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Treatment of Excessive Daytime Sleepiness in Patients with Narcolepsy

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Abstract

Purpose of review The aim of this review is to discuss and summarize the main therapeutic strategies for the management of excessive daytime sleepiness (EDS) in patients with narcolepsy. An overview of novel therapies and potential future options are covered as well.

Recent findings First line treatments for EDS in narcolepsy patients include modafinil/armodafinil and sodium oxybate. Other options with a stimulant effect, such as methylphenidate and amphetamines are considered if the former do not control the symptoms. More recently, pitolisant (H3 receptor inverse agonist) was approved by the European Medicines Agency, and solriamfetol (dopamine and norepinephrine reuptake inhibitor) by the Food and Drug Administration, for the treatment of EDS in adult narcolepsy patients. Sodium oxybate was recently approved for EDS management in paediatric patients from the age of seven. Further studies involving the paediatric population are warranted to have solid evidence in the management of children with narcolepsy. Ongoing research of new molecules is based on several mechanisms of action (histamine antagonists/inverse agonists, GABA receptor modulators), and potential future strategies involve immunologic treatment and hypocretin-based therapies.

Summary Additionally to the wakefulness-promoting agents and stimulants classically used, other pharmacologic options have been recently approved for the treatment of EDS in Europe (pitolisant) and the US (solriamfetol). Emerging treatments are under development; newly developed wakefulness-promoting agents act via different mechanisms of action, whereas other forms of therapy are focused in the underlying hypocretin deficiency that characterizes narcolepsy type 1.

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Introduction

Narcolepsy is a chronic neurological condition in which the main symptom is that of excessive daytime sleepiness (EDS) [1]. According to the third edition of the International Classification of Sleep Disorders [2•], narcolepsy may be divided into two categories: narcolepsy type 1 and type 2, formerly named narcolepsy with and without cataplexy respectively. Narcolepsy type 1 has a distinctive pathophysiology, with loss of hypocretin/orexin-producing neurons in the hypothalamus, leading to CSF hypocretin/orexin deficiency. Narcolepsy type 2 is a more heterogeneous entity; whereas intermediate levels of CSF hypocretin/orexin have been found in some of these patients [3], its exact pathophysiology remains unclear. Symptoms of sleep paralysis, hypnopompic or hypnagogic hallucinations and disturbed night time sleep may also be present in patients with narcolepsy.

EDS or hypersomnolence is defined as an irresistible need to sleep or inability to stay awake during the major waking episodes of the day [2•]. It is the foremost and usually initial symptom in narcolepsy and it is often disabling [4]. Patients with narcolepsy typically present with severe EDS, especially in circumstances that are relatively inactive or monotonous; automatic behaviours during certain activities (e.g. while talking, writing or driving) may be reported as well. Short naps are characteristically refreshing and can associate dreaming. Of note, in children with narcolepsy the presentation may not be as clear, and hyperactive behaviours have been reported in paediatric patients when trying to fight sleepiness [5].

Treatment of narcolepsy remains to be symptomatic. Several pharmacologic options are available for the management of EDS in patients with narcolepsy. Their licenced use may differ between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [6•]. Commonly used medications aiming to improve EDS include modafinil/armodafinil, methylphenidate, amphetamines, sodium oxybate, and pitolisant (Table 1). Recently, a new option to treat EDS has been approved by the FDA, solriamfetol. Changes in dose, agent or combination of medications may be required for an adequate control of EDS [7]. Response to therapy may be evaluated using subjective measures such as the self-reported Epworth Sleepiness Scale or Karolinska Sleepiness Scale. For an objective measurement of daytime sleepiness, the Multiple Sleep Latency Test (MSLT) allows to assess the tendency to fall asleep, and the Maintenance of Wakefulness Test (MWT) the ability to stay awake. Psychomotor vigilance task and other reaction time tests (such as Oxford Sleep Resistance Test) may provide with further information about the impact of sleepiness in these patients while performing specific tasks. However, despite having several subjective and objective tools to measure outcomes, there is no consensus as to how to assess the severity of EDS for further guidance and effective management of these patients [4]. Additionally, as a chronic condition, requiring life-long treatment, adherence to therapy should be routinely assessed in these patients.

An adequate control of EDS is of utmost importance given the forensic implications (e.g. in professional drivers) and significant burden this symptom may be associated with. This article aims to review the current evidence in the management of EDS in patients with narcolepsy.

