Therapeutic Class Overview
Narcolepsy Agents (non-stimulant)

Overview/Summary:
This review will focus on agents used for the symptomatic treatment of narcolepsy. This includes the wakefulness promoting agents armodafinil (Nuvigil®) and modafinil (Modafinil®), along with the central nervous system agent, sodium oxybate (Xyrem®).[1-3] Although several stimulant products are indicated for the treatment of narcolepsy, they will not be covered in this review. Narcolepsy is clinical syndrome that affects the control of sleep and wakefulness. Etiologies of narcolepsy may include loss of orexin signaling, genetic factors and rarely, brain lesions. People with narcolepsy often experience excessive daytime sleepiness (EDS) and intermittent, uncontrollable episodes of falling asleep during the daytime.[4] It is important to note that EDS is distinct from fatigue. Generally, fatigue is a subjective feeling of lack of energy that interferes with normal daily activities while EDS is an inability to stay awake or alert during the time of wakefulness in the sleep-wake cycle.[5] Specifically, modafinil and its R-enantiomer, armodafinil, are Food and Drug Administration (FDA)-approved for EDS associated with narcolepsy as well as EDS that results from obstructive sleep apnea (OSA) and shift work disorder (SWD).[1-2] In addition to EDS in narcolepsy, sodium oxybate is also FDA-approved for the treatment of cataplexy associated with narcolepsy.[3] Cataplexy is a term used to describe a sudden loss of muscle tone or weakness that ultimately leads to loss of voluntary muscle control. Additional symptoms caused by cataplexy can range from slurred speech to total body collapse, depending on the muscles involved. Cataplexy is often triggered by intense emotions such as surprise, laughter, or anger.[5] The exact mechanisms by which these agents exert their therapeutic effects are not completely understood.[1-3]

Efficacy of these agents has been well documented in placebo-controlled trials.[6-34] Head-to-head studies are limited, but it appears as though modafinil and armodafinil are equal in therapeutic effect.[34] Current clinical guidelines have not been updated to include armodafinil's place in therapy. Generally modafinil is recommended as a first line agent for the treatment of EDS. Central Nervous System (CNS) stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives. Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38] For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.[36]

Table 1. Current Medications Available in Therapeutic Class[1-47]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Armodafinil (Nuvigil®)	EDS associated with narcolepsy, OSA and SWD	Tablet: 50 mg 150 mg 200 mg 250 mg	-
Modafinil (Provigil®*)	EDS associated with narcolepsy, OSA and SWD	Tablet: 100 mg 200 mg	✔
Sodium oxybate (Xyrem®)	Cataplexy in narcolepsy; EDS associated with narcolepsy	Oral solution: 500 mg/mL	-

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- EDS in narcolepsy:
  - The ability for patients to remain awake, based on the Maintenance of Wakefulness Test (MWT), was significantly enhanced with each dose of armodafinil studied compared with placebo at the final visit (P<0.01).[6]
  - Modafinil demonstrated a significant improvement in objective and subjective measures of EDS for the modafinil groups compared to placebo (P<0.001 for both). There was also a statistically significant improvement in MWT and overall condition (Clinical Global Impression of Change [CGI-C]) with each dose compared to placebo.[7,8]
  - Sodium oxybate, provided statistically significant improvements in the Epworth Sleepiness Scale (ESS) and CGI-C compared to placebo at end of therapy (P≤0.001 for both).[15]
  - Sodium oxybate plus modafinil significantly improved MWT scores at week eight compared to the placebo group (P<0.001).[16]
- EDS in OSA:
  - Armodafinil and modafinil significantly improved MWT compared to placebo at the conclusion of their respective studies (armodafinil, P<0.001 and P=0.0003; modafinil, P<0.001 for both).[22,23]
- EDS in SWD:
  - Both armodafinil and modafinil were evaluated in one clinical trial each. Patients treated with armodafinil or modafinil showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the nighttime Multiple Sleep Latency Test (MSLT) at the final visit compared with placebo (P<0.001 and P=0.002, respectively).[29,30]
- Cataplexy in narcolepsy:
  - Sodium oxybate resulted in statistically significant reductions in the frequency of cataplexy attacks (P<0.05).[13]
  - In a second trial, patients were randomized to blinded placebo after discontinuing long-term open-label sodium oxybate therapy or blinded sodium oxybate. These patients that discontinued sodium oxybate experienced a significant increase in cataplexy attacks (P<0.001).[14]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - EDS
    - Generally modafinil is recommended as a first line agent.
    - Guidelines have not been updated to include armodafinil's place in therapy.
    - CNS stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives.
    - Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38]
  - For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.36.[18-23]

- Other Key Facts:
  - Modafinil and armodafinil have produced psychoactive and euphoric effects along with other feelings typical of CNS stimulants and have been classified as Schedule IV drugs by the FDA.[1,2]
  - Sodium oxybate includes a black box warning in its FDA approved labeling regarding abuse potential and its depressive CNS effects that has led to serious adverse events and even death. It has been classified as a Schedule III controlled-substance by the FDA.[3]
  - Modafinil and armodafinil are administered once daily. Sodium oxybate has to be taken twice daily, once before bed and then once again approximately 2.5 to 4 hours later.[1-3]
  - Only modafinil is available generically.

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Therapeutic Class Review
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Overview/Summary

This review will focus on agents used for the symptomatic treatment of narcolepsy. This includes the wakefulness promoting agents armodafinil (Nuvigil®) and modafinil (Modafinil®), along with the central nervous system agent, sodium oxybate (Xyrem®).[1-3] Although several stimulant products are indicated for the treatment of narcolepsy, they will not be covered in this review. Narcolepsy is clinical syndrome that affects the control of sleep and wakefulness. Etiologies of narcolepsy may include loss of orexin signaling, genetic factors and rarely, brain lesions. People with narcolepsy often experience excessive daytime sleepiness (EDS) and intermittent, uncontrollable episodes of falling asleep during the daytime.[4] It is important to note that EDS is distinct from fatigue. Generally, fatigue is a subjective feeling of lack of energy that interferes with normal daily activities while EDS is an inability to stay awake or alert during the time of wakefulness in the sleep-wake cycle.[5] Specifically, modafinil and its R-enantiomer, armodafinil, are Food and Drug Administration (FDA)-approved for EDS associated with narcolepsy as well as EDS that results from obstructive sleep apnea (OSA) and shift work disorder (SWD).[1-2] In addition to EDS in narcolepsy, sodium oxybate is also FDA-approved for the treatment of cataplexy associated with narcolepsy.[3] Cataplexy is a term used to describe a sudden loss of muscle tone or weakness that ultimately leads to loss of voluntary muscle control. Additional symptoms caused by cataplexy can range from slurred speech to total body collapse, depending on the muscles involved. Cataplexy is often triggered by intense emotions such as surprise, laughter, or anger.[5] The exact mechanisms by which these agents exert their therapeutic effects are not completely understood.[1-3]

Modafinil and armodafinil have produced psychoactive and euphoric effects along with other feelings typical of CNS stimulants and have been classified as Schedule IV drugs by the FDA. Sodium oxybate includes a black box warning in its FDA approved labeling regarding abuse potential and its depressive CNS effects that has led to serious adverse events and even death. It has been classified as a Schedule III controlled-substance by the FDA. Modafinil and armodafinil are administered once daily. Sodium oxybate has to be taken twice daily, once before bed and then once again approximately 2.5 to 4 hours later.[1-3] Currently, only modafinil is available generically.

