3:** 453–461.
57. Passouant P, Baldy-Moulinier M. Données actuelles sur le traitement de la narcolepsie. Action des imipraminiques. *Concours Médical* 1970; **92:** 1967–1970.
58. Schmidt HS, Clark RW, Hyman PR. Protriptyline: an effective agent in the treatment of the narcolepsy-cataplexy syndrome and hypersomnia. *American Journal of Psychiatry* 1977; **134:** 183–185.
59. Schachter M, Parkes JD. Fluvoxamine and clomipramine in the treatment of cataplexy. *Journal of Neurology, Neurosurgery and Psychiatry* 1980; **43:** 171–174.
60. Shapiro CM. Treatment of cataplexy with clomipramine. *Archives of Neurology* 1975; **32:** 653–656.
61. Guilleminault C, Raynal D, Takahashi S, Carkadon M, Dement W. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. *Acta Neurologica Scandinavica* 1976; **54:** 71–87.
62. Nishino S, Mignot E. Pharmacological aspects of human and canine narcolepsy. *Progress in Neurobiology* 1997; **52:** 27–78.
63. Schrader H, Kayed K, Bendixen Markset AC, Treidene HE. The treatment of accessory symptoms in narcolepsy: a double-blind cross-over study of a selective serotonin reuptake inhibitor (femoxetine) versus placebo. *Acta Neurologica Scandinavica* 1986; **74:** 297–303.
64. Langdon N, Bandak S, Shindler J, Parkes JD. Fluoxetine in the treatment of cataplexy. *Sleep* 1986; **9:** 371–372.
65. Frey J, Darbonne C. Fluoxetine suppresses human cataplexy: a pilot study. *Neurology* 1994; **44:** 707–709.
66. Thirumalai SS, Shubin RA. The use of citalopram in resistant cataplexy. *Sleep Medicine* 2000; **1:** 313–316.
67. Poryazova R, Siccoli M, Werth E, Bassetti C. Unusually prolonged rebound cataplexy after withdrawal of fluoxetine. *Neurology* 2005; **65:** 967–968.
68. Guilleminault C, Mancuso J, Quera Salva MA, *et al.* Viloxazine hydrochloride in narcolepsy: a preliminary report. *Sleep* 1986; **9:** 275–279.
69. Larrosa O, de la Liave Y, Barrio S, Granizo JJ, Garcia-Borreguero D. Stimulant and anticataplectic effects of reboxetine in patients with narcolepsy. *Sleep* 2001; **24:** 282–285.
70. Smith M, Parkes JD, Dahlitz M. Venlafaxine in the treatment of the narcoleptic syndrome. *Journal of Sleep Research* 1996; **5** (Suppl. 1)**:** 217.
71. Thorpy MJ, Snyder M, Aloe FS, Ledereich PS, Starz KE. Short-term triazolam use improves nocturnal sleep of narcoleptics. *Sleep* 1992; **15:** 212–216.
72. Mamelak M, Scharf MB, Woods M. Treatment of narcolepsy with gamma-hydroxybutyrate. A review of clinical and sleep laboratory findings. *Sleep* 1986; **9:** 285–289.
73. Schuld A, Kraus T, Haack M, Hinze-Selch D, Pollmächer T. Obstructive sleep apnea syndrome induced by clonazepam in a narcoleptic patient with REM-sleep-behavior disorder. *Journal of Sleep Research* 1999; **8:** 321–322.
74. Yeh SB, Schenck CH. A case of marital discord and secondary depression with attempted suicide resulting from REM sleep behavior disorder in a 35-year-old woman. *Sleep Medicine* 2004; **5:** 151–154.
75. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Medicine* 2003; **4:** 281–284.
76. Baker TL, Guilleminault C, Nino-Murcia G, Dement WC. Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. *Sleep* 1986; **9:** 232–242.
77. Mayer G, Kesper K, Peter H, Ploch T, Leinweber T, Peter JH. Comorbidity in narcoleptic patients. *Deutsche Med Wochenschr* 2002; **127:** 1942–1946.
78. Montplaisir J, Michaud M, Denesle R, Gosselin A. Periodic leg movements are not more prevalent in insomnia or hypersomnia but are specifically associated with sleep disorders involving a dopaminergic impairment. *Sleep Medicine* 2000; **1:** 163–167.
79. Boivin DB, Montplaisir J, Poirier G. The effects of L-Dopa on periodic leg movements and sleep organization in narcolepsy. *Clinical Neuropharmacology* 1989; **16:** 339–345.
80. Bedard MA, Montplaisir J, Godbout R, Lapierre O. Nocturnal gamma-hydroxybutyrate. Effect on periodic leg movements and sleep organization of narcoleptic patients. *Clinical Neuropharmacology* 1989; **12:** 29–36.
81. Boivin DB, Lorrain D, Montplaisir J. Effects of bromocriptine on periodic limb movements in human narcolepsy. *Neurology* 1993; **43:** 2134–2136.
82. Roth B, Nevsimalova S. Depression in narcolepsy and hypersomnia. *Schweizer Archiv für Neurologie und Psychiatrie* 1975; **116:** 291–300.
83. Kales A, Soldatos CR, Bixler EO, *et al.* Narcolepsy-cataplexy. II. Psychosocial consequences and associated psychopathology. *Archives of Neurology* 1982; **39:** 169–171.
84. Vourdas A, Shneerson JM, Gregory CA, *et al.* Narcolepsy and psychopathology; is there an association? *Sleep Medicine* 2002; **3:** 353–360.
85. Shiba T, Fujiki N, Wisor JP, Dale EM, Sakurai T, Nishino S. Wake promoting effects of thioperamide, a histamine H3 antagonist in orexin/ataxin-3 narcoleptic mice. *Sleep* 2004; **27** (Abstract Suppl.)**:** A241
86. Fujiki N, Yoshida Y, Ripley B., Mignot E, Nishino S. Effects of IV and ICV hypocretin-1 orexin A in hypo-

cretin receptor-2 gene mutated narcoleptic dogs and IV hypocretin-1 replacement therapy in a hypocretin-ligand-deficient narcoleptic dog. *Sleep* 2003; **26:** 953–959.
87. Murillo-Rodriguez E, Arias-Carrion O, Xu M, Blanco-Centurion C, Drucker-Colin R, Shiromani PJ. Time course of survival of hypocretin neuronal transplantation into the pons of adult rats. *Sleep* 2004; **27** (Abtract Suppl.)**:** A238.
88. Lecendreux M, Maret S, Bassetti C, Mouren MC, Tafti M. Clinical efficacy of high-dose intravenous immunoglobulins near the onset of narcolepsy in a 10-year-old boy. *Journal of Sleep Research* 2003; **12:** 347–348.
89. Dauvilliers Y, Carlander B, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. *Annals of Neurology* 2004; **56:** 905–908.
90. Zuberi SM, Mignot E, Ling L, Mcarthur I. Variable response to intravenous immunoglobulin therapy in childhood narcolepsy. *Journal of Sleep Research* 2004; **13** (Suppl. 1)**:** 828.