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# Therapeutic advances in narcolepsy

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**Abstract**

Narcolepsy treatment has changed dramatically over the last century. For the treatment of sleepiness in narcolepsy, we have progressed from the early use of caffeine. We have available a variety of different stimulants, and a wake-promoting agent, modafinil, which is widely regarded as the first-line medication for narcolepsy.

Cataplexy is managed by medications whereas behavioral treatment, such as avoidance of emotion, was the only treatment available in the past. Following the widespread use of antidepressant medications for cataplexy, we now have sodium oxybate, which works by an unknown mechanism but is the only Food and Drug Administration (FDA)–approved medication for cataplexy.

We also recognize that other sleep disorders can occur in narcolepsy, such as obstructive sleep apnea syndrome or rapid eye movement sleep behavior disorder, and new treatments allow these comorbid conditions to be effectively treated.

However, although we cannot cure narcolepsy, the current treatments for excessive sleepiness and cataplexy can be effective for many patients. We are improving the quality of life for our patients without producing clinically significant adverse effects. We need new therapeutic advances and several medications that work, though different mechanisms are likely to be available in the near future.


*Keyword:* Narcolepsy

## 1. Introduction

Narcolepsy was first described over 100 years ago, but most of what we know about the pathology responsible for this disease has been learned during the past few years. Narcolepsy associated with cataplexy is caused by the loss of a relatively few neurons responsible for producing the neuropeptide hypocretin in the central nervous system (CNS).

The onset of narcolepsy typically occurs in adolescence and can consist of several symptoms; however, excessive sleepiness and cataplexy are most characteristic of narcolepsy. Medications directed to the treatment of these symptoms have been stimulants and wake-promoting agents for excessive sleepiness, and antidepressants and sodium oxybate for cataplexy. Auxiliary symptoms of narcolepsy such as disturbed nocturnal sleep, sleep paralysis and hypnagogic hallucinations can be treated with a variety of medications that include all of the above-mentioned medications and others such as hypnotics.

The excessive daytime sleepiness (EDS) associated with narcolepsy has historically been treated with stimulants, such as methylphenidate or dextroamphetamine [1] and, more recently, modafinil [2]. In addition, more recently sodium oxybate has been demonstrated to be effective in the treatment of sleepiness associated with narcolepsy.

## 2. Clinical features

Narcolepsy is a disorder of the CNS for which there is no known cure. Classically, narcolepsy is described as a

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syndrome consisting of EDS, including periods of irresistible sleep, cataplexy, sleep paralysis, and hypnagogic hallucinations.

Narcolepsy typically begins during the second and third decades of life with excessive sleepiness. Additional symptoms include fragmented or disrupted nighttime sleep and automatic behaviors. Narcolepsy can have a profound impact on quality of life and patients are more likely to suffer educational and occupational failures, greatly reduced social activities and a higher incidence of driving and other accidents [3,4].

Cataplexy is the most specific symptom of narcolepsy consisting of an abrupt bilateral loss of skeletal muscle tone. When severe, an episode of cataplexy may cause a patient to collapse to the ground, sometimes suffering injury. During a cataplexy attack, which may last up to several minutes, the patient is unable to move, although the diaphragm and ocular muscles are unaffected. The patient remains awake, aware of his or her surroundings, although sleep may occur if the attack is prolonged. More commonly, attacks of cataplexy are partial, affecting only certain muscle groups, such as the arms, neck or face, and the jaw may sag, the head may drop forward and speech can become garbled [3].

Mostly commonly, cataplexy is caused by laughter or humorous experiences although sometimes even the memory of a humorous event can precipitate an attack. Other emotions can also trigger cataplexy, including anger, embarrassment, surprise, or even sexual arousal [5].

## 3. Epidemiology

Narcolepsy affects approximately 1 in 2000 people in the United States, with a prevalence of approaching that of more familiar diseases such as cystic fibrosis and multiple sclerosis. Although there is a greater incidence of narcolepsy among first-degree relatives, it occurs less frequently than would be predicted based on normal patterns of inheritance. Therefore, it has been suggested that there may be a genetically controlled susceptibility to an environmentally controlled event, such as an autoimmune process. There may be a predisposition for narcolepsy based on race and ethnicity, as a review of the literature indicates that the prevalence of narcolepsy/cataplexy ranges from a low of 0.002% among Israeli Jews to a high of 0.15% among the Japanese general population [6]. A general population study with a representative sample of over 18,000 subjects in five European countries estimated a prevalence of 0.047% [7].

Narcolepsy affects men and women equally, and disease-onset can begin in infancy or as late as old age, but most commonly before age 25 [4]. As narcolepsy may be mistaken for depression, epilepsy, or psychiatric illness, an accurate diagnosis can often require 10 years after the onset of symptoms [8]. The prevalence of cataplexy among patients with narcolepsy varies widely with estimates ranging from 60 to 90%.

Patients report that cataplexy remains persistent with only minor fluctuations in severity; however, a few patients have reported spontaneous remission of cataplexy attacks [9]. It has been suggested that a decline in cataplexy over time may represent the ability of patients to adapt to their illness and learn to avoid situations where cataplexy is most likely to occur [10,11].

## 4. Neurotransmitter and receptor systems

The neuropharmacologic control of sleepiness and cataplexy has been investigated in dogs. In general, cataplexy is aggravated by cholinergic transmission by M2 stimulation and suppressed by monoaminergic transmission, specifically by blockade of postsynaptic $\alpha_{1b}$ adrenergic receptors or stimulation of $\alpha_2$ adrenergic or dopamine $D_2$ inhibitory autoreceptors [12] In dogs with narcolepsy, an increase in M2 receptors in the pons, $\alpha_1$ receptors in the amygdala, $\alpha_2$ receptors in the locus coeruleus and $D_2$ receptors in the amygdala and nucleus accumbens have been reported [12]. Autopsy studies of brains from humans with narcolepsy have reported a decrease in $\alpha_1$ receptors in several brain areas including the cortex, an increase in $\alpha_2$ receptors in the putamen and increases of $D_1$ and $D_2$ receptors in the areas of the striatum [13–15].