Treatment of excessive daytime sleepiness

Pharmacologic treatment

The main characteristics in standard dosage, common side effects, FDA pregnancy category status and relative costs of medications used in the management of EDS in narcolepsy patients are summarized in Table 1.

Modafinil/Armodafinil

Modafinil is a is a benzyhydrylsulfinylacetamide derivative, chemically distinct from other stimulants. The exact mechanism of action of this medication remains unclear, but it seems that its wakefulness-promoting activity is

Table 1. Available drugs for the treatment of excessive daytime sleepiness in adults with narcolepsy

	Standard dosage	Common side effects	FDA pregnancy category	Relative cost
Modafinil	100–400 mg/day	Headache, nausea, insomnia, anxiety	C	Moderate
Armodafinil	150–250 mg/day	Headache, nausea, dizziness, insomnia	C	Moderate
Methylphenidate	10–60 mg/day	Hypertension, palpitations, anxiety, irritability, weight loss	C	Low
Amphetamines	5–60 mg/day	Hypertension, arrhythmias, irritability, aggressiveness, insomnia, abnormal movements	C	Low
Sodium oxybate	4.5–9 g/night	Dizziness, headache, nausea, weight loss, restless leg syndrome, sleepwalking, enuresis, neuropsychiatric symptoms	C	High
Pitolisant	9–36 mg/day	Insomnia, headache, anxiety, depression and nausea	No FDA classification	High
Solriamfetol	75–150 mg/day	Headache, nausea, decreased appetite, insomnia, and anxiety	No FDA classification	High

FDA: Food and Drug Administration

mediated by increasing the extracellular concentration of monoamines, mainly dopamine, but also norepinephrine, as well as a possible action on histamine, adenosine, serotonin and gamma-aminobutyric acid (GABA). Absorption may be delayed by approximately one hour if taken with food. It has a long half-life of 13.8 h, with a maximum concentration achieved at 2-4 h [8]. It is FDA and EMA-approved and the first line treatment for EDS in narcolepsy patients.

The efficacy of modafinil was demonstrated in four class I evidence-based studies [9–12] at doses between 200 and 400 mg per day, objectively improving EDS as shown by MWT and/or MSLT findings. It may be started at 100 mg in the morning and 100 mg at lunchtime, to be increased after 1–2 weeks further up to 300–400 mg daily (taken in one or two doses). The most common side effects include headache, nausea and nervousness. Modafinil has a low risk for tolerance and low potential for abuse [8]. Although rare, a cutaneous rash may arise as a serious side effect from it. It should be used very cautiously in patients with history of psychosis, depression, or mania. Female patients should be aware that modafinil modulates the hepatic cytochrome P450 enzyme activity, potentially leading to an increase in the metabolism of combined hormonal contraceptives, progesterone-only pill and subdermal contraceptive implant. In order to ensure contraceptive efficacy, it is advisable that patients use other contraceptive methods that are not affected by enzyme-inducing drugs while taking modafinil, and for a month after its discontinuation. Interactions with other drugs include reduction of cyclosporine blood concentrations and increased exposure to CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam. Doses may be adjusted if there is hepatic impairment and in geriatric patients.

The R-enantiomer of modafinil, armodafinil, is not available in Europe but is a FDA-approved treatment of EDS in narcolepsy. Although the half-life of armodafinil is similar to that of modafinil, its plasma concentration remains

higher later in the day, which leads to a persistent wakefulness-promoting effect in the afternoon. Its efficacy was objectively and subjectively proven on a single class I evidence study [13]. The daily dose is 150–250 mg to be taken in the morning. Side effects and safety profile are similar to those of modafinil.

Sodium oxybate

The exact mechanism of action sodium oxybate (or sodium salt of gamma hydroxybutyrate) in patients with narcolepsy is poorly understood, but seems to be related to stimulation of $GABA_B$ receptors. Its half-life is short (90-120 min), but the effects persist longer. Sodium oxybate is FDA and EMA approved for the management of cataplexy and EDS in patients with narcolepsy. It may be considered first line EDS treatment, especially when cataplexy is associated.