Efficacy of these agents has been well documented in placebo-controlled trials.[6-34] Head-to-head studies are limited, but it appears as though modafinil and armodafinil are equal in therapeutic effect.[34] Current clinical guidelines have not been updated to include armodafinil's place in therapy. Generally modafinil is recommended as a first line agent for the treatment of EDS. Central Nervous System (CNS) stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives. Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38] For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.[36]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Armodafinil (Nuvigil®)	Wakefulness promoting agents	-
Modafinil (Provigil®*)	Wakefulness promoting agents	✔
Sodium oxybate (Xyrem®)	Central nervous system agent	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Indications[1-3]

Indication	Armodafinil	Modafinil	Sodium oxybate
Cataplexy in narcolepsy			✔
EDS associated with narcolepsy	✔	✔	✔
EDS associated with obstructive sleep apnea	✔	✔	
EDS associated with shift work disorder	✔	✔	

EDS=excessive daytime sleepiness

Pharmacokinetics

Table 3. Pharmacokinetics[1-3]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Renal Excretion (%)	Half-life (hours)
Armodafinil	Not Reported	60	Hepatic	Not reported	15
Modafinil	Not Reported	60	Hepatic, extensive	80	15
Sodium oxybate	88	<1	Hepatic, extensive	1 to 5	0.33 to 0.88

Clinical Trials

The safety and efficacy of armodafinil, modafinil and sodium oxybate in patients with narcolepsy, OSA and/or SWD have been evaluated in several clinical trials and are summarized in Table 4.[6-34]

Armodafinil approval for use in EDS in narcolepsy was based on a single placebo-controlled clinical trial. The ability for patients to remain awake, based on the Maintenance of Wakefulness Test (MWT), was significantly enhanced with each dose of armodafinil studied compared with placebo at the final visit (P<0.01). Additionally, there was a significant difference in the number of patients that showed improvement in overall clinical condition as rated by the Clinical Global Impression of Change (CGI-C) in favor of armodafinil (P<0.001).[6] FDA-approval of modafinil in narcolepsy was established in two clinical trials. Both studies demonstrated a significant improvement in objective and subjective measures of EDS for the modafinil groups compared to placebo (P<0.001 for both doses of modafinil compared to placebo). There was also a statistically significant improvement in the ability to remain awake (MWT) and overall condition (CGI-C) with each dose compared to placebo.[7,8]

Sodium oxybate has been FDA-approved for both EDS and cataplexy in narcolepsy. Each indication was based on the results of two clinical trials, respectively.[13-16] For cataplexy, both the six and nine gram/night doses of sodium oxybate resulted in statistically significant reductions in the frequency of cataplexy attacks (P<0.05 for both).[13] In the second trial involving cataplexy, patients were randomized to placebo after discontinuing long-term open-label sodium oxybate therapy. Patients that discontinued sodium oxybate experienced a significant increase in cataplexy attacks (P<0.001).[14] For the treatment of EDS associated with narcolepsy, sodium oxybate six and nine grams/day, provided statistically significant improvements in the Epworth Sleepiness Scale (ESS) and CGI-C compared to placebo at end of therapy (P≤0.001 for both).[15] The final study showed that MWT scores were significantly improved at week eight in the sodium oxybate and sodium oxybate plus modafinil groups compared to the placebo group (P<0.001).[16]

FDA-approval of armodafinil for use in EDS associated with OSA was evaluated in two placebo-controlled trials. Both studies concluded that armodafinil significantly enhanced the patient's ability to remain awake (measure by MWT) compared to placebo at the conclusion of the studies (P<0.001 and P=0.0003, respectively).[22,23] Similarly, the efficacy of modafinil was established in two placebo-controlled trials that showed that modafinil also significantly improved the patient's ability to remain awake when compared to placebo (P<0.001 for both).[25,26]

The efficacy of armodafinil and modafinil for the treatment of EDS associated with SWD were established in a single clinical trial respectively. Both trials evaluated patients that had excessive sleepiness and who had been symptomatic for at least three months. Patients treated with armodafinil showed a statistically significant prolongation in the time to sleep onset compared to placebo-treated patients, as measured by the nighttime Multiple Sleep Latency Test (MSLT) at the final visit (P<0.001).[29] Modafinil also provided a significant prolongation in the time to sleep onset compared to the placebo group (P=0.002).[30] Tembe et al conducted a head-to-head trial that compared armodafinil to modafinil in patients with SWD. The study compared the response rate, defined as the proportion of patients showing ≥2 grades of improvement based on the Stanford Sleepiness Score (SSS). After 12 weeks of therapy, response rates were not significantly different between groups (P=0.76). Compliance to therapy and adverse events were also similar between groups (P=0.63 and P=0.78, respectively).[34]

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
Narcolepsy				
Harsh et al[6] Armodafinil 150 to 250 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age diagnosed with narcolepsy	N=196 12 weeks	Primary: MWT 0900-1500 sleep latency, CGI-C Secondary: MWT 1500-1900 sleep latency, CGI-C, CDR, ESS, BFI	Primary: Mean MWT 0900–1500 sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group (P<0.01 for all comparisons). Secondary: Mean MWT 1500–1900 sleep latency increased 1.5, 1.6, and 1.6 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 minutes from baseline in the placebo group. The differences for the armodafinil combined group vs placebo and the 150 mg group vs the placebo group were significant (P<0.05 for both comparisons). The proportion of patients with at least minimal improvement in their CGI-C rating was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared to the placebo group (P<0.0001 for all comparisons). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21, 33, and 16%, respectively, for armodafinil 150 mg; 20, 35, and 18%, respectively, for armodafinil 250 mg; 20, 34, and 17%, respectively, for the armodafinil combined group; and 17, 12, and 3%, respectively, for placebo. Power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared to placebo at the final visit (P<0.05). There were not significant effects on mean continuity of attention between the treatment groups. Armodafinil demonstrated significantly greater improvements in quality of episodic secondary memory compared to placebo at the final visit (P<0.05).

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory compared to placebo at the final visit (P<0.05). Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared to placebo at weeks eight (P<0.01 for all comparisons) and 12 (P<0.01) and at the final visit (150 mg/day, -4.1; P=0.0044, 250 mg/day, -3.8; P=0.0015, and combined group, -3.9; P=0.0006). At the final visit, 21% of patients in the armodafinil 150 mg/day group (P=0.0312) and 28% of patients in the armodafinil 250 mg/day group (P=0.0023) had an ESS score <10, compared to only 7% of patients in the placebo group. Improvements in global fatigue were significantly greater with armodafinil compared to placebo at the final visit (150 mg/day, -1.5; P=0.0007; 250 mg/day, -1.3; P=0.0018; combined group, -1.4; P=0.0002; placebo, -0.3). Headache, nausea, dizziness, and decreased appetite were the most commonly reported adverse events with armodafinil.
No authors listed US Modafinil in Narcolepsy Group[7] Modafinil 200 to 400 mg QD vs placebo	DB, MC, PC, RCT Adults 18 to 68 years of age diagnosed with narcolepsy	N=283 9 weeks	Primary: ESS Secondary: MSLT, MWT, CGI-C	Primary: Both modafinil treatment groups reduced mean ESS scores and subjective sleepiness at each time point (weeks three, six, and nine) compared to the placebo group (P<0.001). The two modafinil groups did not differ from each other. Secondary: Mean sleep latency for MSLT significantly increased in both modafinil groups compared to the placebo group (P<0.001). Modafinil groups did not differ from each other. Mean sleep latencies for MWT significantly increased in each of the modafinil groups compared to the placebo group (P<0.001). The two

