

New developments in the management of narcolepsy

Vivien C Abad
Christian Guilleminault

Department of Psychiatry and Behavioral Sciences, Division of Sleep Medicine, Stanford University Outpatient Center, Redwood City, CA, USA

Abstract: Narcolepsy is a life-long, underrecognized sleep disorder that affects 0.02%–0.18% of the US and Western European populations. Genetic predisposition is suspected because of narcolepsy's strong association with HLA DQB1*06-02, and genome-wide association studies have identified polymorphisms in T-cell receptor loci. Narcolepsy pathophysiology is linked to loss of signaling by hypocretin-producing neurons; an autoimmune etiology possibly triggered by some environmental agent may precipitate hypocretin neuronal loss. Current treatment modalities alleviate the main symptoms of excessive daytime somnolence (EDS) and cataplexy and, to a lesser extent, reduce nocturnal sleep disruption, hypnagogic hallucinations, and sleep paralysis. Sodium oxybate (SXB), a sodium salt of γ hydroxybutyric acid, is a first-line agent for cataplexy and EDS and may help sleep disruption, hypnagogic hallucinations, and sleep paralysis. Various antidepressant medications including norepinephrine serotonin reuptake inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants are second-line agents for treating cataplexy. In addition to SXB, modafinil and armodafinil are first-line agents to treat EDS. Second-line agents for EDS are stimulants such as methylphenidate and extended-release amphetamines. Emerging therapies include non-hypocretin-based therapy, hypocretin-based treatments, and immunotherapy to prevent hypocretin neuronal death. Non-hypocretin-based novel treatments for narcolepsy include pitolisant (BF2.649, tiprolisant); JZP-110 (ADX-N05) for EDS in adults; JZP-13-005 for children; JZP-386, a deuterated sodium oxybate oral suspension; FT 218 an extended-release formulation of SXB; and JNJ-17216498, a new formulation of modafinil. Clinical trials are investigating efficacy and safety of SXB, modafinil, and armodafinil in children. γ -amino butyric acid (GABA) modulation with GABA_A receptor agonists clarithromycin and flumazenil may help daytime somnolence. Other drugs investigated include GABA_B agonists (baclofen), melanin-concentrating hormone antagonist, and thyrotropin-releasing hormone agonists. Hypocretin-based therapies include hypocretin peptide replacement administered either through an intracerebroventricular route or intranasal route. Hypocretin neuronal transplant and transforming stem cells into hypothalamic neurons are also discussed in this article. Immunotherapy to prevent hypocretin neuronal death is reviewed.

Keywords: narcolepsy, cataplexy, emerging treatment, sodium oxybate, pitolisant, JZP-110, hypocretin peptide, immunotherapy

Correspondence: Vivien C Abad
Division of Sleep Medicine, Stanford University Outpatient Center, 450 Broadway St. Pavilion C 2nd floor MC 5704, Redwood City, CA 94063, USA
Tel +1 650 723 6601
Fax +1 650 721 3448
Email vivien.abad@stanford.edu

Introduction

Narcolepsy is a chronic disabling condition that is estimated to affect 25–50/100,000 people.¹ “Narcolepsy robs you of your life’s goals and dreams”.² “There is no magic pill that completely controls narcolepsy. Even with the proper dose of my medications and lifestyle modifications, I still have to work hard to function anywhere close to normal”.² These laments articulate the devastating impact narcolepsy wields on the lives of patients.

Surprisingly, there is low awareness and knowledge of narcolepsy among the general public, primary care physicians, and sleep specialists who responded to the AWAKEN survey.³ Recognizing symptoms early, confirming the diagnosis, and treating narcolepsy effectively remains a challenge.

Clinical features

The narcolepsy pentad consists of excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep.^{4–6} Cognitive dysfunction (“brain fog”) includes difficulty focusing, thinking, and concentrating along with automatic behavior and blurry vision.² Depression and anxiety affect both adults and children. Hyperactive/aggressive behavior, problems interacting with peers, and exhibiting psychotic features may be noted in children.

Recurrent sleep attacks lasting less than 10 minutes is the most common presentation, while cataplexy is the most pathognomonic. Extended sleep time, weight gain, and increased body mass index (BMI) may be noted in children.⁷ Cataplexy in adults involves paroxysmal episodes of loss of antigravity muscle tone, while the childhood phenotype consists of a complex movement disorder with persistent hypotonia and prominent buccofacial involvement (jaw opening, eyelid drooping, head rolling, or tongue thrusting movements), also called “cataplectic facies”.^{5,7} Cataplexy is triggered by laughing, sharp remarks, telling or listening to jokes, being tickled or tickling others, surprise, chuckling, meeting famous persons, feeling angry, stressed, or embarrassed/ashamed. Cataplexy attacks can occur spontaneously or during orgasm. Failure to recognize symptoms may delay diagnoses from 8.7 years up to 22.1 years.⁸

Diagnosis, classification, and epidemiology

The International Classification of Sleep Disorders (ICSD-3) classifies narcolepsy into Type 1 (narcolepsy with cataplexy) and Type 2 (narcolepsy without cataplexy).⁹ Type 1 is prevalent in 0.02%–0.18% in the US and Western European populations and in 0.16%–0.18% in the Japanese populations.⁹ The prevalence of Type 2 disease is uncertain, but a point prevalence of 20.5/10,000 has been suggested.⁹ The risk of narcolepsy Type 1 occurring in first-degree relatives of affected individuals is 1%–2%.⁹

