Curr Treat Options Neurol (2015) 17:20
DOI 10.1007/s11940-015-0347-4

Sleep Disorders (S Chokroverty, Section Editor)

Update on Therapy for Narcolepsy

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This article is part of the Topical Collection on *Sleep Disorders*

Keywords Narcolepsy · Cataplexy · Sleepiness · Hypocretin · Treatment · Modafinil · Armodafinil · Sodium oxybate · Methylphenidate · Dextroamphetamine · Lisdexamfetamine · Venlafaxine · Methamphetamine

Opinion statement

Narcolepsy is a severe, incurable, neurological disorder that is treated by pharmacological management of its symptoms. The main symptoms are excessive daytime sleepiness (EDS) and cataplexy, although addition symptoms that may require treatment include sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep. Sodium oxybate and modafinil/armodafinil are the first-line treatments for EDS, and sodium oxybate for cataplexy. Sodium oxybate treats all the symptoms of narcolepsy, whereas modafinil is effective for EDS only. Alternative medications for EDS include methylphenidate or amphetamines such as dextroamphetamine, lisdexamfetamine, methamphetamine, or combination amphetamine salts. Non-FDA approved medications for cataplexy include norepinephrine reuptake inhibitors such as venlafaxine or atomoxetine. Combination therapy can be more effective for sleepiness such as sodium oxybate and modafinil/armodafinil. Medication for narcolepsy is generally well tolerated and usually required life-long although does not eliminate all symptoms of narcolepsy.

Introduction

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

The loss of hypocretin-producing neurons characterizes narcolepsy with cataplexy [3], as do specific genotypes such as human leukocyte antigen DQB1*0602 and to a lesser extent T cell receptor polymorphisms implicated in autoimmune pathways [4]. Two types of narcolepsy are currently recognized in the revised International Classification of Sleep Disorders (ICSD-3) diagnostic criteria [5]. Type 1 narcolepsy, based upon the actual or presumed loss or reduction of hypocretin, has either cataplexy or a reduction in measured cerebrospinal fluid (CSF) hypocretin-1 level. In contrast, type 2 narcolepsy is determined by the absence of both cataplexy and, if a spinal tap was performed, reduced csf

Published online: 09 April 2015

hypocretin levels, and is dependent upon polysomnographic evidence.

The clinical features comprise a main symptom pentad of excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed nighttime sleep (DNS). Patients can have various combinations of all five symptoms, but the most common symptom, and often the first to appear, is EDS, which is present in all patients. Automatic behavior episodes due to sleepiness are common in narcolepsy. Cataplexy occurs in approximately 70 % of narcolepsy patients and may not appear until weeks or months after onset of EDS; it is the pathognomonic symptom for narcolepsy [6]. DNS, with abnormal findings on polysomnography, occurs in up to 90 % of patients and is characterized by awakenings/arousals after sleep onset, increased stage 1 sleep, and frequent sleep stage shifts [7•]. The symptoms of sleep paralysis and hypnagogic/hypnopompic hallucinations are not as prevalent as the other symptoms, but, along with other REM phenomena, aid in making the diagnosis. Other REM phenomena, although not included in the pentad, include frequent vivid, bizarre, lucid and delusional dreams, nightmares, and dreams during naps [8•, 9, 10]. Symptoms of REM behavior disorder (RBD) may also be present in up to 36 % of narcolepsy patients, but are usually not a primary complaint, and RBD or REM without atonia (RWA) may more likely be recognized during polysomnography [11, 12]. A recent study reported that, in addition to symptoms of the narcolepsy pentad, 42.9 % of patients complained of trouble functioning or concentrating during the day and that one quarter of patients (25.8 %) reported difficulties with activities of daily living [13].

Although narcolepsy can have an onset at any age, it is usually within the first two decades of life, with a median age of onset of 16 years [14, 15]. It typically remains undiagnosed until many years after initial symptom onset [16•]. Narcolepsy in children often differs from that in adults, with increased 24-h sleep close to disease onset, hyperactivity, and cataplexy that may not be emotionally induced and may resemble puppet-like movements [17].