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				modafinil groups did not differ from each other. There were significantly more patients with improved CGI-C scores in each of the modafinil groups compared to the placebo group (P<0.005), but the number of patients did not differ between modafinil groups.
No authors listed US Modafinil in Narcolepsy Group[8] Modafinil 200 to 400 mg QD vs placebo	DB, MC, PC, RCT Adults 17 to 67 years of age diagnosed with narcolepsy	N=271 9 weeks	Primary: MWT, CGI-C Secondary: MSLT, ESS	Primary: MWT improved for both modafinil groups vs the placebo group (P<0.001) at each follow-up visit (weeks three, six, nine). The percent of patients with improvement in CGI-C scores at week nine were as follows: modafinil 200 mg, 58%; modafinil 400 mg, 61%; and placebo, 38% (P<0.03). Secondary: MSLT increased by 5.1 minutes with modafinil 400 mg vs 3.5 minutes with placebo (P<0.001). The impact of the 200 mg modafinil dose was not significant. Mean ESS scores were reduced by both treatment groups (P<0.001) vs the placebo group.
Broughton et al[9] Modafinil 200 to 400 mg QD vs placebo	MC, PC, RCT, XO Patients 27 to 59 years of age diagnosed with narcolepsy	N=75 6 weeks	Primary: MWT results, patient assessed sleepiness Secondary: ESS	Primary: MWT (sleep latency) increased by 40% with modafinil 200 mg (P<0.002) and by 54% with modafinil 400 mg (P<0.001) compared to placebo. There was not a significant difference between modafinil groups. Both modafinil groups significantly decreased the patient assessed mean number of involuntary sleep and somnolence episodes by 24% in the 200 mg group and 26% in the 400 mg group as compared to the placebo group (P<0.013 and P<0.007). Secondary: ESS was significantly decreased in modafinil 200 mg (P<0.018) and modafinil 400 mg (P<0.0009) groups compared to the placebo group.
Billiard et al[10]	DB, MC, PC, RCT, XO	N=50	Primary: Results of	Primary: In the patient sleep logs, the number of episodes of sleepiness and

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
Modafinil 100 mg QAM and 200 mg QD at noon (or vice versa) vs placebo	Patients 27 to 54 years of age diagnosed with narcolepsy	12 weeks	sleep logs, CGI Secondary: MWT	duration of daytime total sleep time were significantly reduced in the modafinil groups compared to the placebo group (P=0.05, P=0.0002). The CGI scores were not statistically significantly different between the modafinil group and the placebo group (P=0.19). Secondary: MWT scores were significantly improved in the modafinil group compared to the placebo group (P<0.05).
Boivin et al[11] Modafinil 200 mg QAM and 100 mg at noon vs placebo	DB, PC, RCT, XO Patients 31 to 61 years of age with a history of EDS, cataplexy, at least two sleep onset REM periods and MSLT less than five minutes	N=10 12 weeks	Primary: Subjectively assessed sleepiness, FCRTT, PLM, nocturnal sleep organization Secondary: Not reported	Primary: Subjective sleepiness was significantly reduced in the modafinil group compared to the placebo group (P<0.05) based on home questionnaires. Modafinil significantly reduced the number of gaps and % of error at the FCRTT (P<0.05), but did not significantly reduce the mean reaction time over placebo (P=0.08). Modafinil did not statistically significantly decrease PLMs over placebo (P=0.06). Modafinil did not display negative effects on any of the nocturnal sleep parameters measured (P value not significant). Secondary: Not reported
Thorpy et al[12] Modafinil 200 to 400 mg QD	OL, RCT Adults 17 to 65 years of age diagnosed with narcolepsy who had been receiving methylphenidate for EDS for a	N=40 5 weeks	Primary: ESS, tolerability Secondary: Not reported	Primary: Mean ESS scores were <12 for all groups at the end of the study: 11.3 in the no-washout group, 8.2 for in the washout group, and 10.1 in the taper-down/titrate-up group. Headache was the most frequently reported adverse event during therapy, experienced by 42% of patients in the no-washout group, 36% of patients in the washout group, and 21% of patients in the taper/titrate group.

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
	month			Secondary: Not reported
No authors listed US Xyrem MC Study Group (Abstract)[13] Sodium oxybate 3 g/day vs sodium oxybate 6 g/day vs sodium oxybate 9 g/day vs placebo Stable doses of stimulants were permitted.	DB, MC, PC, PG, RCT Patients with cataplexy in narcolepsy	N=136 4 weeks	Primary: Cataplexy attacks Secondary: ESS, inadvertent daytime naps/sleep attacks and nighttime awakenings, CGI-C	Primary: For weekly cataplexy attacks, only the 9 g/day sodium oxybate group had a significant difference from baseline (P=0.0008). Secondary: For ESS, only 9 g/day of sodium oxybate provided a significant improvement from baseline (P=0.002). The CGI-C demonstrated a dose-related improvement, with a significant difference observed in the at the 9 g dose group (P=0.0002). The frequency of inadvertent naps/sleep attacks and the nighttime awakenings showed similar dose-response trends, becoming significant at the 9 g dose (P=0.0122 and P=0.0035, respectively).
No authors listed US Xyrem MC Study Group[14] Phase I (two weeks): Continue sodium oxybate at the dose	DB treatment withdrawal study design (alternative to conventional DB, PC, RCT) Patients ≥16	N=55 4 weeks	Primary: Cataplexy attacks, treatment-emergent adverse events	Primary: During the two-week DB phase, the abrupt cessation of sodium oxybate therapy in the placebo study patients resulted in a significant increase in the number of cataplexy attacks (median, 21; P<0.001) compared to patients who remained on sodium oxybate (median, 0). Cataplexy attacks returned gradually with placebo study patients reporting a median of 4.2 and 11.7 cataplexy attacks during the first and

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
previously prescribed. Phase II (two weeks): Continue sodium oxybate treatment at previously prescribed dose vs conversion to placebo Stimulants were allowed.	years of age with narcolepsy or symptoms of narcolepsy who were previously stabilized on sodium oxybate 3 to 9 g/day		Secondary: Not reported	second weeks, respectively. There were no symptoms of withdrawal reported by the study investigators. Secondary: Not reported
No authors listed Xyrem International Study Group[15] Sodium oxybate 4.5 to 9 g/day administered at bedtime vs placebo Stimulants were allowed.	DB, MC, PC, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: ESS, MWT, CGI-C Secondary: Not reported	Primary: Study patients displayed dose related decreases in median ESS scores and frequency of weekly inadvertent naps, which were significant at the 6 and 9 g doses (P<0.001 for each). Study patients treated with 9 g of sodium oxybate nightly displayed a significant median increase of >10 minutes in the MWT (P<0.001). Improvements in EDS were incremental in those study patients who received concomitant stimulants alone. Significant improvements in the CGI-C were observed for each group treated with sodium oxybate (P≤0.001). The most common adverse events were mild to moderate and included nausea, dizziness, and enuresis, which seemed to be dose related. Other adverse events less common included feeling drunk, contusion, back pain, muscle cramp, somnolence, disturbance in attention, dysarthria,

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				tremor, disorientation, sleepwalking, dyspnea, and snoring. Secondary: Not reported
Black et al[16] Sodium oxybate 6 to 9 g/day vs modafinil 200 to 600 mg QD vs sodium oxybate 6 to 9 g/day plus modafinil 200 to 600 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with narcolepsy taking 200 to 600 mg of modafinil daily for the treatment of EDS	N=270 8 weeks	Primary: MWT Secondary: ESS, CGI-C	Primary: Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after eight weeks (P<0.001). In the sodium oxybate group, there was no decrease in sleep latency, suggesting that this medication was as efficacious in treating EDS as previously administered modafinil. In the sodium oxybate plus modafinil group, there was an increase in daytime sleep latency from 10.43 to 13.15 minutes (P<0.001), suggesting that this combination of drugs produced an additive effect. Secondary: The sodium oxybate group showed a decrease in median average EES scores, from 15 to 12 (P<0.001). The sodium oxybate plus modafinil group showed a decreased in median average EES scores from 15 to 11 (P<0.001). Treatment with sodium oxybate, alone (P=0.002) and together with modafinil (P=0.023), showed significant overall clinical improvements as compared to the placebo-treated study patients. The placebo and the modafinil-treated study patients demonstrated no significant change in symptoms.
No authors listed Xyrem International Study Group[17] Sodium oxybate 4.5	DB, MC, PC, RCT Patients ≥16 years of age	N=228 8 weeks	Primary: Narcolepsy symptoms, medication use, adverse	Primary: Compared to placebo, nightly doses of 4.5, 6, and 9 g of sodium oxybate for eight weeks resulted in significant decreases in weekly cataplexy attacks of 57.0 (P=0.003), 65.0 (P=0.002), and 84.7% (P<0.001), respectively.