Narcolepsy Type I criteria require cataplexy plus either 1) two sleep-onset REM periods (SOREMPs) on multiple sleep latency test (MSLT) or a SOREMP on nocturnal polysomnogram (PSG) plus one SOREMP on MSLT or 2) cerebrospinal (CSF) hypocretin-1 (hcr1) concentration ≤ 110 pg/mL or $< 1/3$ of mean values obtained in normal subjects with same

standardized assay in addition to EDS.^{9,10} Type 2 narcolepsy patients do not have cataplexy but have EDS confirmation by MSLT or PSG + MSLT and CSF hcr1 concentration is not measured, or CSF hcr1 > 110 pg/mL, or $> 1/3$ of mean values obtained in normal subjects.⁹ Differentiating narcolepsy from other disorders of excessive somnolence may be problematic.¹¹

Pathophysiology and genetics

Loss of up to 95% of hypocretin-producing neurons in the lateral hypothalamus resulting in low CSF hcr1 levels (Type I narcolepsy) appears to be the underlying major pathophysiology.^{10,12}

Narcolepsy is strongly associated with HLA DQB1*06:02, and genome-wide association studies have identified polymorphisms in the T-cell-receptor- α (TCRA) locus on chromosome 14, TNFSF4 (also called OX40L), Cathepsin H (CTSH) the purinergic receptor P2RY11, the DNA methyltransferase DNMT1, and carnitine palmitoyltransferase (CPT1B).^{12–14} TCRA encodes the α chain of the $\alpha\beta$ -heterodimer of the T-cell receptor on CD4⁺ T-helper cells and CD8⁺ T-cytotoxic cells.¹⁵ A third gene mutation is usually suggested as being needed for the autoimmune destruction of the hypocretin/orexin neurons. A combination of genetic and environmental factors could trigger immunological pathways through molecular mimicry or bystander activation, thereby leading to cell death of hypocretin-producing neurons.

Management

Narcolepsy is a life-long illness for which there is currently no cure. Treatment focuses on the following: 1) reduce EDS for fullest return of normal function; 2) minimize nocturnal sleep disruption; 3) treat cataplexy, hypnagogic hallucination (HH), and sleep paralysis (SP); and 4) consider risk–benefit ratio of the drug, cost of medications and ongoing care, and convenience of administration.¹⁶ Quality measures formulated for the care of patients with narcolepsy include three outcome measures – 1) reducing EDS, 2) improving diagnostic accuracy, and 3) reducing adverse events.¹⁷ Seven process measures were designated based on proportion of patients who met criteria that reflect these outcomes.¹⁷ “Functionality” is included in process 5, but it is unclear how “functionality” is defined/quantified and to what extent the patients and their caregivers contribute to this parameter.

Symptom-based current therapy

Treatment of narcolepsy patients is both a science and an art of balancing drug efficacy, convenience of administration, development of drug tolerance, managing drug effects, considering comorbidities, monitoring for evidence of drug abuse,

and, finally, choosing drugs partly based on insurance carrier's "allowed" drugs and patient's copay. It is important that clinicians are familiar with the various narcolepsy medications, mechanisms of action, dosing regimen, rationale for their use, and any drug–drug interactions.^{5,18–25} Table 1 shows various medications used to treat narcolepsy symptoms along with their relevant information. In addition to drug therapy, behavior therapy should be discussed with the patient and should include such topics as regular bedtimes, allowing enough time in bed at night, and taking scheduled naps during the day.

First-line therapy for daytime sleepiness

In adults with narcolepsy, modafinil or its *r*-enantiomer, armodafinil, are first-line therapies.¹⁶ Modafinil selectively activates wake-generating sites in the hypothalamus. Fos immunoreactivity is increased in the tuberomammillary nucleus and in the hypocretin neurons in the perifornical area of the hypothalamus.²⁶ Modafinil binds competitively to dopamine transporter in the cell membrane and is dependent on catecholaminergic (dopamine and adrenergic) signaling for wake promotion.²⁷ Modafinil is a very weak but also very selective dopamine transporter inhibitor.²⁷ Relative to other stimulants that act through catecholaminergic mechanisms, modafinil has low abuse potential, produces wakefulness with an attenuated compensatory sleep thereafter, and does not improve cataplexy. Modafinil (200–400 mg/d) improved daytime somnolence, increased mean sleep latencies on maintenance of wakefulness test (MWT), and improved scores on Clinical Global Improvement of Change (CGI-C).^{28–30} Split dosing (200 mg at 7 am and 200 mg at noon) may be more effective than a single dose in the morning; 600 mg/d split dosing may be needed by some.²⁸ Somnolence was very much improved in 80% and 92%, of users at doses of 400 and 600 mg, respectively.²⁸ Armodafinil has a longer duration of action compared to modafinil; at doses of 100–250 mg/d, mean ESS (Epworth Sleepiness Scale) decreased from 16.9 to 12.6 after 12 months of therapy and percentage of patients with Epworth Sleepiness Scale (ESS) <10 increased from 3.4% at baseline to 31.3%.³¹ "Worst fatigue" scores also declined from 7.8 (7.7 is severe) at baseline to 6.4 after a month's treatment.³¹ A cohort analysis of medical and pharmacy claims reported that mean monthly drug-specific pharmacy costs were lower for the armodafinil cohort vs modafinil cohort (\$11,363 vs \$13,775, $P=0.005$) and that lower total health care costs were also noted with armodafinil.³²

First-line therapy for EDS and cataplexy

Sodium oxybate is a metabolite of γ -amino butyric acid (GABA) that acts as putative neurotransmitter and neuro-modulator.^{16,33} It may also act via specific non-GABAergic

receptors; it also reduces dopamine release. Sodium oxybate (SXB) is first-line therapy for daytime sleepiness and cataplexy.^{16,33} It may improve HH and SP; it may also help consolidate nocturnal sleep. Compared to placebo, SXB effectively reduced daytime sleepiness and improved cataplexy.^{34–36} Sleep attack frequency and duration were significantly reduced at 6 and 9 gram doses. But effect on sleepiness takes at least 8 weeks before it becomes evident. The 9-gram dose significantly reduced nocturnal awakenings.³⁴ The addition of oxybate to modafinil resulted in the most improvement in subjective and objective measures of sleepiness when compared to modafinil alone in a level 1 study.³⁶

