Introduction

The treatments used for narcolepsy, either pharmacological or behavioural, are diverse. However, the quality of the published pieces of clinical evidence supporting them varies widely, and studies comparing the efficacy of different substances are lacking. Several treatments are used on an empirical basis, especially antidepressants for cataplexy, as these medications are already used widely in depressed patients, leaving little motivation from the manufacturers to investigate their efficacy in relatively rare indications. On the other hand, modafinil and sodium oxybate have been evaluated in large randomized placebo-controlled trials. Our objective was to reach a consensus on the use of these two drugs and of other available medications.

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 most common 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 fewer per year to several per day. Other symptoms, referred to as auxiliary symptoms, are less specific and not essential for the diagnosis. These 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, and depressed mood are additional common features of narcolepsy.

The prevalence of narcolepsy is estimated at around 25–40 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, four or five times a day. Cataplexy may vanish after a certain time, spontaneously or with treatment. Hypnagogic hallucinations and sleep paralysis are often temporary. Disturbed nocturnal sleep has no spontaneous tendency to improve with time.

In the revised International Classification of Sleep Disorders [3], three forms of narcolepsy are distinguished: narcolepsy with cataplexy, narcolepsy without cataplexy, and narcolepsy due to a medical condition. The essential diagnostic criteria of narcolepsy with cataplexy are:

A. The patient has a complaint of excessive daytime sleepiness occurring almost daily 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 the MSLT is less than or equal to 8 min, and two or more sleep-onset rapid eye movement periods

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, and depressed mood are additional common features of narcolepsy.

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(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 less than or equal to 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 the same criteria A and D, while 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 the MSLT is less than or equal to 8 min, and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6 h) during the night prior to the test.

The diagnostic criteria of narcolepsy due to a medical condition include the same criteria A and D, while criteria B and C are as follows:

B. One of the following is observed:
   i. A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone (muscle weakness) triggered by emotions is present.
   ii. If cataplexy is not present or is very atypical, polysomnographic monitoring performed over the patient's habitual sleep period followed by an MSLT must demonstrate a mean sleep latency on the MSLT of less than 8 min, with two or more SOREMPs despite sufficient nocturnal sleep prior to the test (minimum 6 h).
   iii. Hypocretin-1 levels in the CSF are less than 110 pg/ml (or 30% of normal control values), provided the patient is not comatose.

C. A significant underlying medical or neurological disorder accounts for the daytime sleepiness.

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 [4], and of a narcoleptic phenotype in orexin (hypocretin) knockout mice [5]. Then came the observation of lowered or undetectable levels of hypocretin-1 in the CSF of most human narcoleptics [6, 7] and the finding that sporadic narcolepsy, in dogs and humans, may also be related to a deficiency in the production of hypocretin-1 ligands [8]. The undetectable hypocretin-1 levels seem to be the consequence of a selective degeneration of hypocretin cells in the lateral hypothalamus. An autoimmune aetiology is hypothesized. However, direct evidence for such a mechanism is still lacking.

Compared with these advances, no revolutionary new treatments have been developed for excessive daytime sleepiness or cataplexy in the last few years, except for the recent trials with intravenous immunoglobulin (IVIg). However, there are several reasons for updating the European Federation of Neurological Societies (EFNS) guidelines on the management of narcolepsy [9]. First, modafinil has been used successfully in Europe for the last 10–15 years, decreasing the need to use amphetamine and amphetamine-like stimulants. Second, sodium oxybate has been approved by the European Medicines Agency (EMEA) for the treatment of narcolepsy with cataplexy and by the Food and Drug Administration (FDA) for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. Third, the newer antidepressants are now widely used in the treatment of cataplexy. The first effort in standardizing the treatment of narcolepsy was the ‘Practice parameters for the use of stimulants in the treatment of narcolepsy’ [10]. 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 – ‘Practice parameters for the treatment of narcolepsy: an update for 2000’ [11]. Then came the guidelines on the diagnosis and management of narcolepsy in adults and children prepared for the UK [12], the EFNS guidelines on management of narcolepsy [9], and finally ‘Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin’ [13], ‘Treatment of narcolepsy and other hypersomnias of central origin’ [14], and ‘Therapies for narcolepsy with or without cataplexy: evidence based review’ [15].