A cholinoceptive hypersensitivity in the basal forebrain and brainstem could explain the abnormal rapid eye movement (REM) sleep patterns observed in patients with narcolepsy, while abnormalities in the mesocorticolimbic dopaminergic systems could explain EDS.

Lin et al. [16] reported that canine narcolepsy, which is phenotypically similar to human narcolepsy, is caused by a mutation of the hypocretin receptor 2 (Hcrtr2) gene. Preprohypocretin knockout mice display behavioral symptoms and electroencephalographic criteria consistent with narcolepsy [17]. Moreover, it was reported that hypocretin levels in cerebrospinal fluid were deficient in 7 of 9 patients with narcolepsy. [18] Hypocretin cells are reduced or absent in patients with narcolepsy. In addition to hypocretin, neuronal activity-regulated pentaxin (NARP) and dynorphin are also reduced with the loss of hypocretin cells, which may contribute to the clinical symptoms [19,20]. The hypocretins, also called orexins, may be the major sleep-modulating neurotransmitters and could potentially provide a novel therapeutic approach to the treatment of narcolepsy.

## 5. Therapeutic options

Although there is no cure for narcolepsy, a number of treatment options are available. Treatment should be

individualized based on the severity of symptoms. It can take weeks or months before an optimal regimen is achieved, although complete control of EDS and cataplexy is rarely possible.

### 5.1. Lifestyle changes

Patient education is an important component of any treatment plan for narcolepsy. Good sleep habits, the avoidance of sleep deprivation and/or irregular sleep patterns, and the scheduling of short naps (10–15 min) two to three times per day can help control EDS and improve alertness. Patients should be warned about the potential hazards of sleepiness relative to driving and working in hazardous settings.

### 5.2. Pharmacologic treatment

Although non-pharmacologic measures can be helpful in treating narcolepsy, most patients require pharmacotherapy [1]. The main goal of pharmacologic treatment for narcolepsy is to keep the patient alert during the day and reduce episodes of cataplexy while also minimizing the incidence of undesirable side effects and adverse events [1].

Lifestyle changes are rarely sufficient to adequately control the symptoms of narcolepsy and, therefore, most patients require life-long medication. Early recognition and institution of effective therapy are key to improving quality of life throughout the life of the patient. Excessive sleepiness is typically managed with stimulants, but other agents, such as modafinil and sodium oxybate, which have fewer adverse effects and less abuse potential, may offer a more efficacious and safer means of promoting daytime wakefulness. The cataplexy associated with narcolepsy can be managed with tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or sodium oxybate.

## 6. Pharmacotherapy

### 6.1. Excessive daytime sleepiness (EDS)

Modafinil is an agent with wake-promoting efficacy similar to that of CNS stimulants, but with better safety profile and a lower potential for abuse and/or dependence. This lower abuse potential is reflected by its Schedule IV labeling in the Controlled Substances Act. The two stimulants amphetamine and methylphenidate, which are Food and Drug Administration (FDA)-approved in the United States for treating narcolepsy-related sleepiness, are Schedule II substances, denoting a high potential for abuse. A third CNS stimulant, pemoline, has recently been withdrawn from the market because of the potential for hepatotoxicity. In addition, sodium oxybate, a Schedule III medication, has been approved by the FDA for the treatment of excessive sleepiness in narcolepsy.

#### 6.1.1. Stimulants

Psychostimulants have been the traditional mainstay of therapy for EDS (Table 1). Amphetamines and methylphenidate are indirect sympathomimetics that increase the level of monoamines within the synaptic cleft by enhancing the release of norepinephrine, dopamine, and serotonin, and also by blocking their reuptake [20]. The main action responsible for the psychomotor stimulatory effects of these agents is on central dopamine systems. Amphetamines also weakly inhibit monoamine oxidase (MAO). Most clinical studies of stimulant medications report objective improvements in somnolence in 65–85% of subjects [20]. Treatment of sleepiness can have a mild beneficial effect on cataplexy.

Common adverse effects associated with these medications include nervousness, headaches, irritability, tremor, insomnia, anorexia, gastrointestinal upset, and heart palpitations [20]. The development of drug tolerance is controversial, with some studies reporting tolerance in 30–40% of patients, others reporting no tolerance, and still others reporting tolerance only at high-stimulant dosages [20]. Drug "holidays" of one to two days per week with lower dosages or no medication are sometimes helpful for patients who develop tolerance, although their efficacy in preventing tolerance is uncertain [21,22]. Drug holidays may also result in the transient return of EDS, which may lead to undesirable consequences for the patient [21,22].

Methylphenidate has similar efficacy to dextroamphetamine but a better therapeutic index because of a lower propensity to produce adverse effects. There is little evidence to support an increased risk of elevated blood pressure in normotensive individuals with commonly used dosages of stimulants [20].

Serious problems with long-term stimulant use are uncommon in most patients with narcolepsy, and the risk of addiction is relatively low (<1–3% of cases), and is not higher than that in other patient groups. However, the risk of addiction is greater in patients taking high dosages of stimulants, in patients who have received long-term treatment with stimulants, and in those with an underlying psychiatric disease [21]. High-dose stimulants, greater than 120% the maximum level recommended by the American Academy of Sleep Medicine have been associated with an increased risk of developing psychosis, psychiatric hospitalizations, alcohol abuse and suicide [23]. Compliance can be a problem with some stimulant medications, and one study showed that during a 24-h monitoring period, 22 of 43 narcoleptic patients took a reduced dosage of their stimulant medication or did not take their medication at all [24].

