



Emerging treatment options for excessive sleepiness associated with narcolepsy

Jonathan RL Schwartz
 Integris Sleep Disorder Center
 and University of Oklahoma
 Health Science Center,
 4200 South Douglas Ave,
 Suite 313, Oklahoma City,
 OK 73109, USA
 Tel.: +1 405 636 1111
 Jonathan.Schwartz@
 Integris-Health.com

Narcolepsy is a chronic neurological sleep disorder characterized by symptoms of excessive sleepiness, cataplexy and abnormal manifestations of rapid eye movement sleep. Several therapeutic options are available for the management of narcolepsy, for which the primary treatment goal is improvement of excessive sleepiness symptoms through the waking period. First-line treatment options include modafinil and the CNS stimulants. Sodium oxybate may also be used for the treatment of cataplexy or as augmentation for refractory sleepiness. The new agent armodafinil may also have a role in the management of this disorder. Evidence supporting the use of these agents and discussion of their place in therapy will be reviewed.

Narcolepsy is a chronic neurological sleep disorder characterized by excessive sleepiness (ES), cataplexy, and abnormal manifestations of rapid eye movement (REM) sleep [1]. Two variants of narcolepsy are recognized by the International Classification of Sleep Disorders: narcolepsy with cataplexy and narcolepsy without cataplexy. Both variants are associated with naps that are refreshing in nature, with normal or moderately disturbed nocturnal sleep, and may be associated with automatic behavior, sleep paralysis and hypnagogic hallucinations [1]. Cognitive deficits, including deficits in attention and memory, are often present [2,3]. Narcolepsy with cataplexy is associated with a sudden, generally brief, loss of bilateral muscle tone induced by an emotional trigger.

Prevalence estimates for narcolepsy with cataplexy vary widely, from 0.02 to 0.18%, depending on study methodologies and geographic location [1,4]. The prevalence of narcolepsy without cataplexy is unknown; however, cases of this disorder may represent up to 50% of patients with narcolepsy [1,5]. The familial risk of narcolepsy with cataplexy has been reported to be low (1–2%) [6], although more recent research suggests that the risk may be as high as 17% [7]. Twin-based studies suggest that the disorder may result from an interaction between environment and a specific genetic background [6]. Current evidence has shown that in most cases of narcolepsy with cataplexy, the probable cause is a deficiency in the hypothalamic neuropeptide hypocretin/orexin [8] with an association with the human leukocyte antigen (HLA) subtype DQB1*0602, suggesting that an autoimmune mechanism may be involved in hypocretin/orexin cell loss [5,6]. The frequency of HLA

DQB1*0602 has been found to be higher in narcoleptic patients with cataplexy (76%) than those without cataplexy (41%) [9].

Emerging treatments for narcolepsy Modafinil

The primary goal of treatment for narcolepsy is to alleviate ES and return patients to normal or near normal function. Although scheduled naps are helpful in combating ES, pharmacological therapy is often needed. Modafinil (Provigil®), a novel wake-promoting agent, is considered by the American Academy of Sleep Medicine in evidence-based guidelines to be a standard therapy for improving wakefulness in patients with narcolepsy [10].

Modafinil is the most studied medication in narcolepsy and has demonstrated efficacy for improving wakefulness with both once- and twice-daily dosing (Table 1) [11–18]. In double-blind, placebo-controlled studies, modafinil at doses up to 400 mg/day has been shown to improve objective (Multiple Sleep Latency Test and Maintenance of Wakefulness Test [MWT]) and subjective (Epworth Sleepiness Scale [ESS]) measures of wakefulness and overall clinical condition (Clinical Global Impression of Change [CGI-C]) [13,14]. The effects of modafinil on wakefulness were maintained throughout two 40-week, open-label extension studies [15]. Additionally, in these long-term studies, modafinil improved both mental and physical composite scores of the 36-Item Medical Outcomes Study Health Survey [15]. The most pronounced changes occurred in the domains of role physical and emotional, vitality, and social function, suggesting a benefit to patients' quality of life. Benefits of modafinil

Keywords: alertness, armodafinil, attention, modafinil, narcolepsy, sodium oxybate, wakefulness



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Table 1. Major clinical studies of modafinil for the treatment of patients with narcolepsy.