Methods and search strategy

The best available evidence to address each question was sought, with the classification scheme by type of study
Methods for reaching consensus

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

The current revision of the EFNS guidelines was prepared by the chairman based on the same databases until November 2009 and circulated among members for endorsement.

Results

Excessive daytime sleepiness and irresistible episodes of sleep

Modafinil is approved for the treatment of excessive daytime sleepiness in narcolepsy by both the EMEA and the FDA; sodium oxybate is approved for the treatment of narcolepsy with cataplexy in adults by the EMEA, and for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy by the FDA. Methylphenidate is approved for the treatment of excessive daytime sleepiness at the national agency level in Belgium, Denmark, Germany, France, and Switzerland, and by the FDA. All other drugs are ‘off-label’.

Modafinil (N06BA07) and armodafinil (FDA approved, EMEA not submitted)

Modafinil is a (2-[(diphenylmethyl) sulfinyl] acetamide) chemically unrelated to central nervous system (CNS) stimulants such as amphetamine and methylphenidate.

Modafinil may enhance the activity of wake-promoting neurons by increasing the extracellular concentration of dopamine [17, 18]. This rise in extracellular dopamine may be caused by blockade of the dopamine transporter (DAT) [19]. Modafinil may also reduce the activity of sleep-promoting (VLPO) neurons by inhibiting the nor-epinephrine transporter (NET) presynaptically [20]. In addition, modafinil could increase the extracellular concentration of 5-hydroxytryptamine in different brain areas [18, 21, 22] as well as the extracellular concentration of histamine [23]. On the other hand, modafinil does not seem to act as an alpha-agonist [24], to have a direct effect on the reuptake of glutamate or the synthesis of gamma-aminobutyric acid (GABA) or glutamate [25], or to require orexin/hypocretin to act on alertness [26].

Modafinil reaches peak bioavailability in about 2h. The main metabolic pathway is its transformation at the hepatic level into inactive metabolites that are eliminated at the renal level. The elimination half-life is 9–14 h. The steady state is reached after 2–4 days.

Co-administration of modafinil with drugs such as diazepam, phenytoin, propranolol, warfarin, some tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) may increase the circulatory levels of those compounds due to the inhibition of certain cytochrome P 450 (CYP) hepatic enzymes. On the other hand, modafinil may reduce plasma levels of oral contraceptives due to the induction of some CYP hepatic enzymes [27]. Hence, women should be advised to use a product containing 50μg or more of ethinylestradiol or an alternative method of contraception while using modafinil.

Armodafinil is the R-enantiomer of modafinil. It primarily affects areas of the brain involved in controlling wakefulness. Despite similar half-lives, plasma concentration following armodafinil administration is higher late in the day than that following modafinil administration, resulting in a more prolonged effect during the day.
and a potential improvement in sleepiness in the late afternoon in patients with narcolepsy [28].

Two Class II evidence studies ([29], 50 patients; [30], 70 patients) and two Class I evidence studies ([31] and [32], 285 and 273 patients, respectively) have shown the efficacy of modafinil on excessive daytime sleepiness at doses of 300, 200, and 400 mg/day. The key points of these studies were: a reduction in 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 [29]; a significant decrease in the likelihood of falling asleep measured by the Epworth Sleepiness Scale (ESS), a reduction of severe excessive daytime sleepiness and irresistible episodes of sleep 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 [30]; consistent improvements in subjective measures of sleepiness (ESS) and in clinician-assessed change in the patient’s condition (Clinical Global Impression), and significant improvement in maintaining wakefulness (MWT) and in decreasing sleepiness judged on the MSLT with both the 200 and the 400 mg/day doses [31, 32].