Table 1
Medications used in the treatment of narcolepsy

| Drug | Primary mechanism of action | Usual daily dosage (mg/day) | Comments |
|---|---|---|---|
| *Excessive daytime sleepiness* | | | |
| Dextroamphetamine (Obetrol®, Biphetamine®) | Indirect sympathomimetic DA > NE | 5–50 | Reverse efflux of DA through the DAT. Inhibition of monoamine storage through VMAT |
| Methylphenidate (Ritalin®) | Indirect sympathomimetic DA > NE | 10–60 | Reverse efflux of DA through DAT |
| Methamphetamine (Desoxyn®) | Indirect sympathomimetic DA > NE | 5–15 | Similar to amphetamine |
| Selegiline (Eldepryl®, Atapryl®, Carbex®) | Irreversible inhibitor of MAO | 20–40 | Converts to L-amphetamine and L-methamphetamine |
| Modafinil (Provigil®) | Unknown; partial dopamine reuptake inhibitor | 100–400 | Also blocks NE reuptake. R enantiomer in development |
| Sodium Oxybate (Xyrem) | Unknown | 4.5–9.0 gm/day | FDA approved for EDS in narcolepsy |
| *Cataplexy* | | | |
| Imipramine (Tofranil®, others) | Block reuptake of NE ≈ 5-HT | 25–200 | Also effective for hypnagogic hallucinations and sleep paralysis. Sedative |
| Clomipramine (Anafranil®, others) | Block reuptake of 5-HT > NE | 10–200 | Anticholinergic effects |
| Desipramine (Norpramin®, others) | Block reuptake of NE > 5-HT | 25–200 | Anticholinergic effects |
| Protriptyline (Vivactil®) | Block reuptake of NE > 5-HT | 5–30 | Slightly alerting |
| Fluoxetine (Prozac®) | Block reuptake of 5-HT ≫ NE = DA | 20–80 | Most widely used SSRI for cataplexy |
| Venlafaxine (Effexor) | Block reuptake of 5-HT >= NE | 37.5–150 | Very effective in cataplexy |
| Atomoxetine (Strattera) | Block reuptake of NE | 40–80 | Slightly alerting |
| Sodium Oxybate (Xyrem) | Mechanism unknown | 4.5–9 gm/day | FDA approved for cataplexy |

5HT, 5-hydroxytryptamine (serotonin); GABA, gammaaminobutyric acid; MAO, monoamine oxidase; NE, norepinephrine; DA, dopamine; DAT, dopamine transporter; VMAT, vesicular monoamine transporter.

#### 6.1.2. Selegiline

Selegiline is a medication with stimulant effects, which is largely used in Europe for the treatment of daytime sleepiness in narcolepsy. Selegiline is an irreversible inhibitor of MAO type B in dosages of up to 20 mg/day, but above this dosage the drug begins to lose its selectivity [25] A diet low in tyramine is, therefore, recommended with higher dosages of selegiline to avoid the risk of hypertensive reactions. Selegiline 10–40 mg/day has produced statistically and clinically significant improvement in symptoms and polysomnographic measures in narcoleptic patients. Selegeline produces dose-dependent REM suppression during nighttime sleep and naps and an increase of sleep and REM latency [26–28]. Daytime sleepiness also improved significantly, and the number of sleep attacks and naps, as well as the frequency of cataplexy, were reduced.

The drug has also been reported to reduce the number of cataplectic attacks by 89% [28]. Selegiline has low abuse potential [29] and may be better tolerated than stimulants [30]. Patients who experience intolerable adverse events with other agents may be good candidates for selegiline therapy. The main advantage of this agent is its anticataplectic activity in addition to its relatively good alerting effect; however, the main disadvantage is having to maintain a low tyramine diet.

#### 6.1.3. Modafinil

Modafinil is regarded as the first-line medication for the treatment of excessive sleepiness in narcolepsy. It is chemically unrelated to CNS stimulants, has a low abuse potential and is not associated with rebound hypersomnolence [30,31]. Modafinil may indirectly increase wakefulness partly through inhibition of gamma-aminobutyric acid (GABA) release by serotonergic mechanisms [32–34]. Selective activation of wake-generating sites in the hypothalamus may be a mechanism of action [17]. Other effects are to inhibit the dopamine reuptake transporter which may enhance wake-promoting neurons, and inhibit the norepinephrine reuptake transporter which may reduce the sleep-promoting effect of the ventrolateral preoptic nucleus [35,36]. The drug does not appear to be directly dependent on dopaminergic pathways [37]. Unlike dextroamphetamine, modafinil had no adverse effects on objective or subjective nocturnal sleep parameters in either healthy volunteers [38] or in patients with narcolepsy [39]. Modafinil has an elimination half-life of 9–14 h, permitting once-daily administration for most patients.

Modafinil has decreased sleep attacks in up to 71% of narcolepsy patients in clinical trials [40,41]. In the two trials of modafinil, which enrolled over 550 patients in the United States, modafinil 200 mg/day or 400 mg/day for up to nine weeks produced significant improvements in objective (multiple sleep latency test (MSLT) and maintenance of wakefulness test (MWT)) and subjective (Epworth sleepiness scale (ESS)) measures of sleepiness [42,43]. Patients receiving modafinil stayed awake up to 75% longer than placebo-treated patients as measured by the MWT, and mean ESS scores decreased from 17 to 18 at baseline to 12 to 14 after treatment with modafinil. The drug was well tolerated, with headache and nausea being reported more commonly with modafinil than placebo.

The changes from baseline on the MWT and MSLT are small; however, these tests were conducted in a controlled laboratory setting designed to maximize the likelihood of sleep onset (i.e., in a darkened room while laying semirecumbent) [44,45]. Under these conditions, small increases in sleep latency (e.g., 1–2 min) can represent clinically significant improvements in wakefulness [46]. However, modafinil did not completely resolve excessive sleepiness; mean sleep latency, although significantly improved, was still considered to be in the mild to moderate range [42,43].

There was no difference in treatment response among those with or without cataplexy. Anticataplectic medications were discontinued during the studies. The incidence of cataplexy as an adverse event ranged from 1 to 4%, with no difference between the treatment and placebo groups. There was no evidence that modafinil had any effect on helping cataplexy or the other ancillary features of narcolepsy, such as hypnagogic hallucinations or sleep paralysis.

The results of the U.S. studies corroborated those by a group of Canadian investigators in a randomized, double-blind, placebo-controlled, six-week trial. In that trial, consisting of three 2-week crossover phases, significant improvements were seen on the MWT and ESS at 200- and 400-mg doses, given twice daily in the morning and at noon [39].