The efficacy of sodium oxybate has been shown in several class I evidence studies [14–17], with an objective reduction of EDS in two of them [16, 17]. A systematic review and meta-analysis supports these findings [18]. Additive effects when in conjunction with modafinil have also been reported [19]. Sodium oxybate is on liquid formulation, and is started at an initial dose of 2.25 g twice nightly (4.5 g/night) for 2–4 weeks. The first dose should be taken in bed before going to sleep, and the second dose 2.5-4 h after the first one. Further adjustments in dosage may be done every 1–2 weeks, by 1.5 g/night/week, up to a maximum dose of 9 g/night (4.5 g twice nightly). Commonly reported side effects include nausea, headache, dizziness and enuresis. Somnambulism, restless legs syndrome, weight loss and neuropsychiatric symptoms have been reported as well. Pre-existing sleep apnoea should be ruled out prior to commencing this medication, and patients should be advised against the use of alcohol or other sedative substances given the risk of respiratory depression. Doses should be adjusted in hepatic impairment and dietetic measures considered in renal impairment due to high sodium content of this medication. Patients should be cautious when operating machinery for at least six hours after taking the second dose. A main concern is that of potential abuse or misuse, although this has been reported to be low in patients with narcolepsy [20].

Methylphenidate

Methylphenidate is a monoamine (mainly dopamine) reuptake blocker. Duration of action is 3-4 h for the immediate release and up to 12 h for extended release formulations. There is one class II evidence study demonstrating its efficacy [21]. Dosage ranges from 10 to 60 mg daily, usually in divided doses. Side effects include irritability, aggressiveness, insomnia, palpitations, hypertension and weight loss. Potential for abuse may be a source of concern, but seems low in patients with narcolepsy [22]. Methylphenidate is considered a second line treatment for EDS [22, 23].

Amphetamines

The wakefulness-promoting effect of amphetamines is achieved through increasing the concentration of dopamine and norepinephrine. Their efficacy was demonstrated in three class II evidence studies [24–26]. The dosage may range from 5 mg to 60 mg daily. Side effects are similar to those of methylphenidate. Psychotic reactions, cardiac arrhythmias and abnormal movements might occur

at large doses. Tolerance and abuse may arise with their use, although addiction to psychostimulants in patients with narcolepsy seems rare [27]. Nevertheless, amphetamines should not be prescribed in patients with cardiovascular risks and history of drug abuse.

Pitolisant

Recently approved by the EMA for the treatment of EDS and cataplexy in narcolepsy patients, pitolisant is a wakefulness-promoting agent that acts as a histamine antagonist/inverse agonist at the H3 receptor. The half-life is 10-12 h with a peak in plasma concentration at 3 h [28].

In the pivotal studies (HARMONY I and HARMONY Ibis) [29•, 30], pitolisant was found to be superior to placebo, but not significantly different from modafinil, in the reduction of EDS (improvement in Epworth score or MWT) at 8 weeks of treatment. A later randomized controlled trial in which the primary endpoint was a reduction in cataplexy [31], supported the efficacy of pitolisant, with a higher reduction on EDS versus placebo at seven weeks of treatment. The initial dose is 9 mg daily (two 4.5 mg tablets), which may be increased weekly up to a maximum of 36 mg daily (two 18 mg tablets). It is taken in a single dose in the morning. Frequently reported side effects include insomnia, headache, anxiety, depression and nausea. EMA recommends that pitolisant is administered cautiously in patients with psychiatric history. Supra-therapeutic doses were linked to QTc interval prolongation; hence, careful monitoring should be done in patients with cardiac disease or concomitant drugs with potential effect to prolong QTc interval. Drug exposure is increased in renal and hepatic impairment, and so 18 mg daily doses should not be exceeded in those circumstances (and it is contraindicated in severe hepatic impairment). The effects of pitolisant on weight and appetite are unclear, therefore its use should be cautious in severe obesity or anorexia [30]. Alternate means of contraception should be used while on pitolisant and for 21 days after discontinuation, as it may lower the efficacy of hormonal contraceptives. Tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) and sedating anti-histamines (e.g. pheniramine maleate, chlorpheniramine, diphenydramine, promethazine, mepyramine) may impair the efficacy of pitolisant. Adjustments of dosage and cautious co-administration should be considered in potent CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin), CYP2D6 inhibitors (e.g. duloxetine, paroxetine, fluoxetine, venlafaxine, bupropion, quinidine), or OCT1 (organic cation transporters 1) substrates, such as metformin [32].