Although SXB is usually well tolerated, mild-to-moderate side effects can occur. Confusion, anxiety, and dizziness at the onset of therapy may be due to the dose being insufficient to induce sleep rapidly (up to 2 hours delay). A faster dose titration may be helpful. If nausea is prominent, adding flavored water may mask its salty taste; the dose may also be reduced. If nausea is severe, a 5-HT₃ antagonist, such as ondansetron, may be prescribed.

Second-line therapy for EDS

Stimulants have traditionally been used to alleviate daytime somnolence; they are indirect sympathomimetic compounds that share a benzene ring with an ethylamine side chain. These drugs include methylphenidate, amphetamines (dextroamphetamine or amphetamine–dextromethamphetamine combination, or amphetamine sulfate). These traditional stimulants increase the release of noradrenaline, dopamine, and serotonin; they inhibit reuptake of amines by dopamine transporter, and synaptic concentration of amines is higher. Wakefulness may be promoted by increased amine signaling through direct effects on the cortex or via subcortical pathways. Central nervous system (CNS) effects increase threefold with the *D*-isomer of amphetamine compared to the *L*-isomer. Rebound hypersomnia can occur at the end of transmitter availability for release. Amphetamine, methamphetamine, and methylphenidate have high abuse potential, and so tolerance may occur.^{19,20,24,25} For these reasons, they are used only under special circumstances. For disabling daytime sleepiness that does not respond to first-line therapy, an intermediate-release formulation of methylphenidate may be useful. For patients who are partial responders to modafinil or armodafinil but who have difficulty performing in the late afternoon, in addition to behavioral measures (two naps), a supplemental dose of a short-acting stimulant, (we prefer methylphenidate) may be added.

For patients who are nonresponders to modafinil/armodafinil or SXB and who have been using amphetamines for their EDS, switching to extended-release formulations

Table 1 Medications for narcolepsy

Drug (brand name)	Level of evidence ^a	Mechanism of action	Dose	Comments
Sodium oxybate (Xyrem)	Standard for cataplexy and EDS (I, IV), option for HH (IV) and SP (IV)	May act via GABA-B or specific GHB receptors; reduces DA release	Prepubertal children: Start at 3 g/night, split into two doses/night. Adolescents and adults, start at 4.5 g/night split into two doses (2.25 g initially and 2.25 g later). Increase by 1.5 g/night at weekly intervals. Usual dose range: 6–9 g/night for adolescents and adults and 4.5–6 g/night for prepubertal children. Always split dosing. Maximum dose: 9 g/night Note: If patient is taking divalproex, reduce SXB dose by at least 20% and monitor patient response. Start 37.5 mg bid with usual dose (75–100 mg bid) OR SL form: Start 37.5 mg q am; Usual dose: 75–150 mg ER. Maximum dose 375 mg for regular or 225 mg XL	FDA category C; not recommended during pregnancy and breast-feeding. Rapidly absorbed, 88% bioavailability; T_{max} =0.5–1.25 hours $T_{1/2}$ =0.5–1 hours. Elimination: lungs/urine. Side effects: Nausea, weight loss, headache, confusion, enuresis, sleep walking; sedation; memory impairment Other comments: Single pharmacy source (Xyrem REMS program) and regular follow-up (q 3 months) with provider. Patient education 1) Store securely out of reach of children/pets. 2) Prepare both doses before bedtime. Take first dose at least 2 hours after eating; dilute each dose in 60 cm ³ water. Take doses while lying in bed (likely to fall asleep within 5–15 minutes or may be dizzy). 3) Remain in bed after both doses. May need to set alarm for second dose 4) allow 6 hours after dose 2 before doing activities requiring alertness. 5) No alcohol or other sedative hypnotics or opioids while on SXB and inform about risk of respiratory depression. 6) Caution on operating dangerous machinery for at least 6 hours after taking dose 2. 7) Report to provider any symptoms of depression, anhedonia, significant appetite and weight change, psychomotor agitation or retardation, fatigue, suicidal ideation. 8) Higher risk of sleep walking, incontinence at night. 9) Caution regarding high salt load 10) Fine-tune timing and dose of medication – may need to either split into three doses, or delay first dose if no sleep onset difficulties but current dose insufficient to maintain entire night's sleep. Cost: A 500 mg/mL, 180 mL bottle is \$4,456 (10 day supply at 9 g/night or 15 night supply at 6 g/night).
Venlafaxine (Effexor)	Guideline for cataplexy (IV)	5-HT ≥ NE reuptake inhibitor		FDA category C; prescribe only if expected benefits outweigh risks. Caution regarding nursing; excreted in breast milk. Well-absorbed; active metabolite is ODV; plasma protein binding (27%, 30% for ODV; found in breast milk; extensive hepatic metabolism; elimination 87% in urine. $T_{1/2}$ =5 hours, $T_{1/2}$ =11 hours (ODV). Extended release: $T_{1/2}$ =10.7 hours, $T_{1/2}$ =12.5 hours (ODV). Side Effects: Nausea, dizziness, sexual dysfunction, dry mouth, headache, blood pressure increase, insomnia, anxiety headache, and loss of appetite. Other Comments: Very effective for cataplexy but has short $T_{1/2}$ so extended formulation is preferred. Has slight stimulant effect; Suicide precautions in depressed patients; Caution against coadministration with MAO) inhibitor. Caution regarding serotonin syndrome with other triptans, tramadol, and other serotonergic drugs. Cost for ER formulation: 37.5 mg (#30): \$124 75 mg (#30): \$139 150 mg (#30): \$151 Tablets (Venlafaxine HCl Oral) 25 mg (#100): \$195 37.5 mg (#100): \$200 50 mg (#100): \$206 75 mg (#100): \$218 100 mg (#100): \$232

