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Review Article

Clinical and practical considerations in the pharmacologic management of narcolepsy

Michael J. Thorpy [a,*], Yves Dauvilliers [b]

[a] Sleep-Wake Disorders Center, Montefiore Medical Center, Bronx, NY, USA
[b] National Reference Network for Narcolepsy, Sleep-Wake Disorders Center, Department of Neurology, Gui-de-Chauliac Hospital, CHU Montpellier, INSERM U1061, France

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ABSTRACT

Despite published treatment recommendations and the availability of approved and off-label pharmacologic therapies for narcolepsy, the clinical management of this incurable, chronic neurologic disorder remains challenging. While treatment is generally symptomatically driven, decisions regarding which drug(s) to use need to take into account a variety of factors that may affect adherence, efficacy, and tolerability. Type 1 narcolepsy (predominantly excessive daytime sleepiness with cataplexy) or type 2 narcolepsy (excessive daytime sleepiness without cataplexy) may drive treatment decisions, with consideration given either to a single drug that targets multiple symptoms or to multiple drugs that each treat a specific symptom. Other drug-related characteristics that affect drug choice are dosing regimens, tolerability, and potential drug–drug interactions. Additionally, the patient should be an active participant in treatment decisions, and the main symptomatic complaints, treatment goals, psychosocial setting, and use of lifestyle substances (ie, alcohol, nicotine, caffeine, and cannabis) need to be discussed with respect to treatment decisions. Although there is a lack of narcolepsy-specific instruments for monitoring therapeutic effects, clinically relevant subjective and objective measures of daytime sleepiness (eg, Epworth Sleepiness Scale and Maintenance of Wakefulness Test) can be used to provide guidance on whether treatment goals are being met. These considerations are discussed with the objective of providing clinically relevant recommendations for making treatment decisions that can enhance the effective management of patients with narcolepsy.

1. Introduction

Narcolepsy, an underdiagnosed, incurable, chronic neurologic disorder, produces dysregulation of the sleep–wake cycle with excessive daytime sleepiness (EDS) and rapid eye movement (REM) sleep phenomena including cataplexy, hypnagogic hallucinations, and sleep paralysis. The estimated prevalence of narcolepsy is 0.05% of the general population [1,2].

Recent advances in the pathophysiology [3], which have resulted in revisions to the diagnostic criteria [4,5], indicate that narcolepsy has an immunologic basis, with autoimmune components that contribute to the characteristic loss of orexin (hypocretin)-producing neurons in genetically predisposed individuals [6,7]. Animal narcolepsy models and optogenetic device studies have shown that hypocretin maintains wakefulness, increases arousal, and suppresses REM and non-REM sleep [8,9]. The observed association of narcolepsy with streptococcal [10] and H1N1 [11] infections and with H1N1 vaccination [12–15] further supports the concept that narcolepsy is an immune-mediated disease.

The loss of hypocretin-producing neurons characterizes a large proportion of patients with narcolepsy [16], as do specific genotypes such as human leukocyte antigen DQB1*0602 and to a lesser extent T-cell receptor polymorphisms implicated in autoimmune pathways [17]. Two types of narcolepsy are currently recognized in the revised International Classification of Sleep Disorders (ICSD-3) diagnostic criteria [5]. Type 1 narcolepsy, based upon the actual or presumed loss or reduction of hypocretin, has either cataplexy or a reduction in measured cerebrospinal fluid hypocretin-1 level. By contrast, type 2 narcolepsy is determined by the absence of both cataplexy and, if a lumbar puncture was performed, reduced cerebral spinal fluid hypocretin levels, and is dependent upon polysomnographic evidence.

The clinical features comprise a symptom pentad of EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and

* Corresponding author. Sleep-Wake Disorders Center, Montefiore Medical Center, 111 East 210th St., Bronx, NY 10467, USA. Tel.: +1 718 920 4841; fax: +1 718 798 4352.
E-mail address: thorpy@aecom.yu.edu (M.J. Thorpy).

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Table 1
Medications available for the treatment of narcolepsy.

Drug	FDA approval (narcolepsy indication)	EMA approval (narcolepsy indication)	Treatment guideline recommendations [42,43]
Antidepressants including SSRIs, SNRIs, and TCAs	No	No	Cataplexy; option for hypnagogic hallucinations and sleep paralysis
Amphetamine salts (Adderall, but not Adderall XR)	Yes (narcolepsy general indication)	No	Daytime sleepiness
Methamphetamine (Desoxyn)	No	No	Daytime sleepiness
Dextroamphetamine sulfate (Dexedrine)	Yes (narcolepsy general indication)	No	Daytime sleepiness
Lisdexamfetamine (Vyvanse)	No	No	Daytime sleepiness
Methylphenidate HCl (Ritalin, but not Concerta/Methylin, Equasym XL)	Yes (narcolepsy general indication)	Yes, but immediate release only (narcolepsy with or without cataplexy in adults when modafinil is ineffective and in children over 6 years)	Daytime sleepiness
Dexmethylphenidate (Focalin)	No	No	Daytime sleepiness
Modafinil (Provigil)	Yes (excessive sleepiness)	Yes (promote wakefulness in narcolepsy)	Daytime sleepiness
Armodafinil (Nuvigil)	Yes (excessive sleepiness)	No	Developed subsequent to the guidelines.
Selegiline (Eldepryl, Zelapar)	No	No	Cataplexy and daytime sleepiness.
Sodium oxybate (Xyrem)	Yes (excessive sleepiness and cataplexy)	Yes (narcolepsy with cataplexy)	Cataplexy, daytime sleepiness, and disrupted sleep; option for hypnagogic hallucinations and sleep paralysis
Mazindol	No	No	Daytime sleepiness and cataplexy
Pitolisant	No	Submitted to EMA (narcolepsy)	Daytime sleepiness

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

disturbed nighttime sleep (DNS). Although patients have various combinations of all five symptoms, the most common symptom, and often the first to appear, is EDS, which is present in all patients. Cataplexy, which occurs in approximately 70% of narcolepsy patients and may not appear until weeks or months after the onset of EDS, is pathognomonic for narcolepsy [18]. Narcolepsy patients also frequently complain of DNS, with frequent abnormal findings on polysomnography, which may be characterized in up to 90% of patients by awakenings/arousals after sleep onset, increased Stage 1 sleep, and frequent sleep stage shifts [19]. The symptoms of sleep paralysis and hypnagogic/hypnopompic hallucinations are not as prevalent as the other symptoms, but aid in making the diagnosis and can have a substantial impact on the patient when they do occur. Other sleep symptoms, although not included in the pentad, include frequent vivid, bizarre, and delusional dreams as well as nightmares [20–22]. Symptoms of REM behavior disorder (RBD) may also be present in up to 36% of narcolepsy patients, but these may not be a primary complaint and RBD may more likely be recognized during polysomnography [23,24].

Although narcolepsy can have an onset at any age, it appears usually within the first two decades of life, with a median age of onset of 16 years [25,26]. It often remains undiagnosed until many years after initial symptom onset [27], a delay that likely results from a confluence of factors such as the lack of symptom recognition among clinicians [28], the lack of a readily available narcolepsy-specific screening instrument, and the presence of physical and neuropsychiatric comorbidities [29–32], some of which may have symptoms that overlap with narcolepsy and result in misdiagnosis [33].

Narcolepsy in children may present differently from that in adults, with increased 24-h sleep close to disease onset, hyperactivity, and cataplexy that may not be emotionally induced and may resemble puppet-like movements [34].

Narcolepsy is associated with a substantial economic burden resulting from higher health care cost and greater resource utilization than among non-narcoleptic individuals [35]. It reduces functional ability, work productivity, quality of life, and psychosocial functioning [36–38], and also increases the risk of work- and driving-related accidents [39,40]. A study by Ohayon et al. [41] has also shown that narcolepsy is associated with an approximately 1.5-fold higher rate of mortality relative to those without narcolepsy.

As there is no cure for narcolepsy, most patients require lifelong pharmacologic management, and practice parameters for the treatment of narcolepsy have been developed, although some years ago (in 2007) [42,43]. Behavior modifications such as maintaining a regular sleep schedule, scheduling unique and long naps timed early in the afternoon, or short naps (15–20 min) distributed across the day may have favorable effects on daytime performance for patients with narcolepsy. There is no established behavioral treatment for cataplexy, although patients can predict situations likely to trigger cataplexy attacks and act accordingly. Thus, behavioral treatment may have some complementary benefits to pharmacologic treatment.

The available pharmacologic therapies include medications that have been approved for the treatment of specific symptoms of narcolepsy, as well as several that are not approved but are used off-label because of their recognized utility in managing symptoms (Table 1). Of the US Food and Drug Administration (FDA)-approved drugs for narcolepsy, methylphenidate, amphetamines, and modafinil/armodafinil are approved only for EDS. Sodium oxybate is approved for both EDS and cataplexy in adults [44] although published recommendations also suggest its use for disrupted sleep and as an option for hypnagogic hallucinations and sleep paralysis [43]. Off-label drugs include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), all of which are recommended for cataplexy and to a lesser extent for hypnagogic hallucinations and sleep paralysis, albeit with a lower level of recommendation than approved drugs, and hypnotics as an option for DNS [43]. Therapies approved in the European Union include sodium oxybate for the treatment of narcolepsy with cataplexy in adults, modafinil to promote wakefulness in adults with narcolepsy, and immediate-release methylphenidate for the treatment of narcolepsy in adults when modafinil is ineffective and in children >6 years of age. Published guidelines also mention selegiline, a monoamine oxidase inhibitor, as an option for EDS, as well as other drugs

not currently available in the United States including mazindol, ritanserin, and reboxetine. Mazindol is an imidazolidine derivative that blocks dopamine and norepinephrine reuptake that may be effective for EDS and cataplexy [45], and is only available in France. Ritanserin is a serotonin-2 antagonist with potential efficacy for EDS, and reboxetine is a norepinephrine reuptake inhibitor that may be effective for cataplexy [43].

A recent practical review of the pharmacologic agents used in clinical practice provided important information relating to their putative mechanisms, indications, and side effects; however, in the clinical setting, decisions on what drug(s) to initiate and when to modify or change therapy are dependent on a variety of factors that need to be considered [46,47]. Therefore, the purpose of this article is to discuss these factors and to provide clinically relevant recommendations for making treatment decisions that can enhance the effective management of patients with narcolepsy. There are several new approaches to therapy such as the histamine receptor inverse agonist/antagonist pitolisant [48] and the non-amphetamine stimulant mazindol [45], which are not available in the United States, as well as experimental therapies including JZP-110 [49,50] and hypocretin-based therapies such as hypocretin cell transplantation [51] or intranasal administration of hypocretin [52]. However, this article focuses on recommended and readily available therapies. The discussion and recommendations that follow reflect, in part, the authors' personal clinical experience in narcolepsy management, and the American and European experiences only.

2. Treatment selection

In clinical practice, consideration of which drug may be most appropriate for initiating therapy in narcolepsy should be based on factors relating to the different symptoms, to patient characteristics, and to the attributes of various drugs.

2.1. Symptom-related considerations

Narcolepsy symptomatology is the primary disease-related consideration in determining an approach to patient management. In particular, treatment decisions are likely to be driven by whether the patient presents primarily with EDS alone or EDS with other REM-sleep phenomena and additional symptoms, as a therapy that is effective for multiple symptoms is usually more appealing in the latter situation than using different drugs for individual symptoms. Although sodium oxybate is only approved in adults for EDS and cataplexy, evidence indicates its utility for DNS and as an option for other REM-sleep phenomena such as frequent disturbing dreams and nightmares, hypnagogic hallucinations, and sleep paralysis [42,43]. Polypharmacy not only increases the complexity of any disease management but is also likely to decrease adherence and to increase the risk of drug–drug interactions. Interactions are also possible with drugs that are being used to treat comorbid conditions, including potential interactions of sodium oxybate with sedative hypnotics and other central nervous system depressants [44].

Cataplexy and EDS are the most recognized symptoms of narcolepsy and initial treatment typically targets these symptoms. EDS, which usually precedes cataplexy as a presenting symptom, is often treated with modafinil as initial therapy, especially if EDS is present in the absence of cataplexy. However, modafinil and most of the stimulant drugs used to treat EDS have little effect on cataplexy or other REM sleep-associated symptoms, and, conversely, most anticataplectic antidepressants have little beneficial effect on EDS [43]. While no drugs are FDA approved for the other symptoms of the pentad, the presence of these other symptoms in patients should result in consideration of medications that can either be used to supplement those for EDS and cataplexy or address the widest possible group of symptoms.

Treatment decisions should also reflect the principal complaint of the patient, which may not necessarily be the same as the presenting symptoms. Importantly, some symptoms may not be spontaneously reported by patients for a variety of reasons including that the patients do not realize that the symptoms are part of narcolepsy (eg, cataplexy), or they may be too embarrassed to raise certain issues on their own (eg, frequent unpleasant and bizarre dreams). A recent study reported that, in addition to symptoms of the narcolepsy pentad, 42.9% of patients complained of trouble functioning or concentrating during the day, and that one-quarter of patients (25.8%) reported difficulties with activities of daily living [32]. Table 2, adapted from Overeem et al. [53], is a comprehensive list of topics that can be recommended for initiating discussion in a clinical interview. These topics provide a starting point for considering approaches to therapy by eliciting information from patients on the narcolepsy symptoms that are less well known (ie, DNS, sleep paralysis, unpleasant dreams, depressive symptoms, and overweight/obesity) but nevertheless result in a substantial impact on the life of the patient, as well as on associated affects such as memory/cognitive impairment and daily function.

To summarize initial treatment selection, we propose to initiate narcolepsy therapy in at least two successive steps. For most patients, the first step requires an agent that is effective for treating daytime sleepiness. Treatment of EDS should be considered mandatory, as EDS is present in all patients and has practical implications with respect to the risk of driving- or work-related accidents. If EDS is present in the absence of cataplexy, treatment can be initiated with monotherapy using either modafinil or sodium oxybate, with the latter being a better choice if any ancillary features of narcolepsy are present (sleep paralysis, hypnagogic/hypnopompic hallucinations, DNS, nightmares, etc.). The second step may require the use of other agents depending on persistence and discomfort related to associated symptoms and their impact on patient function. Multiple medications are also likely to be required in cases of uncontrollable EDS or cataplexy, with the use of sodium oxybate and/or modafinil plus an "as-needed" stimulant (methylphenidate or amphetamine). Behavioral measures such as naps, avoiding sedentary activities, and avoiding driving or dangerous work situations should also be considered in these cases.

2.2. Patient-related considerations

While symptomatology may suggest an initial approach to narcolepsy management, age is an important factor for making treatment decisions.

As onset is typically in children and adolescents, an early diagnosis followed by early initiation of therapy is critical to minimize emotional and developmental problems including reduced scholastic achievement. Pediatric recommendations for the treatment of narcolepsy have not been established, and while few drugs have been evaluated for efficacy or toxicity in children, treatment of pediatric narcolepsy is generally considered similar to that of adults [46]. Other than amphetamines and methylphenidate stimulants, no other medications have been approved by the FDA for the treatment of narcolepsy in children. In Europe, armodafinil and amphetamines have not been approved for narcolepsy by the European Medicines Agency (EMA), and only immediate-release methylphenidate is approved for the pediatric population. However, methylphenidate and the amphetamines can be associated with suppression of growth [54], may predispose to drug abuse and addiction, and severe rashes, although rare in clinical practice, and may be more likely to occur in children on modafinil/armodafinil [55,56]. Limited clinical reports of children with narcolepsy suggest the efficacy and tolerability of modafinil for EDS, venlafaxine for cataplexy, and sodium oxybate for most symptoms, although multiple medications are used in some patients [57–59]. Of note, armodafinil is

Table 2
Suggested topics to cover in the clinical interview for eliciting information from patients on narcolepsy symptoms and their effects, and which may provide a basis for making treatment decisions.

Topic	Issues for discussion with patient
General	Age at onset of EDS and cataplexy, and initial presenting symptoms; are there any possible triggers around onset (eg, infection, vaccination, trauma, or concurrent neurologic illness)?
Sleepiness	How does sleepiness interfere with daily function, with regard to the magnitude of the effects and the quality of the outcomes? What is the pattern of excessive sleepiness: continuous somnolence or sleep attacks? What is the frequency and duration of both involuntary and planned sleep episodes? Are sleep episodes freshening? Can sleep be resisted? Are there dreams or similar phenomena during short naps? What circumstances worsen or improve sleepiness? Since onset, has there been any freedom from sleepiness? Variability of daytime sleepiness during the week versus weekends.
Cataplexy	What is the description of a typical attack, including pattern of weakness? Are attacks mostly partial or complete, unilateral versus bilateral? What is the frequency and duration of episodes? Ensure there is no loss of consciousness. Inquire about spectrum of triggers. Have there been any physical injuries?
Nocturnal sleep	Habitual sleep duration and sleep–wake schedule during the week versus the weekend; subjective sleep latency, and number and duration of awakenings; symptoms of other possible sleep disorders (such as SDB or RLS). Assess sleep hygiene.
Hallucinations	Hypnagogic or hypnopompic? Duration, frequency, and content; associated symptoms of fear and anxiety. Place and time of occurrence of hallucinations.
Sleep paralysis	Duration and frequency. Co-occurrence with hypnagogic/hypnopompic hallucinations?
Automatic behaviors	Establish any examples of automatic behaviors and their circumstances and frequency.
Dreams	Frequent, vivid, bizarre dreams, out-of-body experiences, dreams and naps.
Weight change	Current weight and height to calculate BMI. Was there any change around the onset of narcolepsy symptoms? Current stability of weight; is there any influence of medication on weight?
Eating habits	Abnormal appetite (eg, binge eating or eating at night); influence of meals and their type (eg, high carbohydrate load) on (postprandial) sleepiness.
Mood/anxiety	Are there mood disturbances? Is there a history of depression, anxiety, panic attacks, phobias, or suicide ideation?
Other symptoms	Are there any memory or concentration complaints? If appropriate, ask about sexual problems. Specifically assess fatigue (separate from actual sleepiness).
Psychosocial aspects	Have narcolepsy symptoms of sleepiness or cataplexy influenced social interactions at school or work? Ask about driving.
Family history	Are there any relatives with narcolepsy, daytime sleepiness, or other sleep disorders?
Comorbidities and co-medications	History of cardiovascular diseases, sleep apnea syndrome, diabetes, restless legs syndrome, RBD, and sleepwalking/enuresis. Review of medications or substances acting on central nervous system.

Table adapted with permission from Overeem et al. [53].
Abbreviations: BMI, body mass index; EDS, excessive daytime sleepiness; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome; SDB, sleep-disordered breathing.

similar to modafinil in efficacy for EDS, but in contrast to modafinil, which requires twice-daily dosage, armodafinil is taken once per day. Thus, armodafinil may be of interest as a first choice especially in children who may miss the second intake of modafinil at lunch, or in case of sleep-onset insomnia due to the second modafinil dose. However, parents might be concerned about long-term pharmacologic treatment in a child. Therefore, when possible, a behavioral approach can be taken to control sleepiness using regularly scheduled naps, but if cataplexy impacts quality of life or safety issues, sodium oxybate should be initiated.

As increasing age and overweight/obesity convey an increased risk of cardiovascular disorders including hypertension and heart failure, a high percentage of non-blood pressure dippers has been reported in patients with narcolepsy that may be of clinical relevance by predisposing to cardiovascular events [60]. This latter finding implied the involvement of hypocretin in multiple physiologic functions such as energy homeostasis and cardiovascular control and suggested changes in the autonomic nervous system in hypocretin-deficient narcolepsy [61]. For these reasons, in older and/or obese narcoleptics, it may be appropriate to limit the use of sodium oxybate because of its high salt content. However, anecdotally, sodium oxybate has been used with salt restriction and diuretics, although the efficacy and safety of this combination need to be confirmed. The choice of methylphenidate or amphetamines is also less than optimal in an older population, as these drugs are contraindicated in patients with cardiovascular disorders and glaucoma. Some antidepressants, especially TCAs, are contraindicated in an older population due to the risks associated with their sedating effect, confusional-state urinary retention, and potential for cardiac arrhythmias and induction of orthostatic hypotension [62].

For women of childbearing potential who are using oral contraceptives for birth control, the use of modafinil/armodafinil needs to be discussed with regard to potential interactions that may impact the effectiveness of contraception [55,56]. In these individuals, an increased dose of ethinylestradiol up to 50 μg per day, an all-progesterone oral contraceptive, or an alternative method for birth control should be employed. Another contraindication for the use of sodium oxybate is the need for alertness at night among individuals with infants or young children, especially in the case of a single parent.

As narcolepsy management is a long-term endeavor, the patient should be regarded as an active participant in treatment decisions. Discussions should include information on all the available treatment options, focusing on what can realistically be expected with regard to efficacy and adverse effects. The purpose of these discussions is to elicit informed feedback from the patient as to what might best fit with their symptoms, goals, and lifestyle, thereby increasing the likelihood of higher treatment adherence. Patients should only make changes to their medication regimen under the advice of the clinician.

2.3. Therapy-related considerations

The clinician should have complete familiarity with the mechanisms of action, dosing regimens, and the rationale for specific use of each of the medications [46]. Therapies should be initiated at an appropriate level, and should be titrated up or down as necessary when the need arises. Balance needs to be maintained between efficacy and side effects, as complete elimination of EDS in narcolepsy is rare. Treatment with a dosage that is too low, in an attempt to avoid side effects, can result in discontinuation due to lack of efficacy and adverse effects with only partial improvement of EDS. Titration rate to maximal efficacy while minimizing side effects should be done on an individual basis. However, even FDA-approved maximal doses, such as for modafinil, may not be fully effective in relieving daytime sleepiness; higher doses (up to 600 mg per day) [63], although recommended, may not be reimbursed by healthcare insurers. Discussions about side effects should be individualized

depending upon the patient's age, prior drug experience, personality, and educational level among other considerations. Side effects can occur after therapy initiation and then dissipate with therapy, such as is common with modafinil and sodium oxybate, so premature termination may be inappropriate. Drugs that require tapering rather than abrupt cessation include antidepressant anticataplectic agents, which can induce status cataplecticus [64]. A switch from amphetamines to modafinil or methylphenidate, or the converse switch, can be performed abruptly, whereas a change from anticataplectic agents to sodium oxybate should be done with gradual antidepressant reduction and increasing sodium oxybate titration [65].

Most narcolepsy drugs are FDA – controlled substances, Schedules II, III or IV, which may be disconcerting to both patients and physicians, for the former because of concern with addiction or abuse potential, and for the latter because of the greater burden of record keeping. Dextroamphetamine, lisamphetamine, methamphetamine, and methylphenidate are Schedule II controlled substances (high potential for abuse, which may lead to severe psychologic or physical dependence), sodium oxybate is a Schedule III controlled substance (less potential for abuse, but may lead to moderate or low physical dependence or high psychologic dependence), and modafinil/armodafinil are Schedule IV controlled substances (a low potential for abuse relative to the drugs or other substances in Schedule III). Although excessive dosage and associated adverse effects of stimulant medications have been reported in narcolepsy [66], in clinical practice, patients with narcolepsy rarely abuse drugs for narcolepsy or develop addictions [67,68]. The effect on the reward system that predisposes to reduced addiction may be associated with hypocretin loss [69].

Drug cost, whether borne by the patient or by managed care, can present a barrier to treatment. More recently approved medications are typically associated with high costs, and although some of the drugs for narcolepsy are available as generics (antidepressants, methylphenidate, amphetamines, and modafinil), they may not always be the appropriate choice despite providing a cost advantage. Costs should be considered, but the patients ultimate choice of treatment should be based on clinical considerations as to which medication provides the greatest benefit and the best side-effect profile. Higher costs may be offset by the greater functionality, productivity, and quality of life that can be achieved.

3. Medication strategies

3.1. Methylphenidate and amphetamines

Methylphenidate and amphetamines were available before the new agents such as modafinil/armodafinil and sodium oxybate. Their usefulness is primarily for EDS, except for some mild cases where they have not shown to be effective for cataplexy and other symptoms of narcolepsy. Although cheaper than the newer alternatives, their usefulness is limited by their abuse potential and side-effect profile [66]. Methylphenidate has now been relegated to second-line therapy, with amphetamines and mazindol as third-line therapy, the latter at least in France, as there are few clinical trial data available on their efficacy and safety [43]. If a patient cannot take modafinil or armodafinil or sodium oxybate, or more frequently when these compounds are not fully effective for EDS, then methylphenidate or amphetamine stimulants, as either extended-release forms taken one or two times per day or short-acting forms taken up to four times a day, can be useful. Higher-than-recommended doses (60 mg per day for methylphenidate and 60 mg per day for amphetamine) have been associated with more frequent hospitalizations, cardiac arrhythmias, and psychiatric disturbances in narcolepsy patients [66].

3.2. Antidepressants

Few data exist regarding the efficacy of antidepressants (SSRIs, SNRIs, and TCAs) on cataplexy [70]. However, in clinical practice, case reports have suggested that they can be effective [71–73], especially those with the strongest norepinephrine reuptake inhibition. Thus, SNRIs are the most widely used antidepressants for cataplexy, particularly venlafaxine, which may be effective for cataplexy within 48 h at low doses. Because of its short duration of action, the extended-release form is preferable, starting at a low dose (37.5 mg), but higher doses are often needed (75–300 mg). However, they are limited by side effects that can include insomnia, mental stimulation, and reduced sexual function, and may precipitate other sleep disorders such as RBD [74] and restless legs syndrome (RLS) [75]. They are neither FDA nor EMA approved for cataplexy but can be useful as an alternative to sodium oxybate.

3.3. Modafinil/armodafinil

These medications are effective for EDS but have no effect upon the ancillary symptoms of narcolepsy. Although rare in clinical practice, they can be associated with severe rashes in children [55,56] and can reduce the efficacy of oral contraceptive agents [55,56]. When indicated, they are best taken first thing in the morning on an empty stomach. If headaches occur, temporary adjustment of the dose is usually all that is required. Most patients require the maximum approved dosage (400 mg approved and sometimes up to 600 mg per day for modafinil), but some patients do quite well even on low doses such as 100 mg of modafinil or 50 mg of armodafinil. In combination with sodium oxybate, they have been shown to enhance the improvement of EDS [76]. Among patients taking modafinil/armodafinil who may be required to perform demanding tasks during the course of their daily activities, a supplementary late afternoon dose of a short-acting stimulant, such as Dexedrine or regular methylphenidate, can be used.

3.4. Sodium oxybate

Sodium oxybate, which is FDA approved for sleepiness and cataplexy in adults, is the only medication that can treat, and is recommended for, all the symptoms of narcolepsy [42,43]. Often well tolerated, side effects are very variable from one patient to another. Side effects are usually mild to moderate at worst, but patients may develop nausea, confusion, anxiety, depressive symptoms, RLS, and sleepwalking, or enuresis that may limit its use. In clinical practice, the confusion and neuropsychiatric effects at treatment initiation have been found to be due, at least in part, to a dose that does not rapidly induce sleep, as some patients may take up to 2 h to fall asleep after dosing, thereby causing symptoms of confusion and incoordination in the patient who is still ambulatory at that time. A more rapid increase in dose can improve this situation, and titration to effect is a critical component of patient management with sodium oxybate. Nausea can be helped by adding flavored water to the sodium oxybate solution, which has a salty taste, or by adjusting of the dosage. An oral antiemetic such as a 5-HT3 antagonist (eg, ondansetron) has been used clinically in some patients to help control the nausea. Although this medication best taken on an empty stomach, as a meal may reduce the efficacy, adding of small amount of food, such as a cracker, may help mask the taste.

Although gamma-hydroxybutyrate including sodium oxybate-related deaths have been reported, these events are mainly related to an overdose or illicit use, or in association with concomitant utilization of other sedative drugs [77].

Initial concerns regarding abuse have not been borne out since its approval [78], and its low abuse in the clinical setting may be especially aided in the United States by the requirement of central

pharmacy dispensing. Although its dosing regimen has been of concern to physicians, in clinical practice, few patients have been bothered by taking the medication twice at night. Clinical practice has shown that some patients do well with a single nightly dose, while in others the first and second doses have been adjusted according to clinical needs without loss of efficacy [79].

If cataplexy or EDS is severe, initiating the patient on sodium oxybate plus venlafaxine (for cataplexy) or sodium oxybate plus modafinil (for EDS) is a reasonable initial plan until the sodium oxybate is effective, at which point the other medication may be tapered off.

4. Evaluation of treatment response

Outcome measures represent an important component of monitoring and optimizing treatment for any disease. In the case of narcolepsy, regular assessment after initiation of treatment is a useful approach to drive changes in therapy such as dose adjustment or switching of medications, especially because the level of improvement may not be able to be predicted.

Assessment measures should be based on symptoms, patient complaints, and the goals of the patient with regard to treatment. An important attribute of any measure to be used in evaluating treatment response is its demonstration of sensitivity to change. Objective measures such as the Multiple Sleep Latency Test, the Maintenance of Wakefulness Test, the Sustained Attention to Response Task [80], and the Psychomotor Vigilance Test may be useful for quantitatively evaluating clinical outcomes. However, these objective measures of sleepiness or vigilance may not necessarily correlate with patient function or symptomatic complaints. Additionally they require time, and are complex and not readily reimbursable by insurance carriers. Thus, these tests are infrequently used as a routine measure of treatment efficacy in narcolepsy, but the Maintenance of Wakefulness Test should be proposed for assessment of those who may be employed as drivers.

Of greater relevance from the patient's perspective are subjective measures that focus on the patient complaint and their overall goal of treatment. Several patient-reported outcomes (PROs) address sleep and sleepiness-related outcomes including the Epworth Sleepiness Scale (ESS) [81], often used for narcolepsy screening, and the Karolinska Sleepiness Scale (KSS) [82]. While both the ESS and the KSS measure the magnitude of sleepiness over different recall periods, the Functional Outcomes of Sleep Questionnaire [83] assesses the impact of excessive sleepiness on activities of daily living. Although infrequently used in clinical practice in narcolepsy patients, the Insomnia Severity Index (ISI) [84] may also be considered an option that could be of potential value in some patients at initial and follow-up evaluations, depending on the patient's symptomatic complaints. The ISI is a short self-report questionnaire that assesses the nighttime and daytime components of insomnia, and in the absence of a specific DNS measure may act as an assessment for the presence and impact of DNS in patients with narcolepsy.

Other generic measures focus on quality of life, such as the 36- or 12-item Short Form questionnaires [85,86] and the five-dimension European Quality of Life questionnaire [87], or on specific problems such as depression using the nine-item Patient Health Questionnaire [88] or the Beck Depression Inventory [89]. Ideally, a sleep-related measure as well as a more general health-related quality-of-life measure should be regularly used to monitor patients for treatment effects and general health. The effectiveness of drugs used to treat cataplexy, hallucinations, sleep paralysis, and sleep disturbance is difficult to evaluate, as the methods used to assess both their frequency and intensity remain variable and complex (eg, recall by history only, by scale, by diaries, or by video recordings). However, at least the use of specific diaries is recommended for monitoring the persistence of such symptoms.

Alternative methods of capturing PROs exist including interactive voice response systems, patient portals, or electronic medical records. These methods enable more frequent assessment without the need for clinical office visits, and they also facilitate record keeping and data analysis.

In regard to the changes that may be observed on objective and PRO measures, an important issue in narcolepsy is determining the clinical significance of the changes, as there is a lack of information on what constitutes clinically meaningful improvements. It should also be noted that, while a patient is often the best judge of treatment response, the patient's perspective may not necessarily coincide with that of the clinician, nor does a patient's perceived satisfaction with the treatment necessarily reflect the response that could potentially be achieved. In this regard, the patient's family or teachers, when children are involved, should be considered as a valuable source for evaluating treatment response as the observations of family members may be inconsistent with the patient's perceptions or the patient's report at a clinical visit.

5. Managing comorbid conditions

5.1. Comorbid conditions

Several studies have shown the frequent occurrence of one or more comorbidities among narcolepsy patients, including medical and neuropsychiatric conditions [29–32]. In addition to contributing to the diagnostic delay [27], some disorders have symptoms that overlap with narcolepsy, increasing the complexity of diagnosis, and their management may rely on treatments that mask narcolepsy symptoms, such as antidepressants for depression, stimulant use for attention-deficit hyperactivity disorder, or continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA).

Depressive symptoms are frequent in patients with narcolepsy, especially in the context of cataplexy, but less frequent is a formal diagnosis of major depressive disorder [90]. However, patients with mood disorders should be screened for suicidality prior to initiating sodium oxybate therapy, during therapy, and especially after any increases in dosage. Although a risk of suicide has been recognized in patients with sleep disorders [91,92], including narcolepsy [93], sedative neuropsychiatric medications in combination with sodium oxybate may increase the suicide risk [78]. While validated questionnaires such as the Columbia Suicide Severity Rating Scale [94] are available to monitor this risk, the patient's partner or family should also be informed about watching for behavioral changes that may be indicative of suicidality. In addition, neuropsychiatric medications may impair awareness of ingested medication, thereby leading to an accidental overdose.

Comorbid metabolic conditions such as diabetes may be of particular relevance to narcolepsy because of the associated obesity and weight control issues. While narcolepsy itself is not directly associated with insulin resistance or glucose tolerance [95,96], narcolepsy treatments may have metabolic effects. Sodium oxybate can increase lipolysis, which may contribute to weight loss [97], and stimulants may affect glucose control.

Patients with narcolepsy with a history of cardiovascular diseases should not be treated with stimulants except with low doses of modafinil, low doses of long-release methylphenidate in the absence of modafinil efficacy, or with pitolisant, where available. However, careful follow-up is required in these patients.

Patients with narcolepsy also display a variable array of complex motor phenomena during sleep, encompassing both REM- and non-REM-related parasomnias. REM sleep without atonia together with elementary and complex motor behavior up to clear-cut oneiric enactment, considered an equivalent of RBD, frequently occur in narcolepsy. Non-REM-related parasomnias, somnambulism,

sleep-related eating syndrome, and enuresis are also reported in patients with narcolepsy.

5.2. Treatment-related exacerbation of comorbidities

Narcolepsy treatment may result in exacerbation or precipitation of sleep disorders, including OSA, periodic limb movements (PLMs), RLS, and RBD [98].

In particular, PLMs and RLS, which have been reported to be present in up to 50% and 25%, respectively, of patients with narcolepsy [24,99,100], are associated with a higher nighttime arousal index, thus further disrupting sleep and contributing to daytime sleepiness and fatigue [101–103]. PLMs and RLS can be exacerbated by drugs that increase central nervous system sedation such as sodium oxybate [98,104], as well as antidepressants [74,75], and therefore may require a switch in therapy. RBD may also be induced by antidepressants in patients with narcolepsy [105].

OSA is a comorbidity that is related to increased weight and obesity, has a high prevalence in narcolepsy [106–108], and can lead to a lack of narcolepsy recognition [27,109]. Central sleep apnea and OSA syndromes should be excluded before prescribing sodium oxybate, and sleep apnea treated prior to initiating sodium oxybate therapy. The treatment, usually by CPAP, needs to be maximized before initiating treatment with sodium oxybate, which can also precipitate or exacerbate OSA [110]. However, sodium oxybate is also associated with weight loss in patients with narcolepsy [111].

5.3. Pregnancy

An international survey of 34 sleep medicine clinicians with experience in narcolepsy highlighted that substantial variability exists among clinicians and across countries regarding the management of narcolepsy in pregnancy [112]. The available but limited evidence suggests that, despite narcolepsy drugs receiving a Schedule C classification for pregnancy (ie, risk cannot be ruled out), the risks of toxicity resulting from the utilization of narcolepsy drugs during pregnancy may be overestimated, with little or no evidence for teratogenicity at therapeutic doses [112]. When the pregnancy is planned, management options can be discussed in advance; when unplanned, consideration should be given to adjusting medication regimen depending on the stage of pregnancy. Women going through pregnancy even without medications have a 2% risk of fetal malformation in narcolepsy [113], similar to the general population. While it is necessary to psychologically prepare women for the risk of fetal malformation even under normal clinical conditions, the decision to continue or withhold narcolepsy medications during pregnancy should be made by an informed patient after weighing the risks and benefits. Although, ideally, patients should discontinue medication during the whole time of conception and pregnancy, this may not be possible, especially if the pregnancy is unplanned. Potential management options should include staying on medication with dose reductions, changing medication if appropriate, or stopping the medication. However, treatment cessation may not be advisable in some patients if narcolepsy symptoms are severe and there is a risk of injury to the mother or fetus or an inability to manage daily activities. Clinicians should also note that the best time to avoid medications is within the first 60 days of pregnancy.

There is little information available on the use of narcolepsy medications in nursing mothers. Most hypnotics are contraindicated in nursing mothers due to concerns regarding the depressant effect in the infant, so similarly it would be unwise to use sodium oxybate, especially as it is not known whether it is excreted in human milk [44]. However, sodium oxybate has a short half-life, and in clinical practice some mothers have expressed milk before their nightly dose to give to the infant. Modafinil, methylphenidate, amphetamines, and antidepressants have no specific contraindications in nursing mothers.

6. Managing concomitant medications and other substances

Patients with narcolepsy have a higher prevalence of comorbid conditions relative to matched controls, and they also have significantly higher utilization of a variety of prescription medications [29]. Therefore, an understanding of medication mechanisms of action is critical when making narcolepsy treatment decisions. Examples include the risk of serotonin syndrome due to combinations of antidepressants, and sodium oxybate, which is a central nervous system depressant and may be associated with respiratory depression. Therefore, if treatment with sodium oxybate is considered, not only are sedative hypnotics and alcohol contraindicated [44] but also the use of other central nervous system depressants, such as opioids and divalproex sodium, should be discontinued or reduced [44], with patients being closely monitored if the use of other central nervous system depressants is required. A summary of key drug interactions is provided in Table 3.

The use of lifestyle substances such as caffeine, nicotine, alcohol, cannabis, and other drugs should be assessed and discussed with the patient, and appropriate therapeutic recommendations made. Prior to diagnosis, many patients use caffeine excessively to improve alertness the general stimulation effects are not pleasant even when and patients readily give up or reduce caffeine use when on a specific medication for alertness. Case reports suggest that nicotine may mask or relieve symptoms of narcolepsy, including EDS and even cataplexy [114,115]. Such an interaction is supported by limited data suggesting that nicotine addiction may be mediated by hypocretin pathways [116]. Although narcolepsy symptom relief may be viewed as a benefit of nicotine and may thus be a barrier to smoking cessation in narcoleptics, the act of smoking is itself of concern because of the risk of falling asleep while smoking resulting in injury and damage [114].

Several of the drugs used to treat narcolepsy have warnings regarding the concomitant use of alcohol, including sodium oxybate [44]. However, many patients will be reluctant to completely forego alcohol, and therefore a realistic approach should be taken when providing information on these interactions. Young adults should be especially advised regarding interactions with alcohol and emphasis should be placed on methods to minimize such interactions, including minimal consumption, type of alcohol (beer, wine, or spirits), and timing of alcohol intake. Alcohol should not be present in the body concurrently with sodium oxybate. Timing is likely to be most relevant for sodium oxybate, which is taken only at night, and consideration should be taken of the drug's dosing regimen and the pharmacokinetics of alcohol; skipping the first sodium oxybate dose at night may often be good advice in situations of alcohol consumption.

Nothing has been published about the effects of cannabis on narcolepsy or its interaction with drugs during narcolepsy therapy. Such interactions may become an increasingly open issue with the wider availability of medical marijuana and the recent loosening of restrictions for recreational use in several US states. Anecdotal evidence from clinical practice suggests that there do not seem to be any interactions, although concomitant use of cannabis-containing products is not recommended and may increase some vigilance problems.

7. Summary

Narcolepsy remains a challenging disease for both diagnosis and treatment. However, once the disorder is diagnosed, the challenge of treatment can be lessened if an appropriate and careful

Table 3
Key disease contraindications and potential drug–drug interactions of pharmacologic therapies for narcolepsy*.

Drug	Disease contraindication	Drug interactions
SSRIs	None specified, but depending on individual drug, cautious use in patients with renal or hepatic impairment, and in patients with seizure disorders.	Potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; alcohol; drugs affecting hemostasis; MAOIs; SNRIs; TCAs.
SNRIs	Glaucoma.	Potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; alcohol; drugs affecting hemostasis; MAOIs; SSRIs; TCAs.
TCAs	Glaucoma; seizure.	Alcohol; MAOIs; potential interactions with drugs that inhibit, induce, or are metabolized by specific cytochrome P450 pathways; SSRIs; SNRIs.
Amphetamines	Structural cardiac abnormalities or other serious heart problems; glaucoma.	Insulin; antihistamines; antihypertensives; MAOIs; TCAs.
Methylphenidate (Ritalin)	Structural cardiac abnormalities or other serious heart problems; glaucoma; Tourette's syndrome.	Coumarin-type anticoagulants; MAOIs; TCAs.
Modafinil/armodafinil (Provigil, Nuvigil)	None specified.	Oral contraceptives; potential interactions with drugs that inhibit, induce, or are metabolized by cytochrome P450 pathways.
Selegiline (Eldepryl, Zelapar)	None specified.	Dextromethorphan; meperidine; SSRIs; SNRIs; tramadol; TCAs.
Sodium oxybate (Xyrem)	Succinic semialdehyde dehydrogenase deficiency; cautious use in patients with heart failure, hypertension, or impaired renal function.	Sedative hypnotics; divalproex sodium; alcohol.
Mazindol	May cause valvular cardiac disease.	Antihistamines; antihypertensives; MAOIs; TCAs.
Pitolisant	None specified.	Antihistamines.

Abbreviations: MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

* This table is not comprehensive; product safety information should be consulted for potential interactions with less commonly used drugs. Drug interactions do not necessarily indicate an absolute contraindication, but may require appropriate titration to reduce the risk of interactions.

approach is used when considering treatment options. While symptom presentation, whether EDS alone or with cataplexy and other
symptoms, is an important driver of treatment decisions, patient management needs to incorporate the clinical perspective yet take a patient-centric approach; the patient should be an active participant in the decision-making process. Clinical considerations include the presence of comorbid conditions and their treatment, and their relationship to the different pharmacologic options that are available for narcolepsy. The associated dose regimens need to be clearly conveyed to the patient, taking into account the patients goals and lifestyles, as well as broad recommendations that can then be narrowed and optimized by individualizing the treatment and its dosing for each patient.

Narcolepsy management also requires regular evaluation to identify when changes in medication may be required. Although there is a need for systematic and standardized outcome assessment instruments specific for narcolepsy, a wide variety of measures are available, with the choice of measures based on the outcomes that need to be evaluated. Regardless of the measures used, patients should be evaluated regularly for determining the presence and severity of symptoms, their effects on daily function, whether treatment goals are being met, and the efficacy and safety of medications, which will facilitate effective long-term management and improve the lives of narcolepsy patients and their families.

Conflict of interest

Dr. Thorpy is a member of the speakers' bureau for Jazz Pharmaceuticals, Inc. and Cephalon, Inc. (now Teva Pharmaceutical Industries, Ltd.); Dr. Dauvilliers has received consultancy fees and/or honoraria, and has been a member of the speakers' bureau and/or an advisory board participant for UCB, Bioprojet, and Jazz Pharmaceuticals, Inc.

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