Most patients require lifelong pharmacologic management, and practice parameters for the treatment of narcolepsy have been developed, but not since 2007 [18, 19]. Behavior modifications such as good sleep hygiene including maintaining a regular sleep schedule and scheduling short naps (15–20 min) distributed across the day may have favorable effects on daytime performance for patients with narcolepsy. There is no established behavioral treatment for cataplexy, although patients can predict some situations likely to trigger cataplexy attacks and act accordingly. Thus, behavioral treatment may have some complementary benefits to pharmacologic treatment.

Medications have been approved for the treatment of specific symptoms of narcolepsy, as well as several that are not approved but are used off-label because of their recognized utility in managing symptoms (Table 1). Of the US Food and Drug Administration (FDA)-approved drugs for narcolepsy, methylphenidate, amphetamines, and modafinil/armodafinil are approved only for EDS, and sodium oxybate, the sodium salt of gamma-hydroxybutyrate, is approved for both EDS and cataplexy in adults [20]. Published recommendations also suggest its use for disrupted sleep and as an option for hypnagogic hallucinations and sleep paralysis [19]. In Europe, armodafinil and amphetamines have not been approved for narcolepsy by the European Medicines Agency (EMA). Although not approved by the FDA, medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) are recommended for cataplexy and to a lesser extent for hypnagogic hallucinations and sleep paralysis, and hypnotics as an option for DNS [19]. Therapies approved in the Europe by the EMA include sodium oxybate for the treatment of narcolepsy with cataplexy in adults, modafinil to promote wakefulness in adults with narcolepsy, and immediate-release methylphenidate for the treatment of narcolepsy in adults when modafinil is ineffective and in children >6 years of age. Selegiline, a monoamine oxidase inhibitor, is used in Europe as an option for EDS, as well as other drugs not currently available in the USA including mazindol, ritanserin, and reboxetine. Mazindol, an imidazolidine derivative that blocks dopamine and norepinephrine reuptake that may be effective for EDS and cataplexy [21], is only available in France. Ritanserin, a serotonin-2 antagonist with potential efficacy for EDS, and reboxetine, a norepinephrine reuptake inhibitor, may be effective for cataplexy [19].

There are several new approaches to therapy such as the histamine receptor inverse agonist/antagonist pitolisant [22], which is available in Canada but not in the USA, as well as experimental therapies including JZP-110 from Jazz Pharmaceuticals [23, 24] and hypocretin-based therapies such as hypocretin cell transplantation [25] or intranasal administration of hypocretin [26]. Future potential treatment could include viral vector hypocretin gene transfer [27].

Table 1. Medications used in the treatment of narcolepsy

Drug	Starting daily dose (mg)	Maximum daily dose (mg)	Comments
Norepinephrine reuptake inhibitors, including SSRIs, SNRIs, and TCAs			Cardiovascular and sexual side effects
Venlafaxine	37.5	300	Rebound cataplexy can occur on discontinuation. Available in an extended release formulation
Atomoxetine	10	80	Usually given twice per day
Amphetamine salts (Adderall)	20	60	A combination of four amphetamine salts
Methamphetamine (Desoxyn)	15	60	The strongest amphetamine with strong abuse potential
Dextroamphetamine (Dexedrine)	30	60	Often used as PRN dosing for additive EDS benefit
Lisdexamfetamine (Vyvanse)	20	70	May be better tolerated than other amphetamines
Methylphenidate (Ritalin, Concerta/Methylin, Equasym XL)	30	60	Preferable before using amphetamines
Dexmethylphenidate (Focalin)	5	20	The *d-threo*-enantiomer of racemic methylphenidate
Modafinil (Provigil)	200	400	First-line medication for EDS
Armodafinil (Nuvigil)	150	250	First-line medication for EDS. Longer acting than modafinil
Sodium oxybate (Xyrem)	4.5 g/night	9.0 g/night	First line medication for either EDS or cataplexy
Selegiline (Eldepryl, Zelapar)	20	40	Used mainly in Europe. Breaks down to amphetamine derivatives. Needs a low tyramine diet
Mazindol	1	6	A tricyclic, anorectic, nonamphetamine stimulant
Pitolisant	10	40	Not available in the USA A selective histamine H3 receptor inverse agonist Not available in the USA

SNRIs serotonin–norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

Treatment

Treatment decisions are driven by the presence of EDS alone or EDS with other REM-sleep phenomena and additional symptoms, since a single therapy that is effective for multiple symptoms is usually preferable than using different drugs for individual symptoms [28•]. Sodium oxybate is only approved in adults for EDS with or without cataplexy; however, evidence indicates its utility for DNS and as an option for other REM-sleep phenomena such as frequent disturbing dreams and nightmares, hypnagogic hallucinations, and sleep paralysis [18, 19].