Atomoxetine (Strattera)	Selective NE reuptake inhibitor; may selectively inhibit presynaptic NE transporter	Start 40 mg and titrate. Usual dose 80 mg/d Maximum dose: 95 mg/d	FDA category C. Prescribe to pregnant women only if expected benefits outweigh risks to fetus. Avoid atomoxetine during breast-feeding Well-absorbed; T_{max} = 1–2 hours. Highly plasma protein bound (98%). Metabolism: liver; 4-hydroxyatomoxetine (major active metabolite), N-desmethyl-atomoxetine. Elimination: $T_{1/2}$ = 5 hours. Urine (>80%), feces (<17%). Side Effects: Nausea, dry mouth, headache, increased BP and HR, erectile dysfunction; liver dysfunction Other: Not FDA approved for cataplexy. "Black box" warning regarding increased suicide risk especially in depressed children and adolescents. Monitor for allergic reactions; monitor BP and HR and signs/symptoms of cardiovascular events, liver injury, emergence of psychosis/or mania, clinical worsening, aggressive or unusual changes in behavior, hostility, urinary retention/hesitation, priapism, and other adverse reactions. Monitor growth in children. Cost: 10, 18, 25, 40 mg (#30): \$443–\$483 60 mg (#30): \$482 80 mg (#30): \$520 100 mg (#30): \$520 FDA category C; not recommended during pregnancy and lactation. C_{max} = 13.2 ng/mL, T_{max} = 8 hours, Metabolite (norfluoxetine) C_{max} = 9.7 ng/mL, T_{max} = 48 hours; found in breast milk; crosses the placenta. Metabolism: liver; demethylation into norfluoxetine (active metabolite). Elimination: kidney; $T_{1/2}$ = 3 days (acute administration), 4–6 days (chronic administration), 4–16 days (norfluoxetine, acute and chronic administration). Side effects: Nausea is most common, headache, dry mouth, less sexual dysfunction (erectile and ejaculation problems) than other SSRIs, diarrhea, weight gain Other: "Black box" warning regarding increased suicidal thinking and behavior in short-term studies of children and adolescents with major depression and other psychiatric disorders; advise families to monitor, observe, and report. Avoid alcohol and avoid abrupt discontinuation. May be helpful in narcolepsy patients with comorbid depression or anxiety. Caution regarding serotonin syndrome with other triptans, tramadol, and other serotonergic drugs. Cost: fluoxetine Hcl: 10 mg (#100): \$260 20 mg (#100): \$267 40 mg (#100): \$509 FDA category C. Prescribe to pregnant women only if expected benefits outweigh risks. Caution in nursing Absorption: T_{max} = 4.5–8.4 hours. Distribution: plasma protein binding (98%). Metabolized extensively by liver N-desmethyl-sertraline (metabolite). Elimination: urine (40%–45%), feces (40%–45%, 12%–14% unchanged); $T_{1/2}$ = 26 hours (sertraline), 62–104 hours (N-desmethylsertraline) Side effects: Nausea, sexual dysfunction, weight gain, diarrhea, headache Other: May be better tolerated compared to other SSRIs. Avoid alcohol. "Black box" warning regarding increased suicidal thinking and behavior in short-term studies of children and adolescents with major depression and other psychiatric disorders; advise families of need for observation and reporting to provider. Caution regarding serotonin syndrome with other triptans, tramadol, and other serotonergic drugs.
Fluoxetine (Prozac)	Least selective among specific serotonin reuptake inhibitors; (5-HT > NE = DA)	Start 20 mg q am. Usual dose (20–60 mg) Maximum dose: 80 mg	
Sertraline (Zoloft)	Second most potent serotonin uptake blocker and second most selective blocker of 5HT > NA; more potent DA uptake inhibitor than other SSRIs	50 mg 1x/d Usual dose (50–150 mg) Maximum dose: 200 mg	

(Continued)

Table 1 (Continued)