In two subsequent long-term (40-week), open-label, flexible-dose U.S. studies of modafinil 200–400 mg/day ($n = 478$), the maintenance dose in nearly three-quarters of the patients was 400 mg/day (74%, 77% and 75% of patients receiving 400 mg/day at weeks 8, 24 and 40, respectively) [47]. The proportions of patients who were "much improved" or "very much improved" at weeks 8, 24 and 40 were significantly higher than at week 2 (58%, 59%, and 58% versus 49%; all $P < 0.001$). Mean ESS scores decreased from 16.5 at baseline to 12.4 at 2 weeks and remained consistent thereafter through week 40 (12.2, 12.8 and 12.9 at weeks 8, 24, and 40, respectively; all $P < 0.001$ vs baseline). Headache (13% of patients), nervousness (8%) and nausea (5%) were the most common treatment-related adverse events. Forty-three (9%) patients discontinued therapy due to adverse events and 57 (12%) withdrew due to insufficient efficacy.

Together, the United States and Canadian studies formed the basis for recommending modafinil as a standard of care in a 2000 update to the American Academy of Sleep Medicine guidelines for narcolepsy treatment. [48] The standard-of-care designation, only assigned to modafinil, reflected the favorable risk/benefit profile of modafinil in these three studies, as well as several supporting studies conducted in the United States and France [49,50]. Modafinil has now become the first-line treatment for excessive sleepiness in most patients newly diagnosed with narcolepsy. The medication, sodium oxybate, has been shown to provide additional benefit to improving daytime alertness when given along with modafinil [51].

The overall cardiovascular profile of modafinil is favorable compared with that of the stimulants. Among the notable drug interactions of modafinil was a decrease in the peak plasma concentrations of ethinyl estradiol. As a result, the prescribing information contains a precaution advising women to seek alternative or additional methods of contraceptive while taking modafinil and for one month following discontinuation.

Post-marketing surveillance of modafinil has not detected generalized interest in modafinil as a drug of abuse. However, there have been isolated cases of modafinil abuse reported [52] In addition, United States-based clinical studies in persons experienced with drugs of abuse have demonstrated the modafinil can produce mild psychoactive and euphoric effects consistent with those of CNS stimulants [53,54]. However, results are conflicting in this area, and the severity of these effects tends to be lower than those seen with CNS stimulants.

Several studies have focused on determining optimal dosing protocols for modafinil in narcolepsy patients, including the use of doses higher than the recommended dose of 200 mg, as well as split-dosing to achieve improvements in evening wakefulness. While no dose-response effect was seen for the 400-mg dose compared with 200 mg in the placebo-controlled clinical studies, the first MWT was generally performed an hour after dosing of modafinil, too early for the agent to reach peak plasma concentrations. A more recent study employed a modified version of the MWT that included evening test sessions. This study demonstrated an improved response to the 400-mg dose compared with 200 mg, whether it was given as a single-morning dose or a split-dose in the morning and at noon. The greatest improvements in evening wakefulness were seen with the split-dose regimen [55]. More recently, a 600-mg split-dose regimen (400 mg in the morning and 200 mg in the early afternoon) was found to achieve more consistent wakefulness throughout the day (morning,

afternoon, and evening) compared with 200 or 400 mg qAM or a 400 mg split-dose regimen [56]. Anecdotally, in clinical practice some physicians have reported increased favorable responses with doses up to 1200 mg/day. This contrasts with research studies on fatigue, where significant improvements have not been seen consistently with doses higher than 200 mg/day [57].

An enantomeric form of modafinil may soon be available in the United States. Armodafinil is a combination of R-modafinil and S-modafinil. R-modafinil is a longer-acting isomer of modafinil with a half-life of 10–14 h, whereas S-modafinil has a half-life of 3–4 h. Armodafinil has a $T_{max}$ of 2 h and a half-life of approximately 15 h. This modification of modafinil has a more prolonged effect during the day and may improve daytime sleepiness in the late afternoon and early evening in some patients with narcolepsy. It has been shown to be effective and produces longer wakefulness than modafinil in patients with sleepiness due to acute sleep loss [58].

#### 6.1.4. Sodium oxybate

Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB). In the United States, GHB became available to body builders as an unregulated dietary supplement in health food stores, weight-training gyms, and at fitness centers during the 1980s and was prompted by reports that GHB stimulated the release of growth hormone [59]. Other promoted uses included treatment for insomnia and for weight loss. The sale of GHB increased greatly on the Internet during the 1990s, eventually leading to its popularity as an intoxicant at all-night dance parties, or "raves" [60].

Its increased use, especially in combination with alcohol, resulted in increasing numbers of hospital emergency department visits [61]. In addition, GHB was increasingly being used to facilitate sexual assault. Therefore, the FDA banned the sale of GHB in the United States in 1991 [62] and the US Congress amended the Federal Controlled Substances Act with the passage of the Hilary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law 106–172), [63] which classified unapproved forms of GHB as Schedule I drugs; however, to facilitate the development and eventual use of sodium oxybate for the treatment of narcolepsy, a provision in the law allowed approved forms of the drug to be classified as Schedule III substances.

Pharmaceutical interest in sodium oxybate (originally known only by its chemical name gamma-hydroxybutyrate; GHB) originated in the 1960s during a search for a peripherally acting GABA agonist [64]. Sodium oxybate was initially used as an anaesthetic agent, as it induced a level of unconsciousness that was acceptable for some surgical procedures. Unlike other centrally acting depressants, sodium oxybate induced sleep that closely resembled natural sleep [65]. Thus, early investigators suggested its use for the treatment of disorders of disturbed sleep, such as narcolepsy. The administration of sodium oxybate at bedtime was found to reduce nocturnal awakenings, increase stage 3 and 4 (delta or slow wave) sleep and consolidate REM sleep periods, which coincided with improvements in daytime symptoms, including cataplexy [66].

Several clinical trials with naroleptics during the past 25 years confirmed that the nightly use of sodium oxybate produced significant reductions in cataplexy which were associated with improvements in the quality of nighttime sleep [67–70]. These promising results formed the basis for the formal development of sodium oxybate as a treatment of narcolepsy.