EDS as the sole initial symptom

EDS is most often the presenting symptom, and when it occurs without cataplexy, the considerations include the use of modafinil/armodafinil or sodium

oxybate. Most narcolepsy drugs for EDS are FDA-controlled substances, schedules II, III, or IV, which may be disconcerting to both patients and physicians; for modafinil/armodafinil because of concern with addiction or abuse potential; and for sodium oxybate because of the greater burden of record keeping.

When starting a patient on medication for the first time, considerations will include whether the patient is on an oral contraceptive agent, as modafinil/armodafinil increases the metabolism of ethinylestradiol and therefore may render it ineffective, and so another form of contraception is recommended [29, 30]. If the patient is a young adult, or a mother of young children, sodium oxybate may not be recommended if the patient is unwilling to avoid alcohol, has a very irregular sleep–wake schedule, needs to awaken frequently at night to attend to a child, or is taking other sedative medications.

Sodium oxybate

While no drugs are FDA-approved for the symptoms of the pentad other than EDS and cataplexy, their presence in patients should result in consideration of medications that can either be used to supplement those for EDS and cataplexy or that address the widest possible group of symptoms. If additional narcolepsy features are present such as disturbed nighttime sleep, frequent unpleasant dreams, hypnagogic hallucinations, or sleep paralysis, then sodium oxybate would be an appropriate first choice medication. The usual starting dose is 4.5 g in divided doses, the second 2 1/2 to 4 h after the first dose. Food should not be taken within 2 h of taking the drug. Side effects may include headache or nausea, which is usually self-limited within a few days, although rarely a dose reduction may be required. Side effects are usually mild to moderate at worst, but patients may develop nausea, confusion, anxiety, depressive symptoms, restless legs syndrome (RLS), and sleepwalking, or enuresis that may limit its use. In clinical practice, the confusion and neuropsychiatric effects at treatment initiation have been found to be due, at least in part, to a dose that does not rapidly induce sleep, as some patients may take up to 2 h to fall asleep after dosing, thereby causing symptoms of confusion and incoordination in the patient who is still ambulatory at that time. A more rapid increase in dose can improve this situation, and titration to clinical effect is a critical component of patient management with sodium oxybate. An unpleasant taste may be due in part to the sodium salt effect of the sodium oxybate solution and can be masked by mixing the solution with a flavored water, but not a juice, which may reduce the efficacy of the medication. Although best taken on an empty stomach, as a meal may reduce the efficacy, sometimes, the addition of small amount of food, such as a cracker, may help mask the taste. An oral antiemetic such as a 5-HT3 antagonist (e.g., ondansetron) has been used clinically in some patients to help control the nausea. It may be necessary to limit the use of sodium oxybate in patients with cardiovascular disease because of its high salt content. However, anecdotally, sodium oxybate has been used with salt restriction and diuretics, although the efficacy and safety of this combination need to be confirmed.

Sodium oxybate is a schedule III controlled substance (less potential for abuse, but may lead to moderate or low physical dependence or high psychologic dependence). Initial concerns regarding abuse have not been borne out since its approval [31•], and its low abuse in patients may be due by the requirement of central pharmacy dispensing in the USA. Although its dosing

regimen can be of concern to physicians, in clinical practice, patients are usually not bothered by taking the medication twice at night. Although equal split dosing is recommended, some patients do well with a single nightly dose, while in others, the first and second dose amounts have been adjusted according to clinical needs without loss of efficacy [32]. Although gamma-hydroxybutyrate including sodium oxybate related deaths have been reported, these events are mainly related to overdose, illicit use, or in association with concomitant utilization of other sedative drugs [33].

Central and obstructive sleep apnea syndromes should be determined before prescribing sodium oxybate and, if present, treated prior to initiating sodium oxybate. Treatment, usually by CPAP, should be optimized before initiating treatment with sodium oxybate, which can precipitate or exacerbate OSA [34]. However, sodium oxybate can increase weight loss in patients with narcolepsy, which could benefit any obstructive apnea that is present [35].