For cataplexy, HH, and SP				
Drug (brand name)	Level of evidence ^a	Mechanism of action	Dose	Comments
Protriptyline (Vivactil)	Guideline, Level IV, V	Tricyclic antidepressant. Monoaminergic uptake blocker (NE > 5HT > DA)	5–10 mg bid or tid (5, 10, 20 mg) Maximum dose: 30 mg/d	Safety not known in pregnancy and nursing. Safety and effectiveness not established in children. Well absorbed. T_{max} = 8–12 hours. Metabolism: liver; demethylation. Elimination: urine. Side effects: Dry mouth, constipation, urinary retention Other: Works immediately on cataplexy; but risk of rebound if suddenly stopped; avoid alcohol. "Black box" warning regarding increased suicidal thinking and behavior in short-term studies of children and adolescents with major depression and other psychiatric disorders; advise families of need for observation and reporting to provider. Cardiotoxicity, including heart block, arrhythmias, and sudden death; also higher risk of myocardial infarction; higher risk for seizures; caution against coadministration with and within 14 days of use of MAO inhibitors Cost: 10 mg (#30) is \$26. FDA category C. Prescribe to pregnant women only if expected benefits outweigh risks not for use during nursing.
Clomipramine (Anafranil)		TCA. Monoaminergic uptake blocker (5HT > NE > DA) Clomipramine affects 5HT reuptake, while its active metabolite, desmethylclomipramine, affects norepinephrine uptake; strong affinity for H1 receptor and M1 receptors	Start 50 mg q hora somni Usual dose (75–125 mg) Maximum dose: 250 mg/d	Different pharmacokinetic parameters depending on dose administered. Time to peak 2–6 hours; $T_{1/2}$ = 19–37 hours plasma protein binding (97%); found in breast milk; extensive hepatic metabolism; desmethylclomipramine (major active metabolite). Elimination: feces (24%–32%), urine (51%–60%); $T_{1/2}$ = 32 hours (clomipramine), 69 hours (desmethylclomipramine). Side Effects: Dry mouth, constipation, sweating, dizziness, weight gain, orthostatic hypotension. Other: Avoid alcohol. "Black box" warning regarding increased suicidal thinking and behavior in short-term studies of children and adolescents with major depression and other psychiatric disorders; advise families of need for observation and reporting to provider. Risk of rebound if suddenly stopped; dangerous in overdose; cardiotoxicity including heart block, arrhythmias, and sudden death; also higher risk of myocardial infarction; higher risk for seizures; "Caution with SSRI coadministration and when switching between TCAs and SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine); sufficient time must elapse before starting therapy when switching from fluoxetine (at least 5 weeks may be necessary). Neuroleptic malignant syndrome may occur with neuroleptics". ²⁸ (PDR) Cost: 60 capsules 50 mg is \$60
				FDA category C; should not be used during pregnancy and lactation T_{max} = 2–4 hours; delayed by 1 hour (fed). plasma protein binding (60%). Metabolism in liver elimination: urine (80%) and feces (1%), <10% unchanged; s-enantiomer $T_{1/2}$ = 3–4 hours vs r-enantiomer $T_{1/2}$ = 15 hours. Elimination of s-enantiomer is 3× faster than r-enantiomer.
For EDs				
Modafinil (Provigil)	Standard, Level I, II	Modafinil has r-enantiomer and s-enantiomer mechanism of action is still debated, but DA reuptake inhibition is suspected;	Starting dose 200 mg in am and increase to 400 mg either as single dose at 7 am or split dosing – 200 mg at 7 am and 200 mg at noon. Usual dose: 200 mg 2×/d	

	<p>does not bind to or inhibit enzymes for serotonin, DA, adenosine, galanin, melatonin, melanocortin, hypocrerin, benzodiazepine, orphanin, GABA transporters, NE, choline, GABA transaminase, and tyrosine hydroxylase. In vitro, it binds to DA transporter and inhibits DA reuptake.</p>	<p>Maximum dose: usually 400 mg/d; rare cases 600 mg/d</p>	<p>Readily absorbed. T_{max} =2 hours (fasted). Plasma protein binding (~ 60%). Metabolism in liver: (Modafinil) Feces (1%), urine (80%, <10% parent compound) $T_{1/2}$=15 hours.</p> <p>Side Effects: Headache, rhinitis, nervousness, nausea, dizziness, diarrhea, rare severe skin rash (Stevens-Johnson)</p> <p>Other:</p> <p>No antiepileptic activity. No changes in HR or BP. Generally low abuse potential, schedule IV drug. No evidence of tolerance. Effective or very effective in 60% of patients and partially effective in 20%.¹⁸ If insufficient efficacy or fading out in afternoon, supplement with regular methylphenidate is our preference; others supplement with short acting dextedrine.</p> <p>Caution about increased risk of pregnancy when using steroidal contraceptives and for 1 month after discontinuation of therapy. If switching from stimulants to modafinil, no washout period needed, but if patient has cataplexy, the addition of specific antiepileptic medication may be needed</p> <p>Cost:</p> <p>Modafinil generic 100 mg (#30): \$662 200 mg (#30): \$1,000.08 Provigil 100 mg (#30): \$1,020.60 200 mg (#30): \$1,524.24 FDA Category C; should not be used during pregnancy and lactation r-enantiomer</p> <p>Readily absorbed. T_{max} =2 hours (fasted). $T_{1/2}$ 10–14 hours.</p> <p>Plasma protein binding (~ 60%).</p> <p>Side Effects: Headache, rhinitis, nervousness, nausea, dizziness, diarrhea, rare severe skin rash (Stevens-Johnson)</p> <p>Other:</p> <p>Caution about increased risk of pregnancy when using steroidal contraceptives and for 1 month after discontinuation of therapy</p> <p>If switching from stimulants to modafinil, no washout period needed, but if patient has cataplexy, the addition of specific antiepileptic medication may be needed.</p> <p>Cost:</p> <p>Armodafinil generic 50 mg (#30): \$218 150 or 200 or 250 mg (#30): \$656 FDA Category C;</p> <p>Should not be used during pregnancy unless risk of postponing treatment is higher;</p> <p>Excretion not well characterized; may be risky for nursing child</p> <p>Not recommended in patients <6 years;</p> <p>Plasma protein binding (10%–33%); Rapid and extensive metabolism to α-phenyl-2-piperidine acetic acid (ritalinic acid) (main deesterified metabolite). Elimination: (immediate-release) Urine (78%–97% metabolites [60%–86% ritalinic acid], <1% unchanged), feces (1%–3% metabolites). $T_{1/2}$ =3–4 hours (ritalinic acid), 2.4 hours (children), 3.3 hours (adults).</p> <p>Onset 20–30 minutes for IR and ER formulations; duration of action for IR is 3–5 hours; ER (Metadate CD, Ritalin LA) is 6–8 hours; (Concerta ER) duration is 12 hours; (Ritalin-SR) tablet duration is 2–6 hours; $T_{1/2}$ is IR is 3 hours; $T_{1/2}$ for (Metadate CD) is 6.8 hours; $T_{1/2}$ for Ritalin LA (1.5–4 hours)</p>
<p>Armodafinil (Nuvigil)</p>	<p>Standard, Level I</p>	<p>Usual 150–250 mg given as single morning dose Maximum dose: 250 mg/d</p>	<p>Mode of action unclear; it is the r-enantiomer of modafinil (see previous row)</p>
<p>Methylphenidate 3 forms: 1. Immediate release (methylin, ritalin) 2. Extended release (metadate CD, ritalin LA, concerta)</p>	<p>Guideline, Level II, V</p>	<p>Start with 5 mg am and 5 mg pm (no later than 3 pm); increase by 5–10 mg weekly to control symptoms, then switch to either ER or SR and use IR as add-on at noon for pm sleepiness. Usual dose: 20–40 mg/d in adults Maximum dose: 60 mg/d Usual dose: 5–20 mg/d in children</p>	<p>Increase DA transmission presynaptically and inhibit DA reuptake > reuptake of NE and 5-HT by DAT</p>

