

# Narcolepsy: Treatment Issues

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Pharmacologic management of patients with narcolepsy is usually based on treating the separate symptoms of cataplexy and excessive daytime sleepiness (EDS). For treating cataplexy, the most widely used medications include the antidepressants venlafaxine, imipramine, and protriptyline, usually at lower doses than prescribed with depression, and sodium oxybate. Monoamine oxidase inhibitors are also sometimes used, but much less frequently. The U.S. Food and Drug Administration has approved 4 medications for EDS: dextroamphetamine, methylphenidate, modafinil, and sodium oxybate. Sodium oxybate is the only drug approved for treating both cataplexy and EDS. Modafinil and sodium oxybate have similar, long-term efficacies in treating EDS at prescribed doses.

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Narcolepsy is a complex disease with multiple symptoms that include excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis. Although the central hypocretin system has been found to play a central role in narcolepsy with cataplexy, currently available treatments for human narcolepsy do not target this system, but rather treat narcolepsy symptomatically. Stimulants are given to counter the patient's excessive sleepiness; REM suppressants are used to target cataplexy, hallucinations, and sleep paralysis; and sedatives are used to consolidate sleep.<sup>1</sup> Sodium oxybate ( $\gamma$ -hydroxybutyric acid or GHB) is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of both cataplexy and EDS in patients with narcolepsy. A summary of the major pharmaceutical approaches used to treat narcolepsy is shown in Table 1.<sup>1</sup> It is important to note that the particular symptom that needs the most pharmacologic emphasis varies from patient to patient, but typically, excessive sleepiness is the most

problematic for most patients. Additionally, as with any patients with daytime sleepiness, regular follow-up is important, as these patients require close and careful monitoring.

## NONPHARMACOLOGIC APPROACHES

In addition to pharmacologic management of narcolepsy, nonpharmacologic approaches should be used as supplemental treatment. These approaches include education on the therapeutic expectations of management, having the patient avoid sleep loss or circadian challenges, education about sleep hygiene, and the use of planned naps that can be used to provide temporary alertness.

It is important for patients to have realistic expectations for therapy. For example, they should understand that, with the exception of a high, 100-mg methamphetamine dose, patients with narcolepsy are not going to be as alert as their non-narcoleptic counterparts. To avoid sleep loss and circadian challenges, patients should avoid activities that alter good sleep habits, such as shift work. Sleep loss is an inherent aspect of our 24-hour society. Narcolepsy patients need to guard against extended hours of work and associated sleep loss. They should also avoid any drugs that may cause sleepiness, such as  $\beta$ -blockers. Proper sleep hygiene is important and simply refers to managing sleep habits. Because short naps can differentially refresh narcolepsy patients for a short period,<sup>2</sup> four 15-minute naps scheduled across the day are more beneficial for narcolepsy patients than a 1-hour nap once a day.

## TREATMENT OF CATAPLEXY

In the canine models described in the previous articles in this supplement, cataplectic reduction is achieved through inhibition of adrenergic and, to a lesser extent, serotonergic reuptake.<sup>1,2</sup> In the same way, human cata-

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Table 1. Currently Available Narcolepsy Treatments and Their Pharmacologic Properties<sup>a</sup>