Sodium oxybate is a white to off-white, crystalline powder that is highly soluble in aqueous solutions. It is a normal constituent in the mammalian CNS, where it is referred to as gamma-hydroxybutyrate (GHB).

GHB is produced within the brain where two GHB receptor subtypes with high and low affinity for GHB have been identified. Currently, there exists a large body of data suggesting that GHB functions as a neurotransmitter at physiological concentrations [71,72]. In pharmacologic concentrations, GHB appears to act as a $GABA_B$ receptor agonist [73]. As the administration of GHB is associated with increased serotonin turnover, interactions with endogenous opioids and possible modulation of dopaminergic activity, the pharmacologic effects of sodium oxybate with respect to cataplexy may be complex, involving several receptor systems [72].

Following oral administration, sodium oxybate is rapidly absorbed with an estimated bioavailability of 25%. The results of several pharmacokinetic studies indicate the average time to peak plasma concentration ($T_{max}$) ranges from 0.5 to 1.25 h and the plasma half-life of the drug is 40–60 min [74–77]. When used for the treatment of narcolepsy, one-half of a therapeutic dose of sodium oxybate is administered at bedtime and repeated 2.5–4.0 h later, providing effective plasma concentrations throughout the night while ensuring that the majority of the drug has been eliminated when patients awaken in the morning [29–31] [75–77].

Investigations performed with human subjects indicate that the total exposure (AUC) to sodium oxybate increases disproportionately with dose, such that doubling of the oral dose resulted in a 3.8-fold increase in AUC and a 2.4- to 2.9-fold increase in $C_{max}$ [76]; however, the total overall systemic exposure of sodium oxybate is reduced by the presence of food in the stomach. In one study, the presence of food decreased the $C_{max}$ and AUC by an average of 58% and 37%, respectively [76]. Sodium oxybate should, therefore, be ingested at a regular time with respect to the evening meal to ensure consistent systemic absorption.

The primary route of sodium oxybate metabolism is initiated by the action of GHB dehydrogenase which

catalyses the conversion of oxybate (GHB) to succinic semialdehyde. Subsequently, succinic semialdehyde dehydrogenase converts succinic semialdehyde to succinic acid which enters the Krebs cycle and is ultimately converted to carbon dioxide. [78,79] Only about 5% of a therapeutically administered dose can be recovered from urine [75,76]. Both *in vitro* tests as well as clinical studies in human volunteers have demonstrated that sodium oxybate does not induce hepatic cytochrome P-450 enzymes and that the pharmacokinetic parameters described above are unaffected by chronic administration [77].

While clinical trials with sodium oxybate were primarily designed to measure the efficacy of the drug for the treatment of cataplexy, the effects of EDS have also been measured. In the original four-week double-blind study, sodium oxybate produced a dose-related improvement in EDS, becoming statistically significant at the 9 g dose compared to placebo. This change in EDS was measured using the ESS, which demonstrated a decrease in the median score from 17.0 at baseline to 12.0 at the end of the trial. This improvement occurred while most patients remained on preexisting stimulant medications [80]. In the 12-month extension trial, the continued administration of sodium oxybate resulted in additional improvements in EDS which were maximal after two months [81].

A double-blind, placebo-controlled trial evaluated the effect of sodium oxybate on EDS as a primary endpoint in 228 narcolepsy patients. Compared to placebo, sodium oxybate produced statistically significant improvements in ESS scores and the frequency of sleep attacks at the 6 and 9 g doses. In addition, the investigators in the study rated the overall clinical condition as significantly improved compared to placebo [51].

### 6.2. Cataplexy

While EDS can often be managed with stimulants, such as methyphenidate or modafinil, these medications often do not provide significant relief from cataplexy and additional medications with anticataplectic activity must be used to reduce the frequency and severity of cataplexy.

TCAs were found to be beneficial over 40 years ago and, more recently, SSRIs have been used for the treatment of cataplexy. The recent availability of sodium oxybate represents a significant advance in the treatment of narcolepsy as it is highly efficacious for the treatment of cataplexy in narcolepsy and is effective for the treatment of excessive sleepiness and improving sleep quality in these patients.

#### 6.2.1. Heterocyclic antidepressants

TCAs were the first drugs discovered to have anticataplectic activity. Since the first report describing the anticataplectic effect of imipramine was published in 1960, [82] TCAs have been the most widely prescribed medications for the treatment of cataplexy. The anticataplectic effects of TCAs are generally attributed to their ability to block the presynaptic reuptake of catecholamines, thereby enhancing their post-synaptic activity. While the exact mechanism whereby these drugs produce their beneficial effects in narcolepsy is unknown, several hypotheses have been proposed. For example, the anticataplectic effect may be due to the ability of these drugs to increase muscle tone [83]. Alternatively, their anticataplectic effect may be associated with the ability of TCAs to suppress REM sleep. In support of the latter hypothesis, the use of TCAs may also result in a decrease in other REM-related narcolepsy symptoms, including sleep paralysis and hypnagogic hallucinations; [84,85] however, they have little beneficial effect on EDS.

Although the efficacy of TCAs for the treatment of narcolepsy has never been evaluated in large, controlled studies, small open-label studies and several decades of use have demonstrated desmethylimipramine, protriptyline, imipramine and desipramine have beneficial anticataplectic effects; [86] however, clomipramine remains the most efficacious and widely used. Clomipramine has the most REM-suppressing activity, which may be related to its greater ability to block serotonin reuptake. For many patients, clomipramine can remain effective for many years, although, like all TCAs, tolerance may develop after a few months or even a few weeks of treatment. Increasing the dose may overcome tolerance; however, increasing the dose also increases the development of adverse effects, which eventually limits the amount of drug that can be administered. Clomipramine doses of 10–75 mg daily are generally effective for cataplexy [83,87,88].

Adverse events commonly associated with TCA therapy include nausea, anorexia, dry mouth, urinary retention and tachycardia. Men may encounter decreased libido, impotency or delayed ejaculation. An unusual property of TCAs is the rebound cataplexy which can occur upon abrupt discontinuation of TCA therapy. When severe, this is known as *status cataplecticus* and can be disabling for several days [89].