(Continued)

Initial: 10 mg/d	Not recommended for children with known structural cardiac defects or in patients with advanced symptomatic cardiovascular disease, moderate-to-severe hypertension, hyperthyroidism, and history of drug use. Caution against coadministration or within 14 days of use of MAO inhibitor. Also, monitor for psychosis, mania, seizures, aggression, anorexia, addiction, cardiovascular effects including MI, sudden death.
Titrate: May increase in increments of 10 mg at weekly intervals until optimal response is obtained	Cost:
Give first dose on awakening; additional doses (1 or 2) at intervals of 4–6 hours	Adderall XR 5–30 mg (available as 5, 10, 15, 20, 25, 30) (#100): \$855
When daily dose has been established, switch to Adderall XR 20 am + 10–30 mg regular	Regular formulation 5–30 mg (#100): \$613.
Maximum is 60 mg/d	Generic 5–30 mg regular formulation (#100): \$17
Available as 4.5 mg and 18 mg tablets. Start at 9 mg/d and increase weekly by 9 mg. Usual dose 18–36 mg	Not recommended during pregnancy unless benefit exceeded the risk.
Maximum 36 mg/d	No FDA classification
inverse agonist of the histamine H3 receptor	Side Effects: Insomnia headache, nausea, anxiety, irritability, vertigo, depression, tremor, tiredness, dyspepsia. Serious but rare side effects are abnormal loss of weight and spontaneous abortion.
Not AASM rated	Other:
Not AASM rated, Class II, Class IV	Approved in EU for treatment of narcolepsy with and without cataplexy; improves EDS, attention; reduces cataplexy frequency by 60%. It may lower efficacy of oral contraceptives, and so alternate means of contraception should be done. Supratherapeutic doses led to slight prolongation of QTc interval
Imidazolidine derivative; weak DA-releasing agent but high affinity DA and NE reuptake blocker.	B class. Not recommended in pregnant women
Start at 1 mg/day; usual dose 2–3 mg/d	T _{1/2} 10 hours
	Side Effects: Dry mouth, nervousness, nausea, increased GI upset, weight gain, constipation, headache, dizziness, tachycardia
	Other:
	Class II evidence effective in reducing sleepiness at 2+ 2 mg/d in 53%–60% patients; Class IV evidence of significant improvement of sleepiness in 50%–75% cases. Less abuse potential than amphetamines; available in EU but not US

Notes: AASM Classification of Evidence for patient-care strategies (Morgenthaler PP). Standard: generally accepted patient-care strategy that reflects a high degree of clinical certainty. Uses level I evidence or overwhelming level II evidence. Guideline: a moderate degree of clinical certainty that implies the use of level II evidence or a consensus of level 3 evidence. Option: reflects uncertain clinical use that implies either inconclusive or conflicting evidence. Evidence levels and study design: I – Randomized, well-designed trials with low α and β error; ^a or meta-analyses of randomized controlled trials with homogeneity of results. II – Randomized trials with high α and β error; methodological problems, or high quality cohort studies. III – Nonrandomized concurrently controlled studies (case-control studies). IV – Case-control or cohort studies with methodological problems, or case series. V – Expert opinion, or studies based on physiology or bench research. FDA Pregnancy Classification: A (controlled studies in humans have shown no risk); B (controlled studies in animals have shown no risk); C (uncontrolled studies in animals have shown risk according to their embryo toxic and teratogenic effects); D (controlled studies in humans have shown risk according to their embryo toxic and teratogenic effects). Data from: PDR.net,²⁴ UpToDate,^{2,12} Wise et al.¹⁹ Drugs.com,²⁵ PDR.net.²⁴

Abbreviations: BP, blood pressure; Cmax, maximum concentration; DA, dopamine; EDS, excessive daytime somnolence; FDA, US Food and Drug Administration; GABA, γ -amino butyric acid; GHB, γ -hydroxy butyric acid; HH, hypnagogic hallucination; HR, heart rate; MAO, monoamine oxidase; MI, myocardial infarction; NA, norepinephrine; NE, norepinephrine; ODV, O-desmethylvenlafaxine; SP, sleep paralysis; SSRI, selective serotonin reuptake inhibitor; SXB, sodium oxybate; TCA, tricyclic antidepressant; T_{1/2}, half-life; AASM, American Academy of Sleep Medicine; DAT, dopamine transporter; 5-HT, 5-hydroxytryptamine; HCL, hydroxy chloride; IR, immediate release; ER, extended release; PDR, Physician's Drug Reference; REMS, rapid eye movement sleep; SR, sustained release. Tmax, time at which maximum concentration of the drug is observed.

provide longer duration of action and help alleviate concerns about recreational abuse. MES-amphetamine extended release (Adderall XR) combines the neutral salts of dextro-amphetamine and amphetamine and uses drug-containing beads for a double-pulsed delivery of amphetamines resulting in longer duration of action. This makes it suitable for administration at home with parental supervision and relieves the adolescent patient of the need to take additional medication outside of the home. Another once-daily amphetamine medication is the D-amphetamine prodrug lisdexamfetamine dimesylate (LDX; Vyvanse, Shire Pharmaceuticals, Dublin, Republic of Ireland). Common side effects are reduced appetite and insomnia. Children and adolescents taking LDX may have lower gains in weight, height, and BMI.