Compound	Pharmacologic Properties
<b>Stimulants</b>	
Amphetamine	Increases monoamine release (DA > NE >> 5-HT). Primary effects due to reverse efflux of DA through the DAT. Inhibition of monoamine storage through the VMAT and other effects occur at higher doses. The <i>D</i> -isomer is more specific for DA transmission and is a better stimulant compound. Some effects on cataplexy (especially for the <i>L</i> -isomer) secondary to adrenergic effects occur at higher doses. Available as racemic mixture or pure <i>D</i> -isomer; various time-release formulations available.
Methamphetamine	Profile similar to amphetamine but more lipophilic with increased central penetration.
Methylphenidate	Blocks monoamine (DA > NE >> 5-HT) uptake. No effect on reverse efflux or on VMAT. Short half-life. Available as racemic mixture or as pure <i>D</i> -isomer and in various time-release formulations.
Pemoline	DA uptake inhibition. Low potency. Rarely used due to occasional hepatotoxicity.
Selegiline ( <i>L</i> -deprenyl)	MAO-B inhibitor with in vivo conversion into <i>L</i> -amphetamine and <i>L</i> -methamphetamine.
Modafinil <sup>b</sup>	Mode of action debated but probably involves relative selective DA reuptake inhibition. Fewer peripheral side effects. Low-potency compound. Available as a racemic mixture. Little if any addictive potential but less efficacious than amphetamine or methylphenidate. The <i>R</i> -isomer has a longer half-life and is in development.
<b>Anticatataplectic compounds</b>	
Protriptyline	Tricyclic antidepressant. Monoaminergic uptake blocker (NE > 5-HT > DA). Anticholinergic effects; all antidepressants have immediate effects on cataplexy, but abrupt cessation of treatment can induce very severe rebound in cataplexy.
Imipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (NE = 5-HT > DA). Anticholinergic effects. Desipramine is an active metabolite.
Desipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (NE >> 5-HT > DA). Anticholinergic effects.
Clomipramine	Tricyclic antidepressant. Monoaminergic uptake blocker (5-HT > NE >> DA). Anticholinergic effects. Desmethylclomipramine (NE >> 5-HT > DA) is an active metabolite. No specificity in vivo.
Venlafaxine <sup>b</sup>	Dual serotonin and adrenergic reuptake blocker (5-HT $\approx$ NE); very effective but some nausea. May have less sexual side effects than other antidepressants. Slightly stimulant, short half-life, extended-release formulation preferred.
Atomoxetine <sup>b</sup>	Specific adrenergic reuptake blocker (NE) normally indicated for attention-deficit/hyperactivity disorder. Slightly stimulant, has a short half-life, and reduces appetite.
Fluoxetine	Specific serotonin uptake blocker (5-HT >> NE = DA). Active metabolite norfluoxetine has more adrenergic effects. High therapeutic doses are often needed.
<b>Other</b>	
Sodium oxybate <sup>b</sup> (GHB)	May act via GABA <sub>B</sub> or specific GHB receptors. Reduces DA release. Need bi-nightly dosing with immediate effects on disturbed nocturnal sleep; therapeutic effects on cataplexy and daytime sleepiness often delayed.

<sup>a</sup>Reprinted with permission from Mignot and Nishino.<sup>1</sup>

<sup>b</sup>Recent compounds that can be considered as first-intention treatments in narcolepsy-cataplexy, considering their benefit and side effect profiles when compared with other older medications.

Abbreviations: 5-HT = serotonin, DA = dopamine, DAT = dopamine transporter, GABA<sub>B</sub> =  $\gamma$ -aminobutyric acid B, GHB =  $\gamma$ -hydroxybutyric acid, MAO = monoamine oxidase, NE = norepinephrine, VMAT = vesicular monoamine transporter.

plexy is treated primarily with antidepressants, including serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants. Monoamine oxidase inhibitors are also effective, but are less commonly used. Whereas all antidepressants have an immediate effect on cataplexy, abrupt cessation of treatment can induce cataplectic rebound.

Fluoxetine is a specific serotonin reuptake inhibitor with minimal antihistaminic and anticholinergic effects that is used to treat depression.<sup>3</sup> The therapeutic fluoxetine doses needed to successfully treat cataplexy are much higher than when it is used as an antidepressant: 60 mg of fluoxetine for cataplexy treatment versus 20 to 40 mg of fluoxetine for depression.<sup>1</sup> The active metabolite of fluoxetine, norfluoxetine, has more adrenergic-mediated effects than the parent compound and is more active in the canine model.<sup>4</sup> It also has a very long half-life, on the order of months, so it is very difficult to take a patient off treatment with the medication. This becomes an important consideration when treating a woman who could potentially become pregnant.

Another antidepressant used to treat cataplexy is venlafaxine, which is a bicyclic antidepressant that acts as a specific serotonin-norepinephrine reuptake inhibitor.<sup>1,3</sup> It

affects serotonin reuptake equally or more than norepinephrine, but has less effect on dopamine systems. It is very effective for cataplexy, which may be due in part to its effect on noradrenergic effects. It has less stimulant effect than fluoxetine, as well as a shorter half-life; an extended-release formulation is available and may be preferred for cataplexy.<sup>1</sup> It also has fewer sexual side effects than other antidepressants. The usual dosage is between 75 and 375 mg.

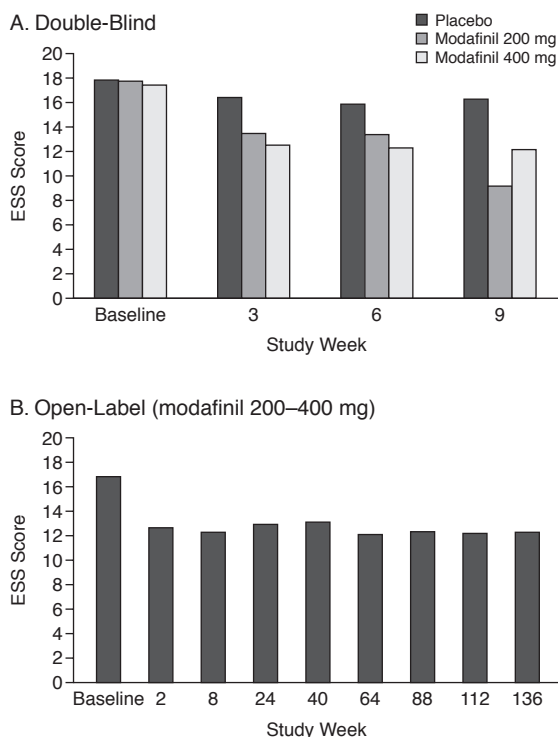
Tricyclic antidepressants used to treat narcoleptic cataplexy include imipramine and protriptyline. Imipramine blocks norepinephrine and serotonin reuptake about equally, and has less effect on dopamine reuptake, whereas protriptyline blocks the reuptake of norepinephrine more than serotonin and dopamine.<sup>1,3</sup> The active metabolite of imipramine is desipramine, which is also available for treating cataplexy. The imipramine dosage used for treating depression is 75 to 300 mg; the dosage used for treating cataplexy is lower. Imipramine is not often used for treating cataplexy because of its relative sedative activity. Protriptyline does not affect sedation, so it is also not commonly used; it has very strong anticholinergic effects.<sup>1,3</sup>

**Table 2. FDA-Approved Narcolepsy Medications<sup>a</sup>**

Drug	Schedule	FDA-Approved Indication	FDA-Approved Dosages
Dextroamphetamine	C-II	Narcolepsy	5–60 mg/d
Methylphenidate	C-II	ADHD with hyperactivity	2.5–40 mg/d
Modafinil	C-IV	ADHD, narcolepsy	5–60 mg/d
		Excessive sleepiness associated with narcolepsy, OSA, and SWSD	100–200 mg/d
Sodium oxybate	C-III	Excessive sleepiness and cataplexy in patients with narcolepsy	3.0–9.0 g total nightly dose

<sup>a</sup>Data from *Physicians' Desk Reference*.<sup>8</sup>  
 Abbreviations: ADHD = attention-deficit/hyperactivity disorder, FDA = U.S. Food and Drug Administration, OSA = obstructive sleep apnea, SWSD = shift work sleep disorder.

**Figure 1. Long-Term Efficacy of Modafinil in Narcolepsy<sup>a</sup>**

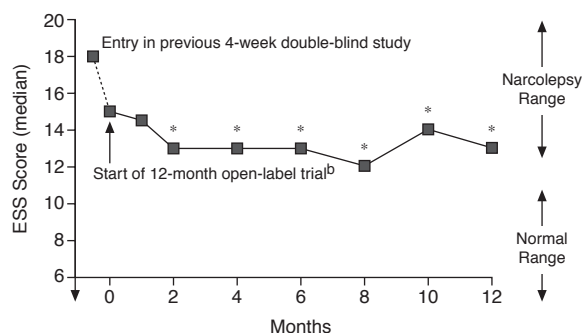


<sup>a</sup>Reprinted with permission from Erman et al.<sup>10</sup>  
 Abbreviation: ESS = Epworth Sleepiness Scale.

The protriptyline dosage used for treating depression is 15 to 60 mg, but the dosage for cataplexy is lower. It is also used to treat mild sleep apnea.

Sodium oxybate is indicated for treatment of cataplexy in narcolepsy. Although the exact mechanism of action in cataplexy remains unknown, the nightly administration of sodium oxybate results in significant improvements in daytime cataplexy attacks, as well as sleepiness.<sup>5,6</sup> It has been suggested that sodium oxybate may act by stimu-

**Figure 2. Long-Term Efficacy of Sodium Oxybate in the Management of Excessive Daytime Sleepiness<sup>a</sup>**



<sup>a</sup>Reprinted with permission from the U.S. Xyrem Multicenter Study Group.<sup>5</sup>

<sup>b</sup>N = 117; stimulant medications maintained.

\*p < .001 vs. baseline.

Abbreviation: ESS = Epworth Sleepiness Scale.

lation of GABA<sub>B</sub> receptors, and possibly other GHB receptors.<sup>1,7</sup> Sodium oxybate has strong effects on dopamine transmission.<sup>1,7</sup> Unlike stimulants, sodium oxybate is taken at bedtime. This compound will be discussed in more detail later in the article.

### TREATMENT OF EXCESSIVE DAYTIME SLEEPINESS

Four drugs have been indicated by the FDA for the treatment of EDS in narcolepsy (Table 2)<sup>8</sup>: dextroamphetamine, methylphenidate, modafinil, and sodium oxybate. Methylphenidate acts by blocking monoamine uptake and is available either as a racemic mixture or as a pure D-isomer; the isomer has a greater binding efficiency.<sup>1,3</sup> Its usual dosage is 10 to 100 mg daily. Dextroamphetamine is the dextrorotatory stereoisomer of the amphetamine molecule; its properties are similar to those of methylphenidate. The dosage for narcolepsy is 5 to 30 mg daily.

Modafinil has few peripheral side effects and lower addictive potential.<sup>1,3</sup> The mechanism of action of modafinil is still debated, but may involve dopamine reuptake inhibition. It is available as a racemic mixture, and the dosage range is 100 to 400 mg daily.

Sodium oxybate is prescribed for treating both EDS and cataplexy (Tables 1 and 2), as described above. It reduces dopamine release at night and may cause a secondary dopamine increase during the day. It is taken twice nightly, half at bedtime and half 2.5 to 4 hours later, for a total dose of 4.5 to 9 g per night.<sup>1,3</sup>

Comparison of the efficacy of these drugs in EDS is complicated because limited data are available comparing similar doses of the different medications. Additionally, the drugs are not compared with each other in the same study, and comparing results across studies is always

**Table 3. Safety and Adverse Events of Narcolepsy Medications<sup>a</sup>**

Amphetamines/methamphetamines	Insomnia, restlessness, tachycardia, psychotic episodes (rare), dizziness, diarrhea, constipation, hypertension, impotence
Methylphenidate	Nervousness, insomnia, anorexia, nausea, dizziness, hypertension, hypotension, hypersensitivity reactions, tachycardia, headache
Modafinil	Headache, nausea, eosinophilia, diarrhea, dry mouth, anorexia
Fluoxetine	Asthenia, nausea, diarrhea, anorexia, insomnia, tremor, anxiety, somnolence
Protriptyline	Orthostatic hypotension, hypertension, seizures, headache, anticholinergic symptoms, impotence, impaired liver function, myocardial infarction, stroke
Venlafaxine	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, abnormal ejaculation/orgasm, impotence in men
Sodium oxybate	Headache, nausea, dizziness, nasopharyngitis, somnolence, vomiting, urinary incontinence

<sup>a</sup>Data from Littner et al.<sup>3</sup> and from product package inserts (available at <http://www.accessdata.fda.gov>).

troublesome. For example, examination of the relative efficacy of methylphenidate, modafinil, and dextroamphetamine in the treatment of sleepiness found that methylphenidate (35% improvement over baseline) and modafinil (38% improvement over baseline) had a much lower effect on sleepiness than dextroamphetamine (88% improvement).<sup>9</sup> However, the dosage of dextroamphetamine used (60 mg) was much higher than normally prescribed.<sup>9</sup>

Modafinil and sodium oxybate, the 2 most commonly used narcolepsy drugs, have both been found to have efficacy in treating EDS during both short- and long-term use. Studies examining their efficacy using the Epworth Sleepiness Scale (ESS) used standard, prescribed doses for their studies (200–400 mg modafinil, 3–9 g sodium oxybate nightly; Figures 1 and 2).<sup>5,10</sup> In the open-label modafinil study,<sup>10</sup> a 2.5- to 3-minute increase in maintenance of wakefulness testing lasted for over 2 years with continued medication (Figure 1). A similar decrease in ESS score was found in the sodium oxybate study,<sup>5</sup> and the decrease also was maintained for at least 1 year (Figure 2). Thus, both treatments were comparable in terms of long-term efficacy in reducing EDS in narcolepsy.

The safety and adverse events of all compounds in this discussion are summarized in Table 3.

## SUMMARY

Pharmacologic management of patients with narcolepsy is usually based on treating separate symptoms, primarily cataplexy and EDS. Treatment options for cataplexy include the antidepressants fluoxetine, venlafaxine, imipramine, and protriptyline, usually at lower doses than prescribed with depression, and sodium oxybate. For treating daytime sleepiness, FDA-approved medications include dextroamphetamine, methylphenidate, modafinil, and sodium oxybate. Sodium oxybate is the only drug approved for treating both cataplexy and EDS. Modafinil and sodium oxybate have similar, long-term efficacies in treating EDS at prescribed doses.

*Drug names:* atomoxetine (Strattera), clomipramine (Anafranil and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), methamphetamine (Desoxyn), methylphenidate (Daytrana, Ritalin, and others), modafinil (Provigil), protriptyline (Vivactil), selegiline (EMSAM, Eldepryl, and others), sodium oxybate (Xyrem), venlafaxine (Effexor and others).

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