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
to 9 g/day QHS vs placebo	with narcolepsy or symptoms of narcolepsy		events Secondary: Not reported	The decrease in cataplexy at the 4.5 g dose was significant compared to placebo at eight weeks of treatment (P=0.003). The reduction in the number of weekly cataplexy attacks was dependent on the length of time study patients received treatment and the amount of medication received. The weekly increase in sodium oxybate dose was associated with fewer adverse events than previously reported in double-blind sodium oxybate studies using fixed doses. The most common adverse events included nausea and dizziness, which demonstrated a clear dose–response relationship. Although greater than 5% of study patients reported emesis, this adverse event was not significantly different than placebo-treated patients. Secondary: Not reported
Black et al[18] Sodium oxybate 4.5 to 9 g/day administered QHS vs placebo	DB, PC, PG, RCT Patients ≥16 years of age with narcolepsy or symptoms of narcolepsy	N=228 8 weeks	Primary: Sleep architecture, narcolepsy symptoms and adverse events Secondary: Not reported	Primary: Following four (P<0.001) and eight weeks (P<0.001) of sodium oxybate treatment, study patients demonstrated significant dose-related increases in the duration of stage three and four sleep, reaching a median increase of 52.5 minutes in patients receiving 9 g nightly. Compared to placebo-treated patients, delta power was significantly increased in all treatment dose groups. Stage one sleep and the frequency of nocturnal awakenings were each significantly decreased at the 6 and 9 g/night doses. The changes in nocturnal sleep coincided with significant decreases in the severity and frequency of narcolepsy symptoms. The most common adverse events included nausea, headache, dizziness, nasopharyngitis, and enuresis with a statistical significant difference in nausea and dizziness compared to placebo. Adverse events

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				were mild to moderate in severity and appeared to be dose-related as documented by study investigators. Secondary: Not reported
Weaver et al[19] Sodium oxybate 4.5 to 9 g/day in two divided doses (QHS and again 2.5 to four hours later) vs placebo	DB, MC, RCT Patients 16 to 75 years of age with narcolepsy who were experiencing cataplexy and EDS with recurrent episodes for ≥3 months	N=285 4 weeks	Primary: FOSQ Secondary: Not reported	Primary: The nightly administration of sodium oxybate showed statistically significant dose-related improvements in functional status and quality of life as evidenced by the total FOSQ (P<0.001), as well as in the activity level (P<0.001), vigilance (P<0.001), general productivity (P=0.002), and social outcomes (P<0.001) subscales. Effect sizes escalated from small effects for the 6 g per day dose of sodium oxybate to large effects for the 9 g/day dose. Secondary: Not reported
Wang et al[20] Sodium oxybate	RETRO Patients receiving sodium oxybate	N=~26,000 68 months	Primary: Occurrence of abuse/misuse of sodium oxybate Secondary: Not reported	Primary: During the study period, 3,781 adverse event reports were reported to the manufacturer worldwide. Overall, there were no new significant safety findings from the postmarketing adverse event profile compared to what was reported in clinical trials described in the product prescribing information. Of those 26,000 patients, 0.2% reported ≥1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, four cases (0.016%) meeting DSM-IV dependence criteria, eight cases (0.031%, including three of the previous four) with withdrawal symptoms reported after discontinuation of sodium oxybate, two confirmed cases (0.008%) of sodium oxybate–facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with one death known to be related to sodium oxybate, and three cases (0.01%) of traffic accidents involving drivers taking sodium oxybate.

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				During the study period, approximately 600,000 bottles of sodium oxybate were distributed, and five incidents (0.0009%) of diversion were reported. Secondary: Not reported
Black et al[21] Sodium oxybate 6 g/day vs modafinil 200 to 600 mg QD vs sodium oxybate 6 g/day plus modafinil 200 to 600 mg QD vs placebo	DB, PC, RCT Patients ≥18 years of age with narcolepsy taking modafinil 200 to 600 mg/day for the treatment of EDS	N=278 8 weeks	Primary: Sleep architecture, MWT Secondary: Not reported	Primary: Following eight weeks of treatment, there was no significant change in total sleep time for any group. Significant changes in total non-REM sleep among patients receiving sodium oxybate and sodium oxybate plus modafinil included a median increase in Stage three and four sleep (43.5 and 24.25 minutes, respectively; P<0.001 for each) and delta power (P<0.001 for each) and significant decrease in the number of nocturnal awakenings in sodium oxybate (P=0.008) and sodium plus modafinil (P=0.014) treated study patients. No significant changes in PSG parameters were noted in patients treated with placebo or modafinil alone. Patients who had been randomized to placebo demonstrated a significant decrease in MWT sleep latency at eight weeks (P<0.001) once they had been switched to placebo following stable chronic modafinil treatment. A slight worsening of EDS indicated by increased ESS scores, was noted in placebo-treated patients (P=0.011) after stopping baseline modafinil, and ESS scores continued unchanged in the group that was randomized to continue modafinil treatment. Sodium oxybate-treated patients and sodium oxybate plus modafinil-treated patients experienced significant improvements in ESS scores (P<0.001 for each). There was no change in ESS scores in the group maintained on modafinil alone.

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				Secondary: Not reported
Obstructive Sleep Apnea				
Roth et al[22] Armodafinil 150 to 250 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of moderate OSA/ hypopnea syndrome and residual excessive sleepiness despite effective, regular, and stable use of CPAP treatment	N=395 12 weeks	Primary: MWT, CGI-C Secondary: ESS, CDR, BFI	Primary: The mean changes in MWT sleep latency across the first four tests were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group at the final visit (P<0.001 for all). There was no difference between the two modafinil doses. The proportions of patients who had at least minimal improvement on the CGI-C were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.001 for all). There was no difference between the two modafinil doses. Secondary: The mean change in ESS total score was significantly greater in the armodafinil combined group compared to the placebo group at the final visit (P<0.001). Mean changes in global fatigue scores were significantly greater in the armodafinil combined group compared to the placebo group at all visits (P<0.05 for all). The mean change in score for worst fatigue during the past 24 hours was statistically greater in the armodafinil combined group compared to placebo at week eight (P<0.05). Mean changes in quality of episodic secondary memory score were significantly greater with armodafinil 150 and 250 mg/day compared to placebo at week four (both, P<0.05) and with armodafinil 250 mg/day vs placebo at week eight (P<0.01). No significant differences in speed of memory or power of attention were found between the armodafinil combined and placebo groups across the

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				first four or last three sessions at any assessment. At weekeight8, mean changes in continuity of attention across the first four sessions were significantly greater in the armodafinil 150 mg/day, 250 mg/day, and combined groups compared to the placebo group (P<0.05 for all). The most frequently reported adverse event was headache, occurring in 17.6% of patients in the armodafinil combined group and 8.5% of patients in the placebo group (P<0.05). The severity of adverse events was generally mild or moderate in patients receiving armodafinil (58.4%) or placebo (46.9%).
Hirshkowitz et al[23] Armodafinil 150 mg QD vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with a diagnosis of OSA/hypopnea syndrome who complained of residual excessive sleepiness during CPAP therapy	N=263 12 weeks	Primary: MWT, CGI-C Secondary: CDR, ESS, BFI	Primary: Armodafinil significantly improved wakefulness compared to placebo. The mean MWT sleep latency increased from baseline by 2.3 minutes in the armodafinil group and decreased by 1.3 minutes in the placebo group (P=0.0003). Armodafinil significantly improved MWT sleep latency compared to placebo at each visit (P<0.01 for all). The proportion of patients with at least ‘‘minimal improvement’’ on the CGI-C scale was greater for armodafinil than placebo (71 vs 53%; P=0.0069). Secondary: As assessed on the CDR, armodafinil significantly improved the quality of episodic secondary memory compared to placebo. The quality of episodic secondary memory increased by 7.6 points from baseline to the final visit for patients in the armodafinil group and decreased by 7.0 points for those in the placebo group (P=0.0102). The mean change from baseline in ESS total score was significantly greater for patients receiving armodafinil than for those receiving placebo (P<0.01 for all).

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				As assessed on the BFI, armodafinil significantly reduced global fatigue and worst fatigue in the past 24 hours at weeks four and 12 and at the final visit compared to placebo (P<0.05 for all).
Krystal et al[24] Armodafinil 200 mg QD vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age diagnosed with OSA	N=249 18 months	Primary: CGI-C as related to sleepiness, mean change from baseline in MWT to mean sleep latency at final visit Secondary: ESS	Primary: The proportion of patients with least minimal improvement on CGI-C was significantly greater in the armodafinil group compared to the placebo group (69 vs 53%; P=0.012). Mean MWT sleep latency was increased following armodafinil (2.6 minutes) compared to placebo (1.1 minutes), but was not statistically significant (P=0.30). Secondary: Mean ESS scores were significantly reduced in study patients treated with armodafinil compared to patients treated with placebo (-6.3 vs -4.8; P=0.003). The most common adverse effects included headache, dry mouth and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Black et al[25] Modafinil 200 to 400 mg QD vs placebo	DB, MC, PC, RCT Adults 18 to 70 years of age with OSA/ hypopnea syndrome and having residual excessive sleepiness during CPAP therapy	N=305 12 weeks	Primary: MWT, ESS Secondary: CGI-C, FOSQ	Primary: Modafinil significantly improved mean sleep latency on the MWT compared to placebo (P<0.001). Modafinil significantly decreased the ESS scores compared to placebo (P<0.001). There were no significant differences in MWT or ESS scores seen between the two modafinil treatment groups (P>0.15 for each). Secondary: At the end of the study, modafinil had significant improvements in CGI-C compared to placebo (P<0.001).

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				Modafinil improved mean FOSQ scores compared to placebo (P<0.02) for vigilance, general productivity, and activity level.
Pack et al[26] Modafinil 200 to 400 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with OSA and hypopnea syndrome, RDI of ≥15 before or in the absence of nCPAP	N=157 4 weeks	Primary: ESS, MSLT and CGI-S at weeks 1 and 4, NPSG, nCPAP use Secondary: Not Reported	Primary; Daytime sleepiness, assessed by the change in mean ESS scores, were significantly reduced from baseline for both the modafinil and the placebo groups at weeks one and four (P<0.001). Additionally ESS scores were significantly improved with modafinil when compared to placebo (P<0.001). A significantly greater percentage of patients in the modafinil group had normalized ESS scores (i.e., <10) at week four compared with the placebo (P<0.01). Post-hoc analysis revealed that subjective daytime sleepiness in patients who were mildly to moderately sleepy (ESS 10 to 14) and severely sleep (ESS ≥15) had significantly improved ESS scores compared to placebo at week four (P<0.01 and P<0.05, respectively. At week four, the mean MSLT sleep latency time improved for patients receiving modafinil and worsened for patients in the placebo group. The mean change in MSLT sleep latency time was significantly different in favor of modafinil (P=0.021). There was no difference in the percentage of subjects who normalized their MSLT (P=0.613). The percentage of patients rated as clinically improved was significantly greater after four weeks of treatment with modafinil 400 mg/day than after treatment with placebo (P=0.035). The percentage of patients in the modafinil treatment group rated as clinically improved after one week of treatment with 200 mg/day was greater than that observed for the placebo group, but the difference in the percentages was not statistically significant. At week four of double-blind treatment, sleep duration, sleep efficiency, and the percent of time spent in sleep Stages 1, 2, 3, and 4 and in REM sleep were comparable to baseline values in both groups, and there were no differences groups. At week four, no significant change from baseline was observed in the RDI within either treatment group. A small but significant difference in the mean change from baseline in the arousal index between the modafinil group and the placebo group was

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				demonstrated (P=0.018). During four weeks of treatment, the mean time of nCPAP use was 6.2 h per night in each group, with no significant change from baseline between the two groups and no significant change from baseline to week four within each group. Secondary: Not reported
Weaver et al[27] Modafinil 200 to 400 mg QD vs placebo	2 DB, MC, PC, RCT (Pooled analysis) Patients 24 to 76 years of age diagnosed with OSA and residual excessive sleepiness associated with CPAP	N=480 4 to 12 weeks	Primary: FOSQ Secondary: Not reported	Primary: After treatment with modafinil, there were greater improvements from baseline in the total FOSQ score (P<0.0001) as well as activity level (P=0.002), productivity level (P=0.007), intimacy and sexual relationships (P=0.01) and vigilance (P<0.001) compared to treatment with placebo. A greater proportion of patients who received modafinil were considered responders compared to patients who received placebo (45 vs 25%; P<0.001). Analysis based on the individual FOSQ questions demonstrated that 18 of the 30 questions increased at least one point for significantly more patients who received modafinil (P<0.05). Secondary: Not reported
Williams et al[28] Modafinil 200 mg QD vs placebo	DB, RCT, XO Men diagnosed with OSA who were modafinil-naïve	N=21 2 days	Primary: Driving simulation, subjective sleepiness Secondary: Not reported	Primary: During CPAP withdrawal, severe sleep-disordered breathing was evident and administration of modafinil improved simulated driving performance (steering variability; P<0.0001, mean reaction time; P<0.0002, lapses on a current task; P<0.01), psychomotor vigilance task (mean one/reaction time and lapses, both P<0.0002), and subjective sleepiness (P<0.01). Secondary: Not reported
Shift Work Disorder				

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
Czeisler et al[29] Armodafinil 150 mg QD administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age who exhibited signs and symptoms of SWD of moderate or greater severity, as documented by a CGI-S rating of four or higher for sleepiness on work nights, including the commute to and from work	N=254 12 weeks	Primary: MSLT, CGI-C Secondary: KSS, CDR	Primary: Armodafinil improved mean nighttime sleep latency (2 to 8 AM) by 3.1 to 5.3 minutes compared to an increase of 0.4 to 2.8 minutes at in patients receiving placebo at the final visit (P<0.001). Of the patients who received armodafinil, 79% were rated as improved in the CGI-C ratings compared to 59% of the patients who received placebo at the final visit (P=0.001). Secondary: Patient-reported levels of sleepiness during the night shift on the KSS were reduced with armodafinil compared to placebo at all visits. Armodafinil improved most items assessed in the electronic diaries, including the maximum level of sleepiness during the night shift and commute home, and mean number of mistakes, accidents, or near misses compared to placebo. Armodafinil significantly improved the mean score for the quality of episodic secondary memory factor compared to placebo at each visit (P<0.001 at weeks four and eight; P=0.002 at week 12; P<0.001 at final visit) and during the first four tests on the final night shift (P=0.002 at 12:30 AM; P<0.001 at 2:30 AM; P=0.02 at 4:30 AM; P=0.006 at 6:30 AM). Armodafinil significantly improved speed of memory from baseline compared to placebo at week eight (armodafinil, -240.9 milliseconds; placebo, -6.5 milliseconds; P=0.02) and week 12 (armodafinil, -307.7 milliseconds; placebo, -115.2 milliseconds; P=0.01). However, this was not significant at the final visit (armodafinil, -257.2 milliseconds; placebo. -140.4 milliseconds; P=0.09). Armodafinil significantly improved mean power of attention at each study visit (P=0.005 at week four; P=0.006 at week eight; P=0.005 at week 12; P=0.001 at final visit) and during the first four tests on the final night shift

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				compared to placebo (P=0.002 at 12:30 AM; P=0.006 at 2:30 AM; P=0.004 at 4:30 AM; P=0.03 at 6:30 AM). Continuity of attention improved at the final visit in patients who received armodafinil compared to those who received placebo (P<0.001). Adverse events included headache, nausea, nasopharyngitis and anxiety. Most adverse events were considered mild or moderate by the investigator.
Erman et al[30] (abstract) Armodafinil 150 mg QD administered one hour prior to night shift vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: SDS-M and FOSQ-10 Secondary: Not reported	Primary: Patients treated with armodafinil experienced significantly greater improvements in SDS-M composite scores at final visit compared to patients treated with placebo (-6.8 vs -4.5, respectively; P=0.0027). Patients in the armodafinil treatment group demonstrated a greater improvement in total FOSQ-10 score from baseline to six weeks compared to placebo (3.6 vs 2.7; P=0.0351); however, there was no difference between treatments at the final visit (3.4 vs 2.7; P=0.0775). Secondary: Not reported
Erman et al[31] Armodafinil 150 mg QD administered one hour prior to night shift vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age suffering from excessive sleepiness associated with SWD	N=383 6 weeks	Primary: CGI-C Secondary: GAF and KSS	Primary: Significantly more patients treated with armodafinil experienced an improvement in CGI-C compared to placebo at three weeks (78 vs 51%; P<0.0001) and at six weeks (80 vs 56%; P<0.0001). Similarly, more patients treated with armodafinil experienced an improvement in late-in-shift CGI-C at the final visit compared to placebo (77 vs 57%; P<0.0001). At the final visit, most patients in the armodafinil group were categorized as 'much improved' (33%) or 'very much improved' (24%) on the late-in-shift CGI-C rating scale. For patients treated with placebo, 38% had 'no change' in their condition compared to only 19% of patients in the armodafinil group. Secondary:

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				The mean (±SD) improvement from baseline in GAF score at the final visit was significantly greater in the armodafinil group compared to the placebo group (9.4 vs 5.0; P<0.0001). Improvements in GAF scores were also significantly greater for armodafinil-treated patients at three weeks (6.9 vs 3.7; P<0.0001) and six weeks (9.8 vs 4.9; P<0.0001) compared to patients treated with placebo. A higher proportion of patients treated with armodafinil had GAF scores greater than 70 ("normal function") at each visit, with almost twice as many patients receiving armodafinil reaching GAF scores greater than 70 at final visit compared to placebo (51 vs 28%; P value not reported). The improvements in KSS scores from baseline to the final visit were significantly greater for armodafinil-treated patients compared to patients receiving placebo (-2.8 vs -1.8; P<0.0001). The KSS scores were also significantly improved in the armodafinil group compared to the placebo group at three weeks (-2.6 vs -1.6; P<0.0001) and six weeks (-2.9 vs -1.8; P<0.0001).
Black et al[32] Armodafinil 100 to 250 mg QD (OSA) or 100 to 250 mg QD 30 minutes to one hour before night shift but no later than 23:00 (SWD)	DB, MC, OL Men and women 18 to 65 years of age with a diagnosis of OSA, SWD, or narcolepsy	N=743 ≥12 months	Primary: Tolerability and efficacy (CGI-C, ESS, BFI) Secondary: Not reported	Primary: Discontinuations due to adverse events occurred in 13% of study patients during the initial study period. Most adverse events were mild to moderate in severity and included headache (25%), nasopharyngitis (17%), and insomnia (14%). Small increases were observed in BP (3.6/2.3 mm Hg), HR (6.7 beats per minute) across all study patient groups with most of the changes occurring by month three. Greater improvement, compared to baseline, on the CGI-C was reported in the three study groups (75 to 92%) at the final visit with the SWD group reporting the greatest improvement. Study patients reported significant improvement at the final visit by 65% with treated OSA (95% CI, 60.2 to 68.9), 88% with SWD (95% CI, 81.3 to 93.9), and 62% with narcolepsy (95% CI, 54.2 to 69.8).

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
				Armodafinil improved wakefulness, measured by the ESS, in the treated OSA and narcolepsy groups, at all follow-up visits compared to baseline. The level of fatigue and its impact on daily activities was consistently reduced from baseline, at all visits, in each of the study groups, measured by BFI scores. Secondary: Not reported
Czeisler et al[33] Modafinil 200 mg QD administered 30 to 60 minutes before the start of work shift vs placebo	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with SWD and worked each month at least five night shifts for ≤12 hours, with ≥6 hours or worked between 10 PM and 8 AM and at least three shifts occurring consecutively	N=204 3 months	Primary: MSLT, CGI-C, Psychomotor Vigilance Test Secondary: Not reported	Primary: The modafinil group produced a significant increase in overall mean MSLT from 2.1 minutes at baseline to 3.8 minutes at endpoint compared to the placebo change of 2.04 to 2.37 minutes (P=0.002). The modafinil group significantly improved the CGI-C test scores with 74% of the patients rated as at least minimally improved compared to 36% in the placebo group (P<0.001). The modafinil group produced a significant decrease in mean number of lapses of attention during the Psychomotor Vigilance Test from baseline vs the placebo group (P=0.005). Secondary: Not reported
Tembe et al[34] Armodafinil 150 mg QD administered one hour prior to night shift	DB, MC, RCT Patients 18 to 60 years of age suffering from excessive sleepiness	N=211 12 weeks	Primary: Proportion of patients showing ≥2 grades of improvement (responder)	Primary: Responder rates with armodafinil (72.12%) and modafinil (74.29%) were comparable (P=0.76). Secondary: Armodafinil and modafinil significantly improved mean sleepiness grades as compared to baseline (P<0.0001).

Table 4. Clinical Trials

Study & Drug Regimen	Design & Demographics	Sample Size & Duration	End Points	Results
vs modafinil 200 mg administered one hour prior to night shift	associated with SWD		based on SSS in both groups Secondary: Improvement in mean SSS grades, compliance, patients' as well as physicians' global assessment for efficacy and safety	At the end of therapy, compliance in both modafinil group (99.31%) and armodafinil group (99.13%) was found to be comparable (P=0.63). Both physicians' and patients' assessment of efficacy was comparable among the treatment groups. Adverse events were similar with modafinil (40.57%) and armodafinil (42.87%; P=0.78). The most commonly treatment-emergent adverse events reported were mild to moderate in severity and included headache, nausea, and dry mouth.

Drug regimen abbreviations: QAM=every morning, QHS=dialy at bedtime, QD=daily
Study regimen abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, XO=cross-over trial
Miscellaneous abbreviations: BFI=Brief Fatigue Inventory, CDR=Cognitive Drug Research, CGI=Clinical Global Impression, CGI-C=Clinical Global Impressions of change, CPAP=continuous positive airway pressure, EDS=excessive daytime sleepiness, ESS=Epworth sleep scale, FCRTT=four-choice reaction time test, FOSQ=functional outcomes of sleep questionnaire, FOSQ-10=functional outcomes of sleep questionnaire short version, GAF=global assessment of functioning, KSS=Karolinska Sleepiness Scale, MSLT=multiple sleep latency test, MWT=maintenance of wakefulness test, nCPAP=Nocturnal polysomnography, nPSG= nocturnal Polysomnogram, OSA=obstructive sleep apnea, PLM=periodic leg movements, PSG=Polysomnogram, RDI=respiratory distress index, REM=rapid eye movement, SDS=Sheehan disability scale, SDS-M= modified Sheehan disability scale, SSS=Stanford sleepiness score, SWD=Shift Work Disorder, US=United States

Special Populations

Table 5. Special Populations[1-3]

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Armodafinil	Limited experience in the elderly; consideration should be given to the use of a lower dose in elderly patients. Safety and efficacy in children <17 years of age have not been established.	No dosage adjustment required. A safe and effective dose for patients with severe renal impairment (CrCl <20 mL/minute) has not been established.	Hepatic dosage adjustment required; with severe hepatic dysfunction, reduce the dose by one half of that recommended for healthy patients.	C*	Unknown; use with caution.
Modafinil	Limited experience in the elderly; consideration should be given to the use of a lower dose in elderly patients. Safety and efficacy in children <16 years of age have not been established.	No dosage adjustment required.	Hepatic dosage adjustment required; with severe hepatic dysfunction, reduce the dose by one half of that recommended for healthy patients.	C*	Unknown; use with caution.
Sodium oxybate	Limited experience in the elderly; monitor elderly patients closely for impaired motor and/or cognitive function. Safety and efficacy in children have not been established.	Not studied with renal dysfunction.	Hepatic dosage adjustment required; with compromised liver function, the starting dose should be decreased by one half.	C*	Unknown; use with caution.

CrCl=creatinine clearance
*A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to armodafinil and modafinil. Register pregnant patients, or pregnant women may enroll themselves by calling 1-866-404-4106 (toll free).

Adverse Drug Events

Table 6. Adverse Drug Events[1-3]

Adverse Event	Armodafinil	Modafinil	Sodium Oxybate
Cardiovascular			
Chest pain	-	3	✔
Hypertension	-	3	6
Palpitations	2	2	-
PuOe increase/decrease	1	-	-
Systolic blood pressure increased	✔	-	-
Tachycardia	-	2	<1

Adverse Event	Armodafinil	Modafinil	Sodium Oxybate
Vasodilation	-	2	-
Central Nervous System			
Abnormal dreams	-	-	3 to 9
Agitation	1	1	✔
Anxiety	4	5 to 21	3 to 6
Ataxia	+	+	✔
Attention disturbance	1	-	3 to 9
Chills	-	-	✔
Confusion	-	-	3 to 6
Depression	1 to 3	2	6
Disorientation	-	-	6
Dizziness	3 to 8	5	17
Dyskinesia	-	1	-
Fatigue/lethargy	2	-	≤6
Fever	1	-	-
Headache	14 to 28	34	22
Hyperkinesia	-	1	-
Hypertonia	-	1	-
Insomnia	4 to 6	3 to 21	5
Mania	-	✔	-
Migraine	1	-	-
Nervousness	1	7	-
Nightmares	-	-	3 to 6
Overstimulation	-	1	-
Paresthesia	1	2	-
Psychotic episodes	-	✔	-
Seizure	-	-	✔
Sleep Disorder	-	-	3 to 6
Sleep paralysis	-	-	3 to 11
Sleep walking	-	-	6
Somnolence	-	2	8
Suicidal ideation	-	-	✔
Syncope	-	-	✔
Tremor	1	1	✔
Vertigo	-	1	-
Dermatological			
Dermatitis	1	-	-
Diaphoresis	-	1	-
Erythema multiforme	-	✔	-
Herpes simplex	-	1	-
Hyperhidrosis	1	-	-
Rash	1 to 4	<1	-
Stevens-Johnson syndrome	✔	✔	-
Endocrine and Metabolic			
Dysmenorrhea	-	-	3 to 6
Gastrointestinal			
Abdominal pain	2	-	3 to 11
Anorexia	1	4	-
Appetite decreased	1	-	-
Bruxism	-	-	-
Constipation	1	2	✔
Diarrhea	3 to 5	6	6 to 8

Adverse Event	Armodafinil	Modafinil	Sodium Oxybate
Dry mouth	2 to 7	4	-
Dyspepsia	2	5	3
Fecal incontinence	-	-	<1
Flatulence	-	1	✔
Mouth ulceration	-	1	-
Nausea	7 to 14	11	21
Thirst	1	1	-
Vomiting	1	-	8
Genitourinary			
Abnormal urine	-	1	-
Enuresis	-	-	3 to 17
Erectile disturbance	-	-	-
Hematuria	-	1	-
Libido decreased	-	-	✔
Polyuria	1	-	-
Urinary Incontinence	-	-	7
Hematologic			
Agranulocytosis	-	✔	-
Eosinophilia	-	1	-
Pancytopenia	✔	-	-
Hepatic			
Liver function test abnormalities	✔	2	-
Musculoskeletal			
Back pain	-	6	-
Hypoesthesia	-	-	6
Myalgia	-	-	✔
Myasthenia	-	-	3 to 6
Weakness	-	-	6 to 8
Respiratory			
Bronchitis	-	-	✔
Cough	-	-	✔
Dyspnea	1	-	✔
Epistaxis	-	1	-
Lung disorder	-	2	-
Nasopharyngitis	-	-	8
Pharyngitis	-	4	-
Rhinitis	-	7	8
Special Senses			
Abnormal vision	-	1	-
Accommodation difficulties	-	1	-
Amblyopia	-	1	6
Blurred vision	-	1	3
Eye pain	-	1	-
Tinnitus	-	-	6
Other			
Allergic contact sensitization	-	-	✔
Anaphylaxis	✔	✔	-
Edema	-	1	-
Flu-like syndrome	1	4	✔
Hypersensitivity reactions	-	✔	✔
Pain	1	-	3
Pallor	-	-	✔

Adverse Event	Armodafinil	Modafinil	Sodium Oxybate
Thirst	-	-	✔
Viral infection	-	-	6

-Event not reported.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[1-3]

Contraindication	Armodafinil	Modafinil	Sodium Oxybate
Concurrent use of alcohol	-	-	✔
Concurrent use of sedative-hypnotic agents	-	-	✔
Hypersensitivity to the drug or any component	✔	✔	✔
Succinic semialdehyde dehydrogenase deficiency	-	-	✔

Boxed Warning for sodium oxybate[3]

WARNING
Sodium oxybate is a gamma hydroxybutyrate, a known drug of abuse. Abuse has been associated with some important central nervous system adverse reactions, including death. Even at recommended doses, use has been associated with confusion, depression, and other neuropsychiatric reactions. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving central nervous system stimulants. Important central nervous system adverse reactions associated with abuse of sodium oxybate include respiratory depression, seizure, and profound decreases in level of consciousness, with instances of coma and death. For reactions that occurred outside of clinical trials, in people taking sodium oxybate for recreational purposes, the circumstances surrounding the reactions often are unclear (e.g., dose of sodium oxybate taken, the nature and amount of alcohol or any concomitant drugs). Sodium oxybate is available through the Xyrem® Success Program, using a centralized pharmacy (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate and the required prescription form. Once it is documented that the patient has read and/or understands the materials, the drug will be shipped to the patient. The Xyrem® Success Program also recommends patient follow-up every three months. Health care providers are expected to report all serious adverse reactions to the manufacturer.

Warnings and Precautions

Table 8. Warnings and Precautions[1-3]

Warning/Precaution	Armodafinil	Modafinil	Sodium Oxybate
Angioedema and anaphylactoid reactions	✔	✔	-
Adjunct to standard treatment(s); will not treat underlying cause	✔	✔	-
Cardiovascular system; therapy has not been evaluated in patients with a recent history of myocardial infarction or unstable angina	✔	✔	-
Central nervous system depression/respiratory depression; potential to impair respiratory drive, especially in patients with already-compromised respiratory function	-	-	✔
Confusion/neuropsychiatric adverse events; emergence requires careful and immediate evaluation	-	-	✔

Warning/Precaution	Armodafinil	Modafinil	Sodium Oxybate
Depression; emergence requires careful and immediate evaluation	-	-	✔
Diagnosis of sleep disorders; therapy should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, obstructive sleep apnea, and/or shift-work disorder has been made in accordance with International Classification of Sleep Disorders or Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria	✔	✔	-
Drugs affecting the central nervous system; may alter judgment, thinking, or motor skills	✔	✔	-
Multi-organ hypersensitivity reactions; discontinue therapy if suspected	✔	✔	-
Patients using cyclosporine; blood levels of cyclosporine may be reduced with therapy	✔	✔	-
Patients using steroidal contraceptives; effectiveness of steroidal contraceptives may be reduced with therapy, alternative or concomitant methods of contraception are recommended	✔	✔	-
Persistent sleepiness; patients with excessive sleepiness should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or other potentially dangerous activity	✔	✔	-
Psychiatric symptoms have been reported	✔	✔	-
Rapid onset of central nervous system depressant effects; only administer at bedtime and while in bed	-	-	✔
Serious rash, including Stevens-Johnson Syndrome; serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children	✔	✔	-
Sleepwalking; episodes should be fully evaluated and appropriate interventions considered	-	-	✔
Sodium intake; appropriate daily intake of sodium should be reviewed in patients with heart failure, hypertension, or compromised renal function (see approved package labeling)	-	-	✔

Drug Interactions

Table 9. Drug Interactions[1-3]

Interaction	Armodafinil	Modafinil	Sodium Oxybate
Barbiturates: increased sleep duration and central nervous system depression.	-	-	✔
Benzodiazepines: benzodiazepine plasma levels may be reduced.	✔	✔	-
Benzodiazepines: increased sleep duration and central nervous system depression.	-	-	✔
Buspirone: increased sleep duration and central nervous system depression.	-	-	✔
Central nervous system depressants: increased sleep duration and central nervous system	-	-	✔

Interaction	Armodafinil	Modafinil	Sodium Oxybate
depression.			
Oral contraceptives: efficacy of oral contraceptives may be reduced.	✔	✔	
Zolpidem: increased sleep duration and central nervous system depression.	-	-	✔

Dosage and Administration

Table 10. Dosing and Administration[1-3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Armodafinil	EDS associated with narcolepsy and obstructive sleep apnea: Tablet: initial, 150 to 250 mg QAM; maximum, 250 mg/day* EDS associated with sleep work disorder: Tablet: initial, 150 mg QD one hour prior to start of work shift; maximum, 150 mg/day	Safety and efficacy in children <17 years of age have not been established.	Tablet: 50 mg 150 mg 200 mg 250 mg
Modafinil	EDS associated with narcolepsy and obstructive sleep apnea: Tablet: initial, 200 mg QAM; maximum: 400 mg/day† EDS associated with sleep work disorder: Tablet: initial, 200 mg QD one hour prior to start of work shift; maximum, 200 mg/day	Safety and efficacy in children <16 years of age have not been established.	Tablet: 100 mg 200 mg
Sodium Oxybate	Cataplexy in narcolepsy and EDS associated with narcolepsy: Oral Solution: initial, 4.5 g/night divided into two equal doses of 2.25 g at bedtime and 2.5 to 4 hours later; maintenance, increase to 6 to 9 g/night in two divided doses	Safety and efficacy in children have not been established.	Oral solution: 500 mg/mL Prescribers must enroll in the Xyrem Success Program.

QAM=every morning, QD=daily
*In patients with OSA, doses up to 250 mg/day, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose.
†Doses up to 400 mg/day, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose.

Clinical Guidelines

Table 11: Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Sleep Medicine: **Practice Parameters for the Treatment of**	• Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most antidepressants and anticataplectics have little effect on alertness.

Clinical Guideline	Recommendations
Narcolepsy and Other Hypersomnias of Central Origin (2007)[35]	However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. • Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy. • Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)**[36]	<u>Excessive daytime sleepiness and irresistible episodes of sleep</u> • Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily. • Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate. • Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration. • The optimal response on excessive daytime sleepiness may take up to 12 weeks. • Supplementation with modafinil is generally more successful than sodium oxybate alone. • Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended. • The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. <u>Cataplexy</u> • First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals. • Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks. • Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common. • Selective serotonin reuptake inhibitors are slightly less active but have

Clinical Guideline	Recommendations
	fewer adverse effects. • Venlafaxine is widely used but clinical evidence supporting its use is limited. • Reboxetine and atomoxetine, also lack published clinical evidence. • Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. • There is no accepted behavioral treatment of cataplexy. <u>Poor sleep</u> • Sodium oxybate appears to be the most appropriate to treat poor sleep. • Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term follow-up. • The improvement in poor sleep reported by some patients once established on modafinil is noteworthy. <u>Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms</u> • Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects. • There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.
American Academy of Sleep Medicine: **Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults (2009)**[37]	<u>Weight reduction</u> • Successful dietary weight loss may improve the apnea-hypopnea index in obese obstructive sleep apnea patients. • Dietary weight loss should be combined with a primary treatment for obstructive sleep apnea. • Bariatric surgery may be adjunctive in the treatment of obstructive sleep apnea in obese patients. <u>Pharmacologic agents</u> • Modafinil is recommended for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea patients who have sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness. • Selective serotonin reuptake inhibitors, protriptyline, methylxanthine derivatives (aminophylline and theophylline), and estrogen therapy are not recommended for treatment of obstructive sleep apnea. <u>Supplemental oxygen</u> • Oxygen supplementation is not recommended as a primary treatment for obstructive sleep apnea. <u>Medical therapies intended to improve nasal patency</u> • Short-acting nasal decongestants are not recommended for treatment of obstructive sleep apnea. • Topical nasal corticosteroids may improve the apnea-hypopnea index in patients with obstructive sleep apnea and concurrent rhinitis, and thus may be a useful adjunct to primary therapies for obstructive sleep apnea.

Clinical Guideline	Recommendations
	Positional therapies • Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for obstructive sleep apnea in patients who have a low apnea-hypopnea index in the non-supine vs that in the supine position.
American Academy of Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[38]	Shift work disorder • Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. • Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. • Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. • Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. • Modafinil is indicated to enhance alertness during the night shift for shift work disorder. • Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

Conclusion

The wakefulness promoting agents armodafinil (Nuvigil®) and modafinil (Modafinil®), along with the central nervous system agent, sodium oxybate (Xyrem®) are FDA-approved for symptomatic treatment in narcolepsy.[1-3] Specifically, modafinil and its R-enantiomer, armodafinil, are indicated for EDS associated with narcolepsy as well as EDS that results from obstructive sleep apnea (OSA) and shift work disorder (SWD).[1-2] Sodium oxybate is indicated for EDS in narcolepsy also for the treatment of cataplexy associated with narcolepsy.[3] The exact mechanisms by which these agents exert their therapeutic effects are not completely understood.[1-3] Modafinil and armodafinil have produced psychoactive and euphoric effects along with other feelings typical of CNS stimulants and have been classified as Schedule IV drugs by the FDA. Sodium oxybate includes a black box warning in its FDA approved labeling regarding abuse potential and its depressive CNS effects that has led to serious adverse events and even death. It has been classified as a Schedule III controlled-substance by the FDA. Modafinil and armodafinil are administered once daily. Sodium oxybate has to be taken twice daily, once before bed and then once again approximately 2.5 to 4 hours later.[1-3] Currently, only modafinil is available generically.

Efficacy of these agents has been well documented in placebo-controlled trials.[6-34] Head-to-head studies are limited, but it appears as though modafinil and armodafinil are equal in therapeutic effect.[34] Current clinical guidelines have not been updated to include armodafinil's place in therapy. Generally modafinil is recommended as a first line agent for the treatment of EDS. CNS stimulants such as methylphenidate and amphetamine/dextroamphetamine as well sodium oxybate are recommended as alternatives. Recommendations regarding the use of certain types of antidepressants vary by guidelines, with some offering a recommendation for use and others not.[35-38] For cataplexy in narcolepsy, sodium oxybate is considered the first-line agent, but its use may be limited due to side effects.[36]

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