#### 6.2.2. Selective serotonin reuptake inhibitors (SSRIs)

As TCAs were known to have beneficial effects on cataplexy, it was natural that medications in the next class of antidepressants were assessed for their anticataplectic activity as soon as they became available. Like TCAs, SSRIs also block the presynaptic reuptake of catecholamines, thereby increasing their activity; however, they are much more selective for serotonin than TCAs. Also like TCAs, SSRIs inhibit nocturnal REM sleep. While several SSRIs have been used for the treatment of cataplexy, data supporting their use consist primarily of case reports indicating that fluvoxamine, zimeldine,

femoxetine, paroxetine and fluoxetine have all demonstrated anticataplectic activity. Fluoxetine appears to be the most commonly used of the SSRIs [90].

As a class, the SSRIs are generally less efficacious than TCAs; however, they are safer and better tolerated than the older antidepressants. In clinical reports describing the use of SSRIs for the treatment of cataplexy, adverse events have included headache, nausea, weight gain, dry mouth and delayed ejaculation [90,91].

#### 6.2.3. Other agents

Monoamine oxidase inhibitors (MAOIs) increase the activity of endogenous catecholamines by inhibiting monoamine oxidase, the enzyme responsible for the intracellular degradation of these neurotransmitters. Although MAOIs have been used for the treatment of cataplexy, the efficacy of these drugs is not supported by controlled clinical trials. Small single-blind and open-label studies suggest that phenelzine and selegiline [26] are both effective and single case reports suggest that tranylcypromine (Parnate) is an effective agent.

Several MAOIs have peripheral as well as central activity and adverse events reported during the treatment of cataplexy have included orthostatic hypotension, edema, weight gain, impotence (men), and difficulty achieving orgasms (women) [92]. A dangerous interaction may occur between these medications and dietary tyramine. The ingestion of tyramine-rich foods, such as aged cheeses and wine may result in hypertensive crisis. Although selegiline has no peripheral activity and does not interact with tyramine, adverse events associated with its use have included dry mouth, headache, insomnia, sweating, muscle twitching, dizziness, irritability, restlessness and tremor [92,28].

Case reports describing beneficial effects have been achieved with mazindol have been published [93,94] Although this drug is no longer available in the United States, it is available for the treatment of cataplexy in other countries. Recently, atypical antidepressant agents that are unrelated to the TCAs and SSRIs have become available for the treatment of cataplexy. One such agent is venlafaxine, which blocks the reuptake of both norepinephrine and serotonin. A small case series suggests that it may be useful for the treatment of cataplexy although tolerance may occur [95]. Other medications that more selectively block norepinephrine reuptake also show some promise; these include viloxazine, reboxetine, and atomoxetine [96,97].

#### 6.2.4. Sodium oxybate

The development of sodium oxybate for cataplexy was a significant departure from TCAs and SSRIs. When administered in pharmacologic doses, GHB (sodium oxybate) is also a $GABA_B$ receptor agonist; however, the exact mechanism of anticataplectic activity remains unknown [73].

The approval of sodium oxybate for the treatment of cataplexy was based upon the results of two trials, demonstrating short- and long-term efficacy. The first was a double-blind, placebo-controlled four-week trial in which nightly sodium oxybate doses of 3, 6 or 9 gm or placebo, taken in two equally-divided doses 2.5–4 h apart, were randomly assigned to 136 narcolepsy patients who suffered from cataplexy. Sodium oxybate reduced the median frequency of weekly attacks by 49% and 69% at nightly doses of 6 and 9 gm, respectively. These improvements were statistically significant compared to placebo. There was no rebound cataplexy noted upon abrupt cessation of treatment at the end of the trial [80].

The second trial, also double-blind and placebo-controlled, was designed to assess the long-term efficacy of sodium oxybate and used a novel drug withdrawal design. In this study, 55 narcolepsy patients with cataplexy were stabilized on nightly doses of sodium oxybate for a minimum of six months (mean 21, range 7–44 months) then were randomized to abruptly begin receiving placebo or remain on sodium oxybate. Those patients who were switched to placebo experienced a gradual return of their cataplexy over a two-week period, which demonstrated that they derived long-term anticataplectic benefits from the medication [98].

One hundred eighteen of the patients enrolled in the initial four-week trial, above, were allowed to continue using sodium oxybate in a 12-month open-label, extension trial. Unlike the first trial, patients were started on dose of 6 gm nightly in two equally divided doses. The trial investigators then adjusted the doses up or down every two weeks until optimal effects were achieved for each patient. Compared to the end of the four-week trial, these patients showed statistically significant benefit after an additional four weeks of therapy, becoming maximal after about eight weeks. After 12 months of treatment, none of these patients displayed evidence of tolerance [81].

These data suggested that a trial longer than four weeks is necessary to fully describe the anticataplectic effects of sodium oxybate and an eight-week double-blind, placebo-controlled trial evaluated 228 narcolepsy patients with cataplexy. Similar to the previous four-week trial, the first four weeks of treatment resulted in median weekly decreases in cataplexy of 43.1%, 51.9% and 61.8% at nightly doses of 4.5, 6 and 9 g, respectively; however, the subsequent four weeks of treatment resulted in further decreases of 57.0, 65.0 and 84.7%. All of these improvements were statistically significant compared to placebo. A major finding of this trial was that sodium oxybate demonstrated efficacy at the 4.5 gm dose compared to placebo. The data resulting from this study indicated that the beneficial effects of sodium oxybate on cataplexy are dependent upon both the dose of sodium oxybate used and the duration of therapy [99].

The result of placebo-controlled trials indicated that adverse events occurring with an incidence of 5% or greater included dizziness (23%), headache (20%), nausea (16%), pain (12%), somnolence (9%), sleep disorder (9%), confusion (7%) infection (7%), vomiting (6%) and enuresis (5%), with most described as mild or moderate in severity. Dizziness, nausea, vomiting and enuresis may be dose-related [Xyrem product information].