Three further studies have dealt with open-label extension data. Beusterien et al. [33] reported significantly high scores on 10 of 17 health-related quality of life scales in 558 narcoleptic patients on a modafinil 400 mg/day dose, with positive treatment effects sustained over the 40-week extension period. Moldofsky et al. [34] reported on 69 patients who entered a 16-week open-label extension trial, followed by a 2-week randomized placebo-controlled 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. Miller et al. [35] 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 over 80% of patients throughout the 40-week study.

According to a Class I evidence study [36] 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 mg and 400 mg once-daily regimen (both p < 0.05). In addition, a Class IV evidence study [37] has indicated that, in patients switched from amphetamine or methylphenidate to modafinil, the frequency of cataplexy may increase due to the mild anticitaplectic effect of the latter.

The most frequently reported adverse effects are headache (13%), nervousness (8%), and nausea (5%). Most adverse effects are mild to moderate in nature [35].

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 [38]. On rare occasions, worsening of cataplexy with modafinil has been observed.

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), and D (controlled studies in humans have shown risk) according to their embryotoxic and teratogenic effects. In the case of modafinil, teratology studies performed in animals did not provide any evidence of harm to the fetus (FDA category B). However, modafinil is not recommended in narcoleptic pregnant women as clinical studies are still insufficient.

A single Class I evidence study was performed in 196 patients randomized to receive armodafinil 150 mg, armodafinil 250 mg, or placebo once daily for 12 weeks [39]. Efficacy was assessed using the Maintenance of Wakefulness test and subjective tests. Compared with baseline measurements, the mean change from baseline at the final visit for armodafinil was an increase of 1.3, 2.6, and 1.9 min in the 150 mg, 250 mg, and combined groups respectively, compared with a decrease of 1.9 min for placebo (p < 0.01 for all three comparisons). However, this study did not provide a comparison of modafinil and armodafinil.

**Sodium oxybate (N07XX04)**

Sodium oxybate is the sodium salt of gammahydroxybutyrate (GHB), a natural neurotransmitter/neuromodulator that may act through its own receptors and via stimulation of GABA-B receptors. However, the mechanism of action of GHB that accounts for its utility in treating the symptoms of narcolepsy is still poorly understood. In particular, it is rather puzzling that although most of the behavioural effects of GHB appear to be mediated by GABA-B receptors, the prototypical
GABA-B receptor agonist baclofen is not active against excessive daytime sleepiness and cataplexy [40], suggesting that GHB and baclofen act at different subtypes of GABA-B receptor [41].

Regarding its pharmacokinetics, sodium oxybate is rapidly absorbed following oral administration, and a plasma peak is reached within 25–75 min of ingestion. Its half-life is 90–120 min, but the effects of sodium oxybate last much longer compared with its half-life. Significant pharmacological interactions have not been described, nor has induction or inhibition of hepatic enzymes.

Two Class I evidence studies [42, 43] and two Class IV evidence studies [44, 45] have shown reduced excessive daytime sleepiness and increased level of alertness, and a more recent Class I evidence study [46] has shown sodium oxybate and modafinil to be equally active for the treatment of excessive daytime sleepiness, producing additive effects when used together.

At doses ranging from 3 to 9 g nightly, adverse effects were dose-related and included dizziness in 23.5–34.3%, nausea in 5.9–34.3%, headache in 8.8–31.4%, confusion in 3.0–14.3%, enuresis in 0–14.3%, and vomiting in 0–11.4% of the cases [42].

Of concern is the abuse potential of GHB. 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 effect. However, a risk management programme in the US permits the safe handling and distribution of the compound and minimizes the risk for diversion [47]. A post-marketing surveillance study involving 26,000 patients from 16 different countries revealed only 10 cases (0.039%) meeting DSM-IV abuse criteria, 4 cases (0.016%) meeting DSM-IV dependence criteria, and 2 cases (0.008%) of sodium oxybate-facilitated sexual assault, indicating that abuse potential in patients with narcolepsy receiving sodium oxybate is very low [48]. Also of concern are the reports implicating sodium oxybate with several cases of worsening sleep-related breathing disturbances [49] or even death [50], although in the latter case patient number 2 died while not using his continuous positive airway pressure device [51]. According to a recent study [52], the administration of 9 g sodium oxybate to patients with mild to moderate obstructive sleep apnoea syndrome does not negatively impact on sleep-disordered breathing, but it might increase central apnoeas in some individuals and should be used with caution.