Solriamfetol

Recently approved by the FDA for the management of EDS in patients with narcolepsy, solriamfetol is a phenylalanine derivative with an effect of dual-acting dopamine and norepinephrine reuptake inhibitor. Its half-life is 6–7.6 h and has a maximum plasma concentration at 1.3–2.5 h [33••]. The efficacy on improving subjective (Epworth score) and objective (MWT) measures of EDS was initially proven in two randomized controlled trials [34, 35]. This was later supported by a phase 3 trial [36••], which demonstrated an improvement on EDS at 12 weeks of solriamfetol 150 or 300 mg daily versus placebo. The

recommended starting dose is 75 mg to be taken upon awakening, which may be doubled after at least 3 days, up to a maximum of 150 mg once daily dose. Most common adverse reactions include headache, nausea, decreased appetite, insomnia, and anxiety. In patients with renal impairment, doses should be adjusted. Due to risk of hypertensive reaction, its use is contraindicated in patients on treatment with monoamine oxidase inhibitors or within 14 days after their discontinuation. Interactions with other concomitant medications that increase the blood pressure and/or heart rate, or with a dopaminergic effect, have not been evaluated, caution should be taken in concomitant administration of these. Patients with history of drug abuse should be carefully evaluated and monitored given the potential for abuse of solriamfetol [37].

Other pharmacologic options

Mazindol is approved in France for its use in the management of EDS in patients with narcolepsy. It is an imidazolidine derivative that blocks the dopamine and adrenaline reuptake. The efficacy was demonstrated in non-controlled studies at a daily dose of 2–3 mg [38]. Side effects included weight loss, dry mouth and nervousness; cardiological monitoring is recommended.

The benefits of controlling EDS have been demonstrated with other medications such as selegiline [39]. Flumazenile, a $GABA_A$ receptor antagonist, was proven effective in a retrospective study including 153 patients with refractory hypersomnolence [40]. A modulator of $GABA_A$ receptor, the antibiotic clarithormyicin, improved hypersomnolence in subjective measures (patients with narcolepsy with cataplexy were excluded) [41].

Conservative or non-pharmacologic treatment

Non-pharmacologic measures to help in the management of EDS may be offered to patients with narcolepsy. Behavioural strategies include having regular sleep-wake patterns and avoiding sedentary activities. Introducing one longer nap in the early afternoon or short (10–20 min) scheduled naps throughout the day may be of help to cope with EDS in some patients with narcolepsy [42]. More recently, some therapeutic techniques included in a structured form of cognitive behavioural therapy for narcolepsy have been presented as potentially helpful in the management of EDS [43].

These recommendations serve as an adjunctive therapy in patients that remain sleepy despite the use of wakefulness-promoting medications [44]. Education of patients and discussion about therapeutic goals is important [4] in order to adjust their treatment regimen as required depending on their routines, social and work commitments.

Paediatric considerations

The presentation of daytime sleepiness in children with narcolepsy has some distinctive features. Paediatric patients with narcolepsy usually have sleep attacks that are longer than in adults, often having 2–3-h naps that are not necessarily refreshing [45]. In some instances, sleepiness is presented as constant waxing and waning drowsiness throughout the day. Additionally, the clinical picture may be characterized by behavioural changes such as restlessness and hyperactivity [46]. These differences in the clinical presentation may lead to stigmatization and delay in diagnosis [47].

There are scarce randomized controlled trials involving the paediatric population with narcolepsy. Therefore, a limited number of drugs are approved for the management of EDS in paediatric patients. FDA-approved medications to treat EDS in this population include methylphenidate, amphetamines and, recently, sodium oxybate (for the treatment of cataplexy and/or EDS in patients from seven years old). Only methylphenidate immediate release is approved by the EMA and its use is allowed in paediatric patients over 6 years old. Open-label studies, series of cases and case reports often support the off-label use of other wakefulness-promoting agents by specialists treating children [48].

Modafinil was found to be effective in 85% of patients included in an international study reporting the clinical experience of several specialized centres treating children with narcolepsy [49]. No severe reactions with skin rash were reported by this group. A clinical trial (NCT00214968) for the study of safety and effectiveness of modafinil in children aged 6–16 has been completed but results are not posted yet [50].

More recently, the FDA has approved the use of sodium oxybate in paediatric patients with narcolepsy from seven years of age. This was following a multicentre, randomized, controlled trial including children and adolescents with narcolepsy with cataplexy that examined the efficacy and safety of sodium oxybate [51••]. Subjects naïve to the drug and patients already taking sodium oxybate were included; once a 2–3-week stable dose period was completed (96 patients), patients were randomized to either placebo (32 patients) or sodium oxybate (31 patients), although a proportion of participants were alternatively included in the open-label treatment arm (33 patients). Following the treatment period, 95 patients were included in the open-label safety period for up to 47 weeks. Sodium oxybate was effective on the primary endpoint (change on number of cataplexy attacks), and showed an improvement in daytime sleepiness measured by the Epworth Sleepiness Scale for Children and Adolescents. The most common adverse effects included enuresis, nausea, vomiting, headache, decreased weight, decreased appetite, nasopharyngitis, and dizziness. Two serious adverse events were reported, one case of acute psychosis and another one of suicidal ideation.