Study	N	Study design	Study drug dosage	Efficacy measures	Efficacy results	Refs
Billiard (1994)	50	12-wk, double-blind, placebo-controlled, crossover study	Modafinil 300 mg/day in split doses (morning and noon) or placebo	Sleep log, VAS, sleep questionnaire, CGI, MWT	MWT: Modafinil had a positive effect on daytime excessive sleepiness as shown by a time effect ($p = 0.01$) and a drug/period effect ($p = 0.0004$) Sleep log: Modafinil was associated with a significant reduction in the number of episodes of sleepiness ($p = 0.05$) and the duration of daytime total sleep time ($p = 0.0002$). There were no significant changes in VAS feelings on awakening, sleep continuity and quality, or CGI	[11]
Broughton (1997)	75	6-wk, randomized, crossover, placebo-controlled, three-period study	Modafinil 200 mg, modafinil 400 mg in divided doses (morning and noon), or placebo	MWT, patient diary, ESS, FCRTT	MWT: Mean sleep latency compared with placebo improved significantly with modafinil 200 mg/day ($p = 0.0002$) and modafinil 400 mg/day ($p = 0.0001$) ESS: Both the 200-mg ($p = 0.018$) and 400-mg ($p \leq 0.001$) groups showed improvement over placebo FCRTT: Performance improved with each dose ($p < 0.03$) at the last session (after the second dose) Patient diary: Modafinil 200 and 400 mg/day reduced the number of involuntary sleep episodes ($p = 0.013$) and severe somnolence ($p = 0.007$)	[12]
US Modafinil in Narcolepsy Multicenter Study Group (1998)	285	9-wk, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension	Double-blind: modafinil 200 mg/day, modafinil 400 mg/day, or placebo, administered once daily Open-label: modafinil 200 to 400 mg/day for ≤ 40 weeks	MSLT, MWT, CGI-C	MSLT: Each modafinil group showed improvements over placebo ($p < 0.001$) MWT: Mean sleep latency improved for both modafinil groups compared with placebo ($p < 0.001$) CGI-C: At week 9, percentage of patients with improved CGI-C ratings was significant for the modafinil 200-mg (65%) and 400-mg (74%) groups compared with placebo (37%; both $p < 0.005$)	[13]

CGI: Clinical global index; CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; FCRTT: Four-Choice Reaction Time Test; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; SF-36: 36-Item Medical Outcomes Study Health Survey; VAS: Visual Analog Scale; WCST: Wisconsin Card Sort Test.

Table 1. Major clinical studies of modafinil for the treatment of patients with narcolepsy (cont.).

Study	N	Study design	Study drug dosage	Efficacy measures	Efficacy results	Refs
US Modafinil in Narcolepsy Multicenter Study Group (2000)	273	9-wk, randomized, double-blind, placebo-controlled, parallel-group study with 2-wk treatment discontinuation phase	Modafinil 200 or 400 mg/day or placebo, administered once daily	MSLT, MWT, ESS, CGI-C	MSLT: MSLT improved in the 400-mg group compared with placebo ($p < 0.001$) MWT: Mean sleep latency improved for each modafinil treatment group compared with placebo (all $p < 0.001$) ESS: At week 3, 6, and 9, ESS improved compared with placebo in both dose groups ($p < 0.001$) CGI-C: At week 9, percentage of patients with improved CGI-C rating was greater for both modafinil 200-mg (58%) and 400-mg (61%) groups compared with placebo (38%; both $p < 0.03$)	[14]
Mitler (2000)	478	Two 40-wk, open-label extension studies of patients who completed either of two 9-wk, double-blind, placebo-controlled studies	Study 1: modafinil 200, 300, or 400 mg/day Study 2: modafinil 200 or 400 mg/day (Investigator-determined optimal dose for each patient in each study)	CGI-C, ESS, SF-36	CGI-C: Disease severity improved in >80% of patients throughout the study ESS: Improvements from open-label baseline were significant ($p < 0.001$) SF-36: Changes from open-label baseline at week 40 were significant ($p < 0.001$) for 6 of 8 domain scores and for the physical and mental health composite scores	[15]
Moldofsky (2000)	69	16-wk, open-label period, followed by 2-wk randomized, placebo-controlled, double-blind period of patients from a 6-wk crossover study	Open-label: modafinil ≤ 500 mg/day (dose individualized) in morning and noon doses Double-blind: modafinil at individual dose or placebo	MWT, patient diary, ESS, FCRTT	MWT: mean sleep latencies were 70% longer with modafinil than with placebo at the end of the double-blind period (week 24) ($p = 0.009$) Diary: Modafinil reduced episodes of severe somnolence plus sleep attacks plus naps compared with placebo ($p = 0.017$) ESS: Scores improved in the treated vs placebo group at week 24 ($p = 0.023$) FCRTT: No significant differences between groups were observed	[16]