Animal studies have shown no evidence of teratogenicity (FDA category B). However, the potential risk for humans is unknown, and sodium oxybate is not recommended during pregnancy.

Amphetamines and amphetamine-like CNS stimulants

Amphetamine (N06BA01)
Amphetamines, including d,l-amphetamine, d-amphetamine (sulphate), and methamphetamine (chlorhydrate), have been used for narcolepsy since the 1930s [53].

At low doses, the main effect of amphetamine is to release dopamine and to a lesser extent norepinephrine through reverse efflux, via monoaminergic transporters, the DAT and NET transporters. 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 [54, 55] 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 [56] showed that long-term drug treatment would result in only a minor reduction in irresistible sleep episode propensity.

The main adverse effects are minor irritability, hyperactivity, mood changes, headache, palpitations, sweating, tremors, anorexia, and insomnia [57], but doses of over 120% of the maximum recommended by the American Academy of Sleep Medicine are responsible for a significantly higher occurrence of psychosis, substance misuse, and psychiatric hospitalizations [58].

Tolerance to amphetamine effect may develop in up to one-third of patients [59]. There is little or no evidence of abuse and addiction in narcoleptic patients [60].

Dextroamphetamine, with a FDA category D classification, and methamphetamine, with a FDA category 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 into two or three 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 a significant improvement for all dosages (10, 30, 60 mg/day) compared with baseline [61]. According to a Class IV evidence study [62], methylphenidate conveyed a good to excellent response in 68% of cases and according to another one [63] methylphenidate produced marked to moderate improvement in 90% of cases. On the MWT, the sleep latencies were increased up to 80% of controls with a 60 mg daily dose [64].

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 [65]. Moreover, in a study assessing the neuronal toxicity of methamphetamine and methylphenidate, methylphenidate failed to induce sensitization to hyperlocomotion, while methamphetamine clearly induced induced behavioural sensitization [66].

Tolerance may develop. Abuse potential is low in narcoleptic patients.

Methylphenidate has no FDA classification because no adequate animal or human studies have been performed. It is contraindicated in pregnant women.

Other compounds

Mazindol (A08AA06)

Mazindol is an imidazolidine derivative with pharmacological effects similar 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 [54] mazindol was effective in 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 [67–70] have shown a 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 nausea, vomiting, headache, dizziness, tachycardia and excessive sweating. Rare cases of pulmonary hypertension and cardiac valvular regurgitation have been reported. For this reason, it has been withdrawn from the market in several countries. Its use in narcolepsy is still warranted according to most experts, but as a third-line treatment and with close monitoring. Tolerance is uncommon, and abuse potential may be low [67]. Mazindol is classified as FDA category B without controlled studies in humans. It is contraindicated in pregnant women.

Selegiline (N04B0D1)

Selegiline is a potent irreversible monoamine oxidase 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 II evidence study [71], selegiline, 10–40 mg daily, reduced irresistible episodes of sleep and sleepiness by up to 45%, and according to another [72], selegiline at a dose of at least 20 mg/day caused a significant improvement of daytime sleepiness and a reduction in irresistible episodes of sleep, as well as a dose-dependent rapid eye movement (REM) suppression during night-time sleep and naps. The results were similar in a Class IV evidence study [73] showing an improvement in 73% of patients. The 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 [71, 72].