The experience of methylphenidate and amphetamines children with attention-deficit hyperactivity disorder may be extrapolated to narcolepsy. In paediatric patients, clinicians should be aware of the potential occurrence of rebound hypersomnia following the wakefulness promoted by amphetamines. Additionally, metabolic or endocrine changes should be carefully monitored in paediatric patients on stimulant medication [48].

A double-blind, randomized, controlled trial for the efficacy and safety of pitolisant in patients with narcolepsy over 6 and below 18 years old is currently ongoing [52].

Pregnancy considerations

The evidence of risk for fetal malformations when treating pregnant patients with narcolepsy is limited. Most drugs to manage EDS in narcolepsy have a category C in the FDA classification (Table 1) which means risk cannot be ruled out (adequate, well-controlled human studies are lacking, and animal studies

have shown a risk to the fetus or are lacking as well; there is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk) [6•]. An international survey study suggests that potential risks of teratogenic toxicity to the fetus may be overestimated by physicians when treating patients with narcolepsy. Most patients with narcolepsy have vaginal delivery without complications, although in rare cases, cataplexy interfered with the delivery [53]. Scheduled naps may be refreshing and beneficial to improve control of EDS. Overall, information about treatment of narcolepsy in pregnant women is lacking.

Emerging therapies

Several molecules acting as H3 antagonists or inverse agonists have been object of Phase I and II studies [54]. The efficacy of JNJ-17216498 compared to modafinil and placebo in patients with narcolepsy was evaluated (NCT00424931), however results are not available yet [55].

The safety and efficacy BTD-001 (a non-competitive $GABA_A$ receptor antagonist) to improve EDS in patients with idiopathic hypersomnia and narcolepsy type 2 has been evaluated in a recent randomized controlled trial (NCT02512588); recruitment is completed but results have not been posted [56].

Similar to gamma hydroxybutyrate, other $GABA_B$ receptor agonists might be considered potentially useful therapies in narcolepsy. A parallel study did not show significant improvement of sleepiness or cataplexy with baclofen when compared to sodium oxybate [57]. However, a recent study showed greater effects of R-baclofen (R-enantiomer of baclofen) in murine models of narcolepsy [58].

A randomized controlled trial (NCT02832336) evaluated the efficacy of caffeine 200 mg daily for a week on improving daytime sleepiness and reaction time in patients with narcolepsy. Results are yet not posted [59].

Different formulations of existing therapies have also been object of several studies. A trial currently ongoing (NCT02720744) aims to assess the efficacy and safety of a once-nightly extended-release sodium oxybate [60]. A combined preparation of modafinil and flecainide (THN102) was studied (NCT02821715) based on potential enhancing effect of promoting wakefulness, however, results are not available [61].

The discovery of hypocretin deficiency as the main pathophysiological mechanism in narcolepsy type 1, opened the research field of hypocretin-based therapies for the management of this condition. Potential options to replace hypocretin in the brain may include intranasal administration of hypocretin peptide, synthetic hypocretin receptor agonists, hypocretin gene therapy, hypocretin neuronal transplantation and therapeutic antibodies [62]. Blood brain barrier penetration is a major limitation in the development of hypocretin replacement therapies, and so small molecule orexin/hypocretin agonists may represent the most viable strategy [63]. Given the probable immunologic involvement in the pathophysiology of narcolepsy type 1, therapies including immunosupressants and intravenous immunoglobin have been tried, with mixed results [33••].

Endocrine therapy is another potential area of interest in patients with narcolepsy. Thyrotropin releasing hormone (TRH) and its agonists, seem to have a wakefulness-promoting effect in canine narcolepsy, however, further research is required to ascertain the potential efficacy and side effects in humans [64].

Conclusions

EDS is often an incapacitating symptom in patients with narcolepsy that requires long-term treatment. Several pharmacologic options including wakefulness-promoting agents and stimulant medications are available. Nevertheless, classical symptomatic treatments are often unsatisfactory or lead to significant side effects. Novel wakefulness-promoting medications have been recently approved for the treatment of EDS in narcolepsy. Additionally, hypocretin and immune-based therapies, are an exciting prospect of potential treatments, but will require further research studies.

Compliance with Ethical Standards

Conflict of Interest
Laura Pérez-Carbonell declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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