The use of illicit forms of sodium oxybate (GHB) has been reported to result in addiction and withdrawal when used frequently and at high doses [100]. In contrast, the therapeutic use of sodium oxybate for the treatment of narcolepsy has not been associated with physical dependence even when used for at least four years [81].

### 6.3. Nocturnal sleep

Nocturnal sleep is typically disturbed in patients with narcolepsy. Attempts to improve the quality of nocturnal sleep have improved the quality of life for patients with narcolepsy although there is no evidence that it leads to improved daytime alertness.

#### 6.3.1. Sodium oxybate

Patients taking sodium oxybate at bedtime and again during the night experience positive changes in daytime symptoms, which coincided with changes in their sleep architecture. Despite the effect of sodium oxybate as a hypnotic, sleep latency actually increases as the pathological sleepiness associated with narcolepsy is diminished [101]. Patients experience significantly fewer nocturnal awakenings although total sleep time is unaffected. The most dramatic effect of sodium oxybate is the increase in stage 3 and 4 sleep (slow wave or delta sleep) which corresponded with a significant and dose-related increase in delta power. The increase in stage 3 and 4 sleep occurred at the expense of stage 1 sleep, leaving stage 2 sleep relatively unaffected. The total amount of REM sleep increased at the beginning of sodium oxybate treatment, later decreasing with increasing dose and duration of therapy [98]. These findings were repeated in a double-blind trial in 228 narcolepsy patients where the nightly administration of sodium oxybate increased the duration of stage 3 and 4 sleep by 24 and 50 min per night at nightly doses of 6 and 9 g, respectively [99]. These same doses also decreased the number of nighttime awakenings. These improvements in sleep architecture were statistically significant compared to placebo (Orphan Medical, unpublished data on file).

#### 6.3.2. Other agents

In a short-term study of nocturnal sleep in 10 narcolepsy patients taking 0.25 mg of the hypnotic, triazolam, at bedtime there was evidence of improved sleep efficiency and overall sleep quality [102]. There was no evidence for improved daytime sleepiness as a result of the improved nocturnal sleep.

### 6.4. Sleep paralysis and hypnagogic hallucinations

The heterocyclic compounds such as imipramine, clomipramine and protriptyline can be effective for the treatment of sleep paralysis or hypnagogic hallucinations; however, there are few reports of their effectiveness. Imipramine and viloxazine have been shown to be effective for hallucinations [103,104]. In addition, the newer antidepressants, particularly venlafaxine, have been shown to be helpful.

The effect of sodium oxybate on the auxiliary symptoms of narcolepsy, such as hypnagogic hallucinations and sleep paralysis, has not been clearly established. Initial preliminary studies have shown a beneficial effect upon these symptoms [105,70], but in the studies, leading the FDA approval of sodium oxybate, the small number of patients with these auxiliary symptoms did not allow enough power to determine a clear benefit. However, in the 228 patient study, although the low baseline frequency of symptoms precluded any clear evidence of improvement in REM-related symptoms, with the 6gm dose a statistical improvement in sleep paralysis was seen [99].

### 6.5. Quality of life

Similar to any patient with a chronic illness, patients with narcolepsy experience clinical symptoms that have a major impact on physical and psychosocial function and hence on quality of life [106]. Assessment of quality of life in patients with narcolepsy helps to determine the social characteristics and perceived needs of patients and to document the prevalence of the clinical features of narcolepsy and their impact on quality of life.

Two 9-week, multicenter, double-blind, placebo-controlled trials of modafinil conducted in the United States were the first clinical trials in narcolepsy to include health-related quality of life assessments [42,43]. A total of 481 patients completed the double-blind baseline and endpoint questionnaires: 161 received modafinil 200 mg, 157 received modafinil 400 mg, and 163 received placebo [107]. Quality of life was assessed using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and several supplemental scales that focused specifically on issues relevant to quality of life in patients with narcolepsy. Compared with population norms, patients with narcolepsy showed substantial burden in vitality, social functioning, and performing usual activities. The modafinil 400 mg and 200 mg groups exhibited significantly ($P < 0.05$) higher scores on 10 and 9 of the 17 items from the SF-36 and supplemental scales, and improvements were noted at week 4 and were maintained

throughout the study. These subjects reported more energy, fewer difficulties performing usual activities, fewer interferences with social activities, more improved psychological well-being, higher productivity, more increased ability to pay attention, and more improved self-esteem than placebo recipients.

During a 40-week, open-label extension study of modafinil, quality of life scores at weeks 4, 8, 24 and 40 were significantly ($P < 0.001$) improved compared with open-label baseline scores for 6 of 8 SF-36 domains scores [47] confirming and extending results reported for the two 9-week double-blind studies [42,43].

Sodium oxybate 6 and 9 g in a double-blind placebo-controlled trial has been shown to improve quality of life as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ) [108]. There were significant improvements in the FOSQ total score as well as general productivity, vigilance, activity level and social outcomes subscales for the 9 g dose. Similar results were seen for the 6 g dose except for the general productivity subscale. There was no change in intimacy/sexual relationships.

## 7. Future treatments of narcolepsy

Research into new treatments for narcolepsy is very active. These potential new treatments have been reviewed in detail by Mignot and Nishino [109]. They can be thought of as comprising three groups: hypocretin and hypocretin analogues, immunotherapy, and a mixed group of other treatments (Table 2).

### 7.1. Hypocretin and hypocretin analogues

The recent finding by Lin and colleagues [110] that canine narcolepsy is caused by a mutation of the Hcrtr2 gene provides a greater understanding of the mechanisms underlying sleep disorders. The hypocretin (orexin)-containing neurons are known to project to brainstem regions linked to motor inhibition as well as to locus coeruleus (norepinephrine), raphe (serotonin), laterodorsal tegmental nuclei (acetylcholine), and ventral tegmental (dopamine) neuron [111]. Loss of function of the hypocretin system could cause cataplexy through inhibition of the brainstem's motor excitatory system or reduced excitatory output to the motor inhibitory system, or it could increase sleepiness through inhibiting the cholinergic and aminergic arousal systems or reduced excitatory output to the forebrain's hypnogenic systems.