Selegiline is another FDA category B drug without controlled studies in humans. It is contraindicated in pregnant women.
Only two studies [75, 76] looked at the effects of a behavioural regime in a clinically meaningful time range (2–4 weeks). In the latter study, involving 29 treated narcoleptic patients randomly assigned to one of three treatment groups – (1) two 15-min naps per day, (2) a regular schedule for nocturnal sleep, and (3) a combination of scheduled naps and regular bedtimes – the best response was found in the third treatment group. All other studies considered only acute (1–2 days) manipulations. Among those, a study by Mullington and Broughton [77] tested two napping strategies: a single long nap placed 180 degrees out of phase with the nocturnal mid-sleep time (i.e. with the mid-nap point positioned 12h after the nocturnal mid-sleep time), and five naps positioned equidistantly throughout the day, with the mid-nap time of the third nap set at 180 degrees out of phase with the nocturnal mid-sleep 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 and, essentially, take one or more naps during the day.

Pemoline (N06BA05)

Pemoline, an oxazolidine derivative with long half-life (12h) 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: a Class II evidence study [60] using three dosages (18.75, 56.25, and 112.50mg/day), which did not show an improvement of wakefulness, and a Class IV evidence study [74], which showed a moderate to marked improvement in sleepiness in 65% of narcoleptic patients. However, due to potential lethal hepatotoxicity, the medication has been withdrawn from the market in most countries.

Behavioural treatments

Although non-pharmacological treatments of narcolepsy have more or less always been part of an integrative treatment concept, only a few systematic studies have been performed investigating the impact of such approaches on the symptoms of narcoleptic patients.

Class II and 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 [75, 76] looked at the effects of a behavioural regime in a clinically meaningful time range (2–4 weeks). In the latter study, involving 29 treated narcoleptic patients randomly assigned to one of three treatment groups – (1) two 15-min naps per day, (2) a regular schedule for nocturnal sleep, and (3) a combination of scheduled naps and regular bedtimes – the best response was found in the third treatment group. All other studies considered only acute (1–2 days) manipulations. Among those, a study by Mullington and Broughton [77] tested two napping strategies: a single long nap placed 180 degrees out of phase with the nocturnal mid-sleep time (i.e. with the mid-nap point positioned 12h after the nocturnal mid-sleep time), and five naps positioned equidistantly throughout the day, with the mid-nap time of the third nap set at 180 degrees out of phase with the nocturnal mid-sleep 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 and, essentially, take one or more naps during the day.

Recommendations

The first-line pharmacological treatment of excessive daytime sleepiness and irresistible episodes of sleep is not unequivocal. In cases when the most disturbing symptom is excessive daytime sleepiness, modafinil should be prescribed based on its efficacy, limited adverse effects, and easiness of manipulation. Modafinil can be taken in variable doses from 100 to 400mg/day, given in one dose in the morning or two doses, one in the morning and one early in the afternoon. However, it is possible to tailor the schedule and dose of administration according to the individual needs of the patient. On the other hand, when excessive daytime somnolence coexists with cataplexy and poor sleep, sodium oxybate may be prescribed, based on its well-evidenced efficacy on the three symptoms. However, this benefit should be balanced with its more delicate manipulation: the dose should be carefully titrated up to an adequate level over several weeks; the drug should not be used in association with other sedatives, respiratory depressants and muscle relaxants; vigilance should be held for the possible development of sleep-disordered breathing; and depressed patients should not be treated with this drug. Sodium oxybate should be given at a starting dose of 4.5g/night, increasing by increments of 1.5g at 4-week intervals. Adverse effects may require to reduce the dose and titrate more slowly. The optimal response on excessive daytime sleepiness may take as long as 8–12 weeks. Supplementation with modafinil is generally more successful than sodium oxybate alone. Methylphenidate may be an option in case modafinil is insufficiently active and sodium oxybate is not recommended. Moreover, the short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Methylphenidate LP and mazindol may be of interest in a limited number of cases.