Second-line therapy for cataplexy, SP, HH

Antidepressant reuptake inhibitor medications or tricyclic antidepressants are second-line alternatives to treat cataplexy, SP, and HH. Drug categories are: 1) Serotonin–norepinephrine reuptake inhibitors – venlafaxine, which has a short duration of action, but extended-release formulation is available; desmethyl venlafaxine or atomoxetine are alternatives, 2) selective serotonin reuptake inhibitors (fluoxetine), or 3) tricyclic antidepressants (protriptyline, imipramine, or clomipramine) (Table 1). Of the above medications, venlafaxine is our preferred add-on to SXB.

Not included in Table 1 is reboxetine, a selective norepinephrine reuptake inhibitor that reduced cataplexy in 12 subjects with Type 1 narcolepsy; this medication is, however, not available in the United States.¹⁶ Selegiline, a MAO Type B inhibitor, at a dose of 10 mg 2 times/d suppressed REM sleep and increased sleep-onset and REM-onset latencies on both PSG and MSLT, and patients reported significant improvement in daytime sleepiness, reduced number of naps needed, and reduced frequency of cataplexy.³⁷ Although selegiline is listed as an option for narcolepsy therapy,¹⁶ it is not usually prescribed because the high dose required makes it a nonselective MAO inhibitor with increased risk of food/drug interactions.

A large proportion of narcolepsy patients complain about cognitive issues (50%)² and severe fatigue (45%–62.5%);^{2,38} mood disorder (27%)³⁹ and anxiety (21.1%)³⁹ are also common. Fatigued patients have higher depression scores, but ESS scores do not differ from the nonfatigued narcoleptics. Severe fatigue significantly correlated with more functional impairment; the most impaired domains were in mobility, ambulation, social interaction, recreation, and pastimes.³⁸ Complaints of fatigue, anxiety, or depression should be investigated and addressed.

Other comorbidities

Hypercholesterolemia (odds ratio [OR], 1.51), diseases of the gastrointestinal tract (OR, 3.27), heart disease (OR, 2.07), upper respiratory tract diseases (OR, 2.52), and hypertension (OR, 1.32) are frequently observed;³⁹ care for these conditions have to be coordinated with primary and specialty care. Obesity affects more than 50% of children with narcolepsy; 9% of obese children and 3% of nonobese children with narcolepsy met sleep apnea criteria.⁴⁰ Weight management programs with diet and exercise should be undertaken, and sleep apnea should be treated before starting SXB.

Nocturnal sleep can be disrupted by periodic leg movements of sleep (PLMS); associated restless legs syndrome (RLS); disturbing dreams sometimes associated with abnormal behavior, and thus called “REM sleep behavior Disorder (RBD)” despite the very different etiologic background and pathophysiology of the classical RBD syndrome; nocturnal eating disorder; and nocturnal awakenings. RLS symptoms can be moderately severe, occur every night, and may be present diurnally. RLS, PLMS, and violent dreaming may be exacerbated by SXB or antidepressant usage and may require a change in therapy, behavioral measures, and iron supplementation (if serum ferritin levels are low). These associated comorbidities may require specific syndromic treatments.

Narcolepsy management during pregnancy

Management of narcolepsy during pregnancy requires a full discussion with the patient of risks and benefits of continued use of their usual narcolepsy drugs during pregnancy, delivery, and while nursing compared to risks of not taking their usual drugs. Most of the standard narcolepsy therapies are FDA pregnancy category C drugs (Table 1). Thorpy et al⁴¹ reviewed the literature and conducted a survey that revealed variability in how pregnant narcoleptics are managed. Most narcolepsy patients have vaginal deliveries without complications; although some required cesarean section, surgical or anesthetic risk did not increase.⁴¹

New developments and future therapies

Emerging therapy for narcolepsy focuses on a multipronged approach: nonhypocretin therapies, hypocretin-based therapy, and immunotherapy to prevent hypocretin neuronal loss.

Nonhypocretin therapies

Nonhypocretin therapies include 1) histamine receptor H3 antagonists/inverse agonists, 2) novel monoaminergic reuptake inhibitors that may target specific neurotransmitters, 3) drugs developed to treat other conditions like idiopathic hyper-

somnia or attention-deficit-hyperactivity-disorder (ADHD) or stimulant abuse that may target multiple reuptake sites, 4) novel slow-wave sleep (SWS) enhancers may help consolidate disrupted night sleep, 5) thyrotropin-releasing hormone (TRH) analogs, and 6) new formulations and/or delivery systems or pediatric indications for existing medications.