Replacement of hypocretin-1 might be an effective treatment option. However, hypocretin-1 does not cross the blood-brain barrier. Intracerebroventricular (ICV) hypocretin-1 can suppress cataplexy and improve sleep in narcoleptic mice, but it is not effective in hcrt2 mutated dogs. Intranasal administration holds promise, as hypocretin can get into the brain when administered through the nasal route [112].

Hypocretin gene therapy, by overexpressing the hypocretin gene, has been shown to be effective in mice [113]. The transplantation of neonatal rat hypothalami into the brainstem of adult rats in an attempt to give hypocretin producing cells, is a possibility, although in other disorders such as Parkinson's disease, graft survival is a problem. Immune reactions to the grafts is possible in view of the autoimmune hypothesis of pathophysiology. Stem cell grafts might be a possibility.

### 7.2. Immunotherapy

Narcolepsy is a presumed autoimmune disorder and attempts to modify the immune process have been undertaken with limited success. Treatments have focused on trying to influence the immune response soon after the onset narcolepsy. Steroids and immunosuppressant medications, plasmapheresis and intravenous immunoglobulin therapy have all been tried with limited success.

Table 2
Future treatments of narcolepsy

| Method | Primary mechanism of action | Comments |
|---|---|---|
| *Hypocretin-based treatments* | | |
| Intranasal hypocretin-I | Direct hypocretin stimulation | Able to get into the brain via nasal route |
| Hypocretin cell transplantation | Replacement of hypocretin cells | Graft survival may be a problem |
| Hypocretin gene therapy | Overexpression of hypocetin | Shown to be effective in mice |
| Stem cell transplantation | Replacement of hypocretin cells | May be feasible in future |
| *Immunotherapy* | | |
| Steroids | Suppression of immune response | Limited success so far |
| Plasmapheresis | Removal of autoantibodies | Invasive and limited success |
| Intavenous immunoglobulins (IVIg) | Removal of autoantibdoies | May be effective in early onset narcolepsy |
| *Other treatments* | | |
| Thyrotrophin (TRH) analogues and promotors | TRH is a stimulating neuropeptide Metallopeptidase inhibitor increases TRH. | In development |
| Histamine (H3) antagonists | Histamine stimulation | Several in development |

Steroid and immunosuppressive treatment in dogs with narcolepsy more than doubled the time to cataplexy onset, and the time spent in cataplexy was reduced by more than 90% [114]. Others have not found an effect in the narcoleptic dog [115]. Steroids given soon after the onset of the disorder have been tried in at least one human. An eight-year-old boy with onset of symptoms within three months was given prednisone but showed no evidence of improvement [116].

Plasmapheresis has been attempted and at least one patient appeared to improve in daytime sleepiness and cataplexy only to relapse a few weeks later. A second course of plasmapheresis again improved symptoms; however, the patient was subsequently treated successfully with sodium oxybate [117].

Intravenous immunoglobulins (IVIg) are believed to remove autoantibodies. IVIg was initially tried in one 10-year-old boy with improvement in symptoms of sleepiness and cataplexy [118]. A larger study of four patients showed improvement in cataplexy only, especially in the three patients who had the shortest time from onset of symptoms [119]. A further report of four patients demonstrated improved sleepiness but not cataplexy [120] However, IVIg has been shown to be partially effective in hcrtr2-mutated canines in whom autoantibodies are not thought to play a role, suggesting that the effect may have an alternative explanation other than clearance of autoantibodies [121].

### 7.3. Other treatments

Thyrotrophin-releasing hormone (TRH) and TRH agonists have alerting properties [122,123]. TRH is a small peptide of three amino acids that in high dose stimulates wakefulness [124] TRH is excitatory on neurons and enhances dopamine and adrenergic transmission, and may promote wakefulness by direct effect on thalamocortical pathways. TRH has been shown to have anticataplectic activity in the narcoleptic canine [122]. Inhibition of the TRH-degrading enzyme inhibitor, metallopeptidase, may be a promising treatment in the future.

Histamine 3 (H3) receptors regulate the release and synthesis of histamine. Stimulation of the H3 receptors causes sedation, whereas antagonism causes wakefulness[125]. H3 antagonists have been shown to be effective on sleepiness and cataplexy in canines [126]. They also promote wakefulness in mice with ablation of hypocretin neurons (orexin/ataxin-3) [127].

## 8. Conclusions

Narcolepsy is a chronic neurologic disorder characterized by EDS, cataplexy, hypnagogic hallucinations, sleep paralysis and disturbed nocturnal sleep. Although patients report EDS and cataplexy as the most frequent symptoms of this condition, EDS is generally considered to be the most debilitating.

Currently, a number of different drug therapies are available for the treatment of the symptoms of narcolepsy. Modafinil and sodium oxybate have shown strong evidence of improvement in daytime alertness and their combination appears to offer additional benefits.

Sodium oxybate has demonstrated efficacy for the treatment of cataplexy and there is evidence that it diminishes the occurrence of hypnagogic hallucinations and sleep paralysis. It also can improve nocturnal sleep quality. In some cases of narcolepsy uncomplicated by obstructive sleep apnea or other sedating medications, sodium oxybate may be considered as a first-line therapy.

Other agents such as antidepressants of the TCA and SSRI classes are often effective but must be used in combination with hypnotic and stimulant medications if insomnia and/or EDS are co-existent symptoms. These agents may also diminish the occurrence of sleep paralysis and hypnagogic hallucinations. Newer atypical antidepressants may also be beneficial; however, additional information on the safety and efficacy of these agents for the treatment of cataplexy is needed. The use of MAOIs should be reserved for narcolepsy patients refractory to other, safer drug therapies.

A disadvantage of sodium oxybate or modafinil is cost. Due to the relatively rare nature of the disease, the cost of drug development must necessarily be borne by a relatively small patient population. Thus, the cost of modafinil or sodium oxybate treatment is more expensive than other treatments, especially older stimulants and antidepressants which have been available in generic form for many years; however, as modafinil and sodium oxybate are FDA-approved for the treatment of excessive sleepiness and/or cataplexy, insurance providers typically provide reimbursement.

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