Behavioural treatment measures are always advisable. Essentially, the studies available support on a B Level the recommendation to have regular nocturnal sleep times and to take planned naps during the day, as naps temporarily 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
Sodium oxybate is the single drug approved for cataplexy by the EMEA and the FDA. In addition, tricyclic antidepressants have the indication ‘cataplexy’ at the national agency level in Italy, Spain, Sweden, Switzerland, and the United Kingdom, as do SSRIs in Belgium, Denmark, France, Germany, and Switzerland. All other medications are ‘off-label’.

Sodium oxybate (N07XX04)
A Class I evidence study [42] and a Class IV evidence study [45] have shown a significant dose-dependent reduction of the number of cataplectic attacks in large samples of patients (136 in the first study and 118 in the second) using 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 Class I evidence study [78] 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 cataplectic attacks compared with the patients who remained on sodium oxybate. Ultimately, the Xyrem International Study Group [79] conducted a Class I evidence study with 228 adult narcolepsy with cataplexy patients randomized to receive 4.5, 6, or 9 g 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 cataplectic attacks of 57.0, 65.0, and 84.7%, respectively.

Adverse effects and abuse potential have been dealt with above.

Non-specific monoamine uptake inhibitors (N06AA)
The first use of tricyclics for treating cataplexy dates back to 1960, with imipramine [80]. This was followed by desmethylimipramine [81], clomipramine [82], and protriptyline [83].

Clomipramine, a drug that 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 [84] and four Class IV evidence studies [56, 82, 85, 86]. 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 these.

Adverse effects consist of anticholinergic effects including dry mouth, sweating, constipation, tachycardia, weight increase, hypotension, difficulty in urinating, and impotence. One trial [86] mentioned the development of tolerance after 4.5 months. Patients may experience with tricyclics a worsening or de novo onset of REM sleep behaviour disorder. Moreover, there is a risk, if the tricyclics are suddenly withdrawn, of a marked increase in the 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 category B). However, the newborns of mothers submitted to longstanding treatment with high doses of antidepressants may show symptoms of atropine intoxication. Thus, if cataplexy is mild, it is advisable to cease the anticataplectic 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 reuptake inhibitors (SSRIs) (N06AB)
These compounds are much more selective than tricyclic antidepressants towards the serotoninergic transporter. However it has been shown that their activity against cataplexy is correlated with the levels of their active noradrenergic metabolites [87]. In comparison with tricyclics, higher doses are required, and the effects are less pronounced [88].

According to a Class II evidence study [89], femoxetine, 600 mg/day, reduced cataplexy. In addition, two Class III evidence studies [90, 91] have shown fluoxetine (20–60 mg/day), and one Class III evidence study [84]...
has shown fluvoxamine (25–200 mg/day), to be mildly active on cataplexy. In Class IV evidence studies, citalopram, a very selective serotonin uptake inhibitor, proved active in three cases of intractable cataplexy [92], and escitalopram, the most selective serotonin uptake inhibitor, led to a significant decline in the number of cataplectic attacks per week while excessive daytime sleepiness remained unchanged [93].

Adverse effects are less pronounced than with tricyclics. They include CNS excitation, gastrointestinal upset, movement disorders, and sexual difficulties. The risk of a marked increase in number and severity of cataplectic attacks has been documented after discontinuation of SSRIs [94]. Tolerance to SSRIs does not develop.

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

**Norepinephrine reuptake inhibitors**

In a Class III evidence study [95], viloxazine (N06AX09) at a 100 mg dose daily significantly reduced cataplexy. The main advantage of this compound rests in its limited adverse effects (nausea and headache in one subject only out of 22).

In a Class IV evidence study [96], 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 in cataplexy [97]. 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/serotonin reuptake inhibitors**

Venlafaxine (N06AX16) (150–375 mg/day), was given to four subjects for a period of 2–7 months [98]. An 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. Venlafaxine’s main adverse effects are gastrointestinal. Increased heart rate and blood pressure may be observed at doses of 300 mg or more. Tolerance was reported in one subject. Venlafaxine is not recommended in pregnant narcoleptic women.

Recently, a pilot study on duloxetine, a new norepinephrine and serotonin reuptake inhibitor, was conducted in three patients who had narcolepsy with cataplexy. A rapid anticataplectic activity associated with excessive daytime sleepiness improvement was observed [99].

**Other compounds**

**Mazindol (A08AA06)**

Mazindol has an anticataplectic property in addition to its alerting effect. According to a Class II evidence study [54], mazindol at a dose of 2 + 2 mg/day (over 4 weeks) did not alter the frequency of cataplexy. On the other hand, in one Class IV evidence study [70], the ‘percentage of efficacy’ was 50%, and in another Class IV evidence study [68], 85% of subjects reported a significant improvement in terms of cataplexy.

Potential adverse effects have been reviewed above.

**Selegiline (N04B0D1)**

Selegiline has a potent anticataplectic effect in addition to its relatively good alerting effect. According to one Class I evidence study, selegiline reduced cataplexy up to 89% at a dose of 10 – 40 mg [71], and, according to a second, reduced cataplexy significantly at a dose of 10 mg × 2 [72]. 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 serotonin. 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 their mild cataplexy is no longer controlled.

**Behavioural 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 is helpful in reducing cataplexy, but it can hardly be considered as a recommendation or ‘treatment’.
**Poor sleep**

**Benzodiazepines (N05CD) and non-benzodiazepines (N05CF)**

A single Class III evidence study [100] has shown an improvement in 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 in excessive daytime sleepiness was recorded. No study has been performed with either zopiclone or zolpidem or zaleplon.

**Sodium oxybate (N07XX04)**

The US Xyrem studies have shown a significant decrease in the number of nighttime awakenings, with sodium oxybate 9 g [42] and a significant improvement of nocturnal sleep quality \( p = 0.001 \) characterized by increased slow wave sleep [45]. Most importantly, a recent Class I evidence study in patients receiving sodium oxybate and sodium oxybate/modafinil evidenced a median increase in stages 3 and 4 and delta power, and a median decrease in nocturnal awakenings [101]. Interestingly, clinical experience suggests that poor sleep is the first symptom to improve with sodium oxybate, and that efficacy on poor sleep foresees efficacy on the other symptoms.

The adverse effects are the same as already listed.

**Modafinil (N06BA07)**

In the US Modafinil in Narcolepsy Multicenter Study Group [32] a small improvement in sleep consolidation was evidenced through increased sleep efficiency. Thus, it is always advisable to wait for the effects of modafinil before prescribing a special treatment for disturbed nocturnal sleep in narcoleptic patients.

**Behavioural therapy**

No study has ever been conducted to investigate the effects of behavioural treatments on night-time sleep in narcoleptic patients, in clinically relevant settings.

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**Recommendations**

Based on several Class I evidence (Level A rating) studies, the 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 of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Adverse effects may need the dose to be reduced and titrated more slowly. Most patients will start to feel better within the first few days, but the optimal response at any given dose may take as long as 8–12 weeks. As indicated above, the drug should not be used in association with other sedatives, respiratory depressants, and muscle relaxants, vigilance should be held for the possible development of sleep-disordered breathing, and depressed patients should not be treated with the drug. Second-line pharmacological treatments are antidepressants. Tricyclic antidepressants, particularly clomipramine (10–75 mg), are potent anticonvulsive drugs. However, they have the drawback of anticholinergic adverse effects. The starting dosage should always be as low as possible. SSRIs are slightly less active but have fewer adverse effects. The norepinephrine-serotonin reuptake inhibitor venlafaxine is widely used today but lacks any published clinical evidence of efficacy. The norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the well-evidenced efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. There is no accepted behavioural treatment of cataplexy.

**Hallucinations and sleep paralysis**

The 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. An improvement in cataplexy is most often associated with a reduction in hallucinations and sleep paralysis. A Class I evidence study [42] did not reveal any significant differences in hypnagogic hallucinations and sleep paralysis when compared with placebo. However, this study was not powered to detect a difference in hypnagogic hallucinations. On the other hand, a Class IV evidence study [44] with 21 narcoleptic patients administered increasing nightly doses of sodium oxybate up to 9 g showed an increasing number of patients reporting fewer hypnagogic hallucinations and less sleep paralysis. There is no report on any attempt to modify the occurrence of hypnagogic hallucinations or sleep paralysis by behavioural techniques.
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Associated features

Obstructive sleep apnoea/hypopnoea syndrome

According to several publications [105, 106], the prevalence of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is greater in narcoleptic patients than in the general population. One potential explanation is the frequency of obesity in narcolepsy, which could predispose to OSAHS. Only one Class IV study has described the effect of continuous positive airway pressure (CPAP) in narcolepsy patients with OSAHS: excessive daytime sleepiness did not improve in 11 of the 14 patients treated with CPAP [107].

Periodic limb movements in sleep

Periodic limb movements in sleep (PLMS) are more prevalent in narcolepsy than in the general population [106, 108]. This applies particularly to young narcoleptic patients. L-Dopa [109], GHB [110], and bromocriptine [111] are effective treatments of PLMS in narcolepsy patients. 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 [112–115].

Antidepressant drugs and psychotherapy are indicated. However, there is no systematic study of these therapeutic procedures in depressed narcoleptic patients.

Parasomnias

Narcoleptic patients often display vivid and frightening dreams and REM sleep behaviour disorder (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 individuals with narcolepsy has ever been conducted.

In the case of RBD, its occurrence in narcoleptic patients is remarkable for three reasons. First, the age of onset of RBD in narcoleptic patients is younger than in the other forms of chronic RBD. Second, the frequency of the episodes is less marked and RBD events are usually less violent than in the other forms of RBD. Third, RBD may precede narcolepsy by several years.

There is no available report of any prospective, double-blind, placebo-controlled trial of any drug specific for RBD in narcoleptic subjects, and only a few case reports of narcoleptic subjects with RBD. The use of clonazepam was reported as successful in two cases [102, 103]. In one case [100], clonazepam led to the development of obstructive sleep apnoea 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 per night [104]. Adverse effects such as sleepiness, hallucination, and headache were recorded in one third of patients.

Recommendations

OSAHS should be treated no differently in narcoleptic patients than the general population, although it has been shown that CPAP does not improve excessive daytime sleepiness in most narcolepsy subjects. There is usually no need to treat PLMS in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (Level C) as in non-narcoleptic depressed patients.

Recommendations

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

Recommendations

Patients’ groups

Interaction with those who have narcolepsy is often of great benefit to the patient and his or her spouse...
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, because of the implications for treating a relatively common and debilitating disease.

There are three focuses for future therapy:

- Symptomatic endocrine/transmitter-modulating therapies, including thyrotrophin-releasing hormone and thyrotrophin-releasing hormone agonists; slow-wave sleep enhancers (selective GABA-B agonists), and histaminergic H3 receptor antagonists/inverse agonists. Several histaminergic compounds are currently being studied for the treatment of excessive daytime sleepiness. A published pilot study has shown encouraging results [116].
- Hypocretin-based therapies: hypocretin agonists, hypocretin cell transplantation, and gene therapy.
- Immune-based therapies, particularly IVIg. These therapies are given close to disease onset and are supposed to modulate the presumed but not proven autoimmune process that causes the hypocretin deficiency. A beneficial effect in particular on cataplexy has been claimed [117]. Note, however, that all the studies were small and not blinded, that possible spontaneous fluctuations may have influenced outcome, and that the placebo effect may be large [118].

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 new symptomatic treatments and of treatments directed at replacing hypocretin or even preventing the loss of neurons containing the neuropeptide may become a reality in the near future.
Dr Dolenc-Groselj received honoraria from Medis (the Slovenian representative for Xyrem) for invited talks.

Dr Lammers is a member of the Xyrem (UCB Pharma) advisory board and has received honoraria from UCB for invited talks.

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 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.

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