Modafinil/armodafinil

Modafinil/armodafinil will treat the EDS effectively but has no effect on other narcolepsy REM phenomena. Because of the longer half-life and the once-a-day dosing, armodafinil is usually the first-line medication for treating EDS. The usual starting dose is 150 mg; however, if the patient is drug naive or sensitive to medications, a starting dose of 50 mg can be given with titration to an effective dose. Most patients with narcolepsy and severe sleepiness require the maximally approved dose of 250 mg of armodafinil. Dose forms include 50, 150, 200, and 250 mg. The newer formulation of armodafinil 250 mg is clinically equivalent to two tablets of modafinil 200 mg, and therefore cheaper; however, if armodafinil is not approved by the insurance carrier, generic or brand modafinil can be prescribed, although the cost for 400 mg is more than that for 250 mg of armodafinil. The medication is usually taken as early as possible in the morning, preferably with some water before getting out of bed, to allow the onset of action before breakfast is taken, as food will delay the absorption and reduce the maximum blood concentration. The medication is usually well tolerated, however side effects may include headache or nausea, which are usually self-limited within a few days, although rarely a dose reduction may be required. In women of child-bearing age on an oral contraceptive agent, an increased dose of ethinylestradiol up to 50 μg/day, an all progesterone oral contraceptive, or an alternative method for birth control should be employed. Modafinil/armodafinil are schedule IV controlled substances (a low potential for abuse relative to the drugs or other substances in schedule III).

Initial concurrent EDS and cataplexy presentation

As modafinil/armodafinil and most of the stimulant drugs used to treat EDS have little effect on cataplexy or other REM sleep-associated symptoms, and most anticataplectic medications have little beneficial effect on EDS, single drug therapy usually involves sodium oxybate [19]. Sodium oxybate is usually started at a total dose of 4.5 g with an approximately weekly increase by 1.5 g to

an effective dose that is typically between 6 g and the maximal dose of 9 g. Sodium oxybate is very effective for cataplexy and may be the most effective medication available for that symptom; however, EDS may require the addition of synergistic medications such as modafinil/armodafinil. The combination of sodium oxybate plus modafinil has been shown to be the most effective combination for EDS in randomized clinical trials [36].

To summarize initial treatment selection, for most patients, the first step requires an agent that is effective for treating daytime sleepiness. If EDS is present in the absence of cataplexy, treatment can be initiated with monotherapy using either modafinil or sodium oxybate, with the latter a better choice if any ancillary features of narcolepsy are present (sleep paralysis, hypnagogic/hypnopompic hallucinations, DNS, nightmares, etc.). When both EDS and cataplexy occur concurrently, sodium oxybate is the first choice with subsequent addition of modafinil/armodafinil if necessary.

Inability to initiate treatment with modafinil/armodafinil or sodium oxybate

Methylphenidate

Treatment may require the use of other agents if modafinil/armodafinil or sodium oxybate cannot be used. For EDS, the considerations would be one of the stimulants, either methylphenidate or one of the amphetamine drugs. Methylphenidate and the amphetamines were available before the new agents such as modafinil/armodafinil and sodium oxybate. Their usefulness is primarily for EDS, since except for some mild cases, they have not been shown to be effective for cataplexy or the other symptoms of narcolepsy. Although cheaper than the newer alternatives, their usefulness is limited by their abuse potential and side effect profile [37].

Methylphenidate has now been relegated to second-line therapy, with amphetamines and mazindol as third-line therapy, the latter only in France, since there are few clinical trial data available on their efficacy and safety [19]. When a patient cannot take modafinil or armodafinil or sodium oxybate, then methylphenidate, because of a slightly better safety profile, may be the initial choice at a dose of 10 mg, or extended release form, 20 mg once a day. These doses can be titrated to a recommended maximum dose of 60 mg/day. Higher than recommended doses in narcolepsy patients, such as 60 mg/day for methylphenidate, have been associated with more frequent hospitalizations, cardiac arrhythmias, and psychiatric disturbances [37]. Dexmethylphenidate is the *d-threo*-enantiomer of racemic methylphenidate hydrochloride, which is a 50:50 mixture of the *d-threo* and *l-threo*-enantiomers and produces similar stimulation as methyphenidate.

Amphetamines

Dextroamphetamine, lisdexamfetamine, methamphetamine, and methylphenidate are schedule II controlled substances (high potential for abuse which may lead to severe psychologic or physical dependence). Although excessive dosage and associated adverse effects of stimulant medications have been reported in narcolepsy [37], in clinical practice, patients with narcolepsy rarely abuse drugs for narcolepsy or develop addictions [38, 39]. This may in part be

due to an effect on the reward system that predisposes to the reduced addiction associated with hypocretin loss [40]. Other side effects include potential for cardiovascular events including stroke, myocardial infarction, elevated blood pressure and heart rate, and psychiatric symptoms, including psychosis and mania. Growth suppression can occur in children [41].

Dextroamphetamine, which is FDA approved for narcolepsy, is available in 5 mg tablets given three to four times a day or 5, 10, or 15 mg sustained release capsules once a day. Maximum doses of 60 mg are recommended.

Alternative amphetamine treatment might involve a combination amphetamine medication such as Adderall, which may have fewer side effects than dextroamphetamine alone. Adderall contains four amphetamine agents: racemic amphetamine aspartate monohydrate, racemic amphetamine sulfate, dextroamphetamine saccharide, and dextroamphetamine sulfate in equal amounts. It is a dopamine and norepinephrine-releasing agent, mildly serotonergic, and available in two formulations: an instant release (IR) and extended release (XR) form. The IR form is FDA-approved for narcolepsy, whereas the XR formulation is not indicated for narcolepsy. It is available in multiple IR and XR capsule dose forms. Most patients seem to prefer the XR, once-a-day formulation. A starting dose of 20 mg XR is appropriate and can be adjusted accordingly.

Lisdexamfetamine is not FDA-approved for narcolepsy but is often used as it is better tolerated in some patients than other amphetamines. It is available in multiple capsule forms from 10 to 70 mg and is recommended at a starting dose of 30 mg once a day taken with or without food.

Methamphetamine is regarded as the strongest of the amphetamines but also has a greater abuse and side effect potential. It is not FDA-approved for narcolepsy and is only used in the severest of patients who do not respond to other medications. It is only available in 5 mg tablets.

Norepinephrine reuptake inhibitors

Norepinephrine reuptake inhibitors (NRIs) are not FDA-approved for narcolepsy and have no effect on EDS. Few data exist regarding the efficacy of SSRIs, SNRIs, and TCAs on cataplexy [42]. However, in clinical practice, case reports have suggested that they can be effective for cataplexy [43–45], especially those medications with the strongest norepinephrine reuptake inhibition. SNRIs are widely used for cataplexy, particularly venlafaxine, which may be effective for cataplexy within 48 h at low doses. Because of its short duration of action, the extended-release form is preferable, starting at a low dose (37.5 mg), but higher doses are often needed (75–300 mg). However, SNRIs are limited by side effects that can include insomnia, mental stimulation, and reduced sexual function, and may precipitate other sleep disorders such as RBD [46] and RLS [47]. These anticataplectic agents can induce status cataplecticus if stopped suddenly [48]. However, they can be useful as an alternative to sodium oxybate. If cataplexy or EDS is severe, initiating the patient on sodium oxybate plus venlafaxine (for cataplexy) or sodium oxybate plus modafinil (for EDS) is a reasonable initial plan until the sodium oxybate is effective, at which point the other medication may be able to be tapered off.

Alternative SNRIs include atomoxetine, which is available in multiple dose forms from 10 to 100 mg capsules. Starting doses are 10 mg once a day, or in three divided doses up to a maximum of 80 mg a day.

Other SSRIs or TCAs that were more commonly used in the past include fluoxetine, protriptyline, and clomipramine, but these have largely been replaced because of improved efficacy and reduce side effects of the SNRIs.

Maintenance therapy

Once therapy has been initiated, frequent adjustments are usually necessary particularly in the first few months. Sodium oxybate is increased at approximately weekly intervals by 1.5 g per night, but the increase should be quicker in patients with severe symptoms or slower in those with initial adverse effects. The usual effective dose for EDS and cataplexy is between 6 and 9 g per night. If EDS is not controlled by sodium oxybate, modafinil/armodafinil can be added. Rarely, cataplexy may not be controlled by sodium oxybate, and an SNRI such as venlafaxine may be added.

Patients on modafinil may find a midday dose improves duration of effect into the evening, for example 200 mg in the morning and 200 mg at noon [49]. If insurance allows, 400 mg in the morning and 200 mg at noon for a total dose of 600 mg may be most helpful for some patients [49]. For patients only on modafinil/armodafinil when maximum dosage has been reached if EDS is still a concern, a small dose of short acting stimulant can be added, "as needed." For example, methylphenidate 10 mg or dextroamphetamine 5 mg early morning if morning alertness is a concern or late afternoon if evening alertness needs to be attained. Behavioral measures such as naps, avoiding sedentary activities, and avoiding driving or dangerous work situations should also be considered in these cases.

Narcolepsy in special conditions

Children

Pediatric recommendations for the treatment of narcolepsy have not been established, and while few drugs have been evaluated for efficacy or toxicity in children, treatment of pediatric narcolepsy is generally considered similar to that of adults [50•]. Other than amphetamines and methylphenidate, no other medications have been approved by the FDA for the treatment of narcolepsy in children. In Europe, the EMA has only approved methylphenidate immediate release for the pediatric population. Severe rashes, although rare in clinical practice, may be more likely to occur in children on modafinil/armodafinil [29, 30]. Reports of children with narcolepsy suggest efficacy and tolerability of modafinil for EDS, venlafaxine for cataplexy, and sodium oxybate for most symptoms, although multiple medications may need to be used in some patients [51–53]. Once-a-day armodafinil may be a first-choice medication for children especially in children who may miss the second dose of modafinil at lunch, or if sleep onset insomnia due to the second

modafinil dose is a concern. A behavioral approach to control sleepiness by regularly scheduled naps can be helpful, but if cataplexy impacts quality of life or safety issues, sodium oxybate should be initiated.

Narcolepsy in the elderly

Treatment for narcolepsy is usually no different in the elderly. The choice of methylphenidate or amphetamines is less than optimal in an older population, since these drugs are contraindicated in patients with cardiovascular disorders and glaucoma. Some anticataplectic medications, such as the TCAs, can be of concern in an older population due to the risks associated with their sedating effect, confusional state, urinary retention, and potential for cardiac arrhythmias and induction of orthostatic hypotension [54].

Pregnancy

Narcolepsy drugs have a schedule C classification for pregnancy (i.e., risk cannot be ruled out), yet the risks of toxicity resulting from utilization of narcolepsy drugs during pregnancy are often overestimated, with little or no evidence for teratogenicity at therapeutic doses [55•]. Healthy women going through pregnancy without medications have a 2 % risk of fetal malformation [56], similar to that of narcolepsy patients. The decision to continue or withhold narcolepsy medications during pregnancy should be made by an informed patient after weighing the risks and benefits. Although ideally, patients should discontinue medication during all of conception and pregnancy, this may not be possible, especially if the pregnancy is unplanned. Management options include staying on medication with dose reductions, changing medication if appropriate, or stopping the medication. However, treatment cessation may not be advisable in some patients if narcolepsy symptoms are severe and there is a risk of injury to the mother or fetus or an inability to manage daily activities.

There is little information available on the use of narcolepsy medications in nursing mothers. Modafinil, methylphenidate, amphetamines, and antidepressants have no specific contraindications in nursing mothers. Hypnotics are contraindicated in nursing mothers due to the depressant effect in the infant, so similarly, it would be wise to avoid using sodium oxybate. It is not known whether sodium oxybate is excreted in human milk [20]. However, sodium oxybate has a short half-life of only about 60 min, and in clinical practice, some mothers have expressed milk before their nightly dose to give to the infant.

Summary

Narcolepsy remains a challenging disease for both diagnosis and treatment. There are no curative treatments but only symptom control. The challenge of treatment can be lessened if an appropriate and careful approach is used when considering treatment options. Sodium oxybate and modafinil/armodafinil are the first-line medications for the treatment of narcolepsy. When used effectively they can greatly reduce the

impact of EDS and eliminate or nearly eliminate cataplexy. Second-line medications include the stimulant, methylphenidate and third-line amphetamines for EDS; and second-line the NRIs for cataplexy. Combination therapy is often necessary to obtain maximal symptom relief.

Compliance with Ethics Guidelines

Conflict of Interest

Michael J. Thorpy declares the receipt of honoraria and consulting fees from Jazz Pharmaceuticals, Inc. and Cephalon, Inc. (now Teva Pharmaceutical Industries, Ltd.).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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