CGI: Clinical global index; CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; FCRTT: Four-Choice Reaction Time Test; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; SF-36: 36-Item Medical Outcomes Study Health Survey; VAS: Visual Analog Scale; WCST: Wisconsin Card Sort Test.

Table 1. Major clinical studies of modafinil for the treatment of patients with narcolepsy (cont.).

Study	N	Study design	Study drug dosage	Efficacy measures	Efficacy results	Refs
Schwartz (2003)	32	3-wk, randomized, double-blind, crossover, three-period study	Modafinil 200 or 400 mg/day once daily or 400 mg/day in split doses	MWT, CGI-C, ESS	MWT: Sleep latency was significantly longer with both 400-mg regimens of modafinil than the 200-mg regimen (both $p < 0.05$). Patients receiving the 400-mg split-dose regimen had greater improvement in the evening than those receiving 200 mg once daily ($p < 0.001$) or 400 mg once daily ($p < 0.05$) CGI-C: Both 400-mg groups showed greater improvement in evening sleepiness than the 200-mg/day group (both $p < 0.05$) ESS: Mean scores in all modafinil groups showed significant improvement from baseline ($p < 0.001$)	[17]
Schwartz (2004)	24	3-wk, randomized, double-blind, parallel-group study	Modafinil 400 mg once daily or modafinil 600 mg/day in split doses	MWT, CGI-C, WCST	MWT: In the evening session, the 600-mg split-dose regimen resulted in greater mean improvement from baseline than the 400-mg/day regimen ($p < 0.05$) CGI-C: The percentage of patients rated as at least improved was greater in the 600-mg split-dose group (100%) than in the 400-mg/day group (92%; $p < 0.05$) WCST: Both modafinil doses (combined) improved executive function compared with baseline ($p < 0.05$)	[18]

CGI: Clinical global index; CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; FCRTT: Four-Choice Reaction Time Test; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; SF-36: 36-Item Medical Outcomes Study Health Survey; VAS: Visual Analog Scale; WCST: Wisconsin Card Sort Test.

on cognition have also been reported. A 6-week, three-period crossover study found that modafinil doses of 200 and 400 mg improved performance on the Four-Choice Reaction-Time Test compared with placebo [12]. After 3 weeks of receiving modafinil 400 mg (single dose) or 600 mg (split dose), patients showed significant improvements over baseline in the Wisconsin Card Sort Test [18]. The extent to which some patients experience late-day ES

with modafinil therapy is unknown; however, some patients may require multiple doses [17,18].

Modafinil is well tolerated in patients with narcolepsy and adverse events have generally been mild or moderate and transient in nature [12–15,17,18]. Headache has been the most frequently reported adverse event [13–15]. Modafinil has not shown an adverse effect on sleep integrity or sleep architecture [12–14,16–18]. Modafinil is a US Drug Enforcement Agency schedule IV agent [19].

Table 2. Augmentation studies of sodium oxybate for the treatment of patients with narcolepsy.