Histamine receptor antagonists

Histaminergic neurons in the posterior hypothalamus stimulated by hypocretin neurons, control wakefulness, feeding, learning, and memory via four aminergic G-protein-coupled receptors: H1, H2, H3, and H4.^{42,43} H3 acts as an autoreceptor and as a presynaptic heteroreceptor.⁴³ H3 suppresses histamine neuronal firing and inhibits synthesis and release of histamine. H3 also inhibits the release of neurotransmitters acetylcholine, noradrenaline, and dopamine.⁴³

Pitolisant (Wakix, Bioprojet Pharma, Paris, France) previously called (BF2.649) is an inverse agonist of the H3 receptor.⁴⁴⁻⁴⁶ Oral pitolisant has orphan drug status in the EU and in the US. Pitolisant received approval in EU in March 2016 for the treatment of adults with narcolepsy Type I or Type II.^{45,46} Pitolisant is initiated at 9 mg/d and titrated weekly to a maximum of 36 mg/d; dosage can also be reduced by 4.5 mg/d if needed. The maximum dose is 18 mg/d if renal or moderate hepatic impairment are present.⁴⁵ It is contraindicated if there is severe hepatic impairment. As shown in Phase III trials, HARMONY [-I, -Ibis, -III], pitolisant reduced daytime sleepiness (with ESS and MWT confirmation), improved level of attention on sustained attention to response tasks – No-Go index, and decreased frequency of cataplexy attacks.⁴⁴⁻⁴⁶ Pitolisant reduced ESS to -5.8 ± 6.2 compared to -6.9 ± 6.2 with modafinil and -3.4 ± 4.2 with placebo, when compared to baseline values.⁴⁴ CGI-C analysis showed 73%, 86%, and 56% improvement for pitolisant, modafinil, and placebo, respectively.⁴⁴ In HARMONY CTP (NCT 1800045), pitolisant resulted in 64% reduction of cataplexy episodes, significant improvement in ESS scores, and increased MWT sleep latency by 80%. No drug abuse potential was observed. Much higher doses (108–216 mg) produced slight prolongation of QTc interval. Pitolisant may reduce efficacy of oral contraceptives, and so alternative methods of contraception should be utilized. A double-blind trial to evaluate safety and efficacy in narcoleptic children 6 years to less than 18 years of age (P11-06, NCT02611687) followed by a prolonged open-label period trial (P11-11) is being conducted.⁴⁷ A 12-month long-term safety and efficacy study, HARMONY III, (NCT01399606) is ongoing. There are also trials with pitolisant as an add-on drug: 1) to sodium oxybate in HARMONY IV (NCT 01789398) and

2) to modafinil in (NCT01067235); both trials have been completed but results are not available.⁴⁷

Other histamine receptor antagonists

Several H3 antagonists have advanced to clinical trials with completion of Phase I studies (BF2.649, PF-03654746, GSK189254, GSK239512, MK-0249, MK-3134, JNJ-17216498, and ABT-286) to evaluate the pharmacokinetics and tolerability of single- and multiple-dose administration to treat various neurologic conditions.⁴⁸ An open-label, dose-escalation study with a double-blind, randomized, placebo-controlled withdrawal to examine the effects of H3 antagonist GSK189254 in narcolepsy patients was terminated, and the study results are not posted. The efficacy of H3 antagonists in addressing insomnia issues in narcolepsy has not been determined.

JNJ-17216498 (NCT00424931) completed Phase II study enrolled 16 patients to evaluate efficacy of a single dose of JNJ-17216498 (10 mg, 50 mg) compared to placebo and modafinil 200 mg 2 times/d, using polysomnography, MWT, and questionnaires.⁴⁷ Results are not yet available.

JNJ 28583867 is a potent H3 antagonist and is a highly selective inhibitor of serotonin transporter. In rats, it significantly increased extracellular levels of serotonin with smaller increases of norepinephrine and dopamine; it decreased NREM sleep, increased wake-after-sleep onset, and potently suppressed REM sleep.⁴⁹ It has not been tested in humans.

PF-03654746 (NCT01006122) has been tested in a randomized, double-blind, placebo-controlled, crossover assignment, safety and efficacy study with starting dose of 0.25 mg titrated to a maximum of 2 mg to evaluate effects on daytime somnolence using MWT 20-minute test. The results are available at clinicaltrials.gov but have not been published. Changes in MWT 20-minute test mean sleep latency did not appear to significantly differ from controls, and changes in cataplexy episodes from baseline were no better than the placebo group. These results suggest that PF-03654746, at the doses utilized, may not be useful in the treatment of either EDS or cataplexy in narcolepsy.⁴⁷

Novel monoaminergic reuptake inhibitors

Dopamine reuptake inhibitors are likely to be mild stimulants, while inhibitors of adrenergic reuptake may improve cataplexy. Drugs that target multiple reuptake sites that have been developed for other conditions like idiopathic hypersomnia or ADHD or treatments for stimulant abuse may subsequently be considered for narcolepsy treatment.

JZP-110 (ADX-N05) is a phenylalanine-derived ([R]-2-amino-3-phenylpropylcarbamate hydrochloride)

wake-promoting agent that is a dopamine and norepinephrine reuptake inhibitor. It does not release monoamines nor does it inhibit serotonin reuptake; it also does not inhibit MAO-A enzymatic activity.⁵⁰ In randomized, double-blind, placebo-controlled clinical trials, JZP-110 underwent Phase II (NCT01485770)⁵⁰ and Phase II B (NCT01681121)⁵¹ testing in adults with narcolepsy with and without cataplexy.^{50,51} After 4 weeks of JZP-110 at doses of 150 mg (weeks 1, 3) and 300 mg (weeks 2, 4), ESS decreased -6.7 in the treatment group ($n=33$) compared to -2.4 in the placebo group ($n=33$). MWT (40-minute test) mean-sleep-latency (MWT SL) after 2 weeks at the 300 mg dose was 12.7 ± 10.6 minutes longer compared to placebo results of 0.9 ± 6.0 minutes.⁵⁰ A parallel group trial using 150 mg \times 4 weeