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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