Study	N	Study design	Study drug dosage	Efficacy measures	Efficacy results	Refs
US Xyrem® Multicenter Study Group (2002)	136	4-week, randomized, multicenter, double-blind, placebo-controlled study	3, 6, or 9 g sodium oxybate or placebo nightly in two equal, divided doses 113 (83%) patients remained on a stable dose of stimulant	Patient diaries (frequency of cataplexy attacks, inadvertent naps, nocturnal awakenings), ESS, CGI-C	Diaries: The number of cataplexy attacks decreased with 6 ($p = 0.053$) and 9 g ($p = 0.0008$) sodium oxybate compared with placebo. Inadvertent naps/sleep attacks were reduced with both doses ($p < 0.05$), and nocturnal awakenings were reduced with 9 g sodium oxybate ($p < 0.01$) vs placebo ESS: Scores were significantly lower at the 9-g dose compared with placebo ($p = 0.0001$) CGI-C: Sodium oxybate-treated patients showed a dose-related improvement that was significant at the 9-g dose ($p = 0.0002$)	[24]
US Xyrem® Multicenter Study Group, (2003)	118	12-month, open-label study; extension of randomized, double-blind study [24]	Sodium oxybate 3, 4.5, 6, 7.5 or 9 g nightly in two equal, divided doses. 104 (88%) patients remained on a stable dose of stimulant	Patient diaries (frequency of cataplexy attacks, sleep quality, alertness, concentration), ESS, CGI-C	Diaries: The frequency of cataplexy attacks decreased from double-blind baseline in the total population ($p < 0.001$). Nocturnal sleep quality, alertness, and concentration also improved ($p < 0.001$) ESS: Daytime sleepiness improved significantly from double-blind baseline, with maximal improvement achieved at 2 months ($p < 0.001$) CGI-C: At 2 months, approximately 80% of patients had a positive response to treatment ($p < 0.05$)	[25]
Mamelak, (2004)	25	14-week, open-label, dose-escalation study	Sodium oxybate beginning at 4.5 g and rising to 9 g nightly in two equal, divided doses. 21 (84%) patients remained on stable dose of modafinil or stimulant	Nocturnal PSG, ESS, MWT	PSG: After increasing initially, the total duration of REM sleep decreased in a dose-related manner. Slow-wave sleep and delta power increased with increasing doses of sodium oxybate. Improvements were also reported in nocturnal sleep latency, total sleep time, and nocturnal awakenings MWT: Mean sleep latency increased significantly from baseline ($p < 0.001$ at final visit)	[26]

CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; MWT: Maintenance of Wakefulness Test; PSG: Polysomnogram; REM: Rapid eye movement.

Table 2. Augmentation studies of sodium oxybate for the treatment of patients with narcolepsy (cont.).

Study	N	Study design	Study drug dosage	Efficacy measures	Efficacy results	Refs
					ESS: Scores improved steadily and dose-dependently from baseline after week 4 of treatment ($p < 0.001$ vs baseline)	

CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; MWT: Maintenance of Wakefulness Test; PSG: Polysomnogram; REM: Rapid eye movement.

Stimulants

CNS stimulants, such as amphetamines or methylphenidate, have been available for decades for the treatment of ES in patients with narcolepsy [20]. Clinical studies have shown the CNS stimulants to be effective for ES associated with narcolepsy, and CNS stimulants are recommended for use as monotherapy or augmentation therapy [10,20]. Recommended dose ranges are 10–80 mg/day for methamphetamine and 10–100 mg/day for amphetamine and methylphenidate [10]. Their use is somewhat limited by the potential development of tolerance, the occurrence of adverse events, and their status as schedule II agents [20].

Sodium oxybate

Some patients with narcolepsy may require augmentation therapy to treat their symptoms. Sodium oxybate (Xyrem®), a CNS depressant, may be used in conjunction with modafinil or a stimulant to reduce cataplexy and for treatment of ES in patients with narcolepsy [21].

Early clinical studies indicated that sodium oxybate had the potential to reduce cataplexy attacks associated with narcolepsy [22] and improve sleep quality [23]. Since then, published reports show the efficacy of sodium oxybate for this disorder in combination with a stimulant or modafinil (Table 2). In a 4-week, double-blind, placebo-controlled study, treatment with sodium oxybate at a dose of 6 or 9 g/day resulted in fewer cataplexy attacks, night-time awakenings, and inadvertent daytime naps, and reduced daytime sleepiness as determined by the ESS [24]. This effect was maintained when sodium oxybate was administered in a 12-month, open-label study [25]. The improvements in sleepiness with sodium oxybate may be related to changes in sleep architecture, specifically, increases in slow-wave sleep at all sleep stages, including REM sleep [26].

The most common adverse events with sodium oxybate have included nausea, headache, dizziness, confusion, enuresis, pain, and

somnolence [24,25]. Sodium oxybate is a schedule III agent. Although data are limited, the risk of withdrawal syndrome in patients with narcolepsy who have received sodium oxybate appears to be minimal [21,27–29], and rebound cataplexy has not been reported upon discontinuation [30]. Sodium oxybate must be taken at bedtime and again 2.5–4 h later, 2 h after eating must elapse before the first dose is taken, and both doses must be taken while the patient is seated in bed [21].

Armodafinil

Modafinil is approved for once-daily dosing, though some patients may require two doses to sustain waking throughout the waking day. For these patients, administration of a second modafinil dose mid-day [17,18] or augmentation with a short-acting stimulant may be beneficial. Armodafinil, the *R*-enantiomer of modafinil, is being evaluated as an alternative option.

Modafinil is a racemic compound, containing equal amounts of *R*- and *S*-modafinil. Pharmacokinetic studies have shown that of the two enantiomers, *R*-modafinil has a significantly longer plasma half-life than the *S*-enantiomer (10–14 vs 3–4 h) [31–33]. Following chronic administration of modafinil, the proportion of circulating *R*-modafinil can be as much as three times greater compared with circulating *S*-modafinil. Thus, the wake-promoting effects of racemic modafinil may theoretically be attributable to the *R*-enantiomer.

After a single 200-mg dose of modafinil or armodafinil in healthy volunteers during a period of acute sleep loss, plasma concentrations of modafinil were higher than armodafinil within the first 3 h; however, concentrations of armodafinil were higher later in the waking day (6–14 h after administration). In addition, armodafinil was associated with improved wakefulness and sustained attention later in the day compared with modafinil on a mg-to-mg basis [34].

Highlights

- Excessive sleepiness (ES) is a characteristic symptom of narcolepsy.
- The treatment goal for patients with narcolepsy is to improve ES symptoms through the waking period.
- Treatment options include the wake-promoting agent modafinil and the CNS stimulants. Sodium oxybate may be used for cataplexy or as augmentation therapy for residual sleepiness.

The efficacy of armodafinil in the treatment of narcolepsy has been assessed throughout the day in a double-blind study in which patients received armodafinil 150 mg, armodafinil 250 mg, or placebo once daily for 12 weeks [35]. Significant improvements in mean MWT sleep latency were noted at both early (09:00–15:00) and late (15:00–19:00) time points at the final visit, indicating that once-daily armodafinil improves the ability to sustain wakefulness throughout the day. Compared with placebo, a greater proportion of patients receiving armodafinil had at least minimal improvement in CGI-C. Patients treated with armodafinil showed significant improvements compared with baseline in measures of attention and memory as determined by the Cognitive Drug Research battery of tests. Differences between armodafinil treatment and placebo were also observed in the ESS. Headache, nausea, dizziness and decreased appetite were the most commonly reported adverse events. Most adverse

events were mild-to-moderate in nature, occurred during the first 2 weeks of treatment and were self-limiting.

Expert commentary & outlook

Treatment of narcolepsy remains a challenge and requires lifestyle modifications, such as improved sleep hygiene and scheduled naps, as well as pharmacological therapy. Modafinil has been well studied in patients with narcolepsy and shown to be effective and well tolerated in patients with ES associated with narcolepsy. CNS stimulants, such as methylphenidate or amphetamine, may also be used as monotherapy. In some patients with more severe ES, a combination of modafinil with a stimulant may be required. In patients who have narcolepsy with cataplexy or refractory sleepiness, sodium oxybate may be beneficial. The tricyclic antidepressants and selective serotonin reuptake inhibitors have been used for cataplexy and other ancillary symptoms of narcolepsy. Although modafinil is dosed once daily, some patients may require a mid-day dose. Armodafinil represents a potential new therapeutic option in the treatment of narcolepsy, with improved wake-promoting effects throughout the day and benefits in aspects of cognitive function. Further research will continue to define the role these and other agents have in the area of narcolepsy.

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Affiliation

Jonathan RL Schwartz, MD,
 Medical Director, *Integris Sleep Disorder Center and Clinical Professor,*
University of Oklahoma Health Science Center, 4200 South Douglas Ave, Suite 313, Oklahoma City, OK 73109, USA
 Tél.: +1 405 636 1111
 Jonathan.Schwartz@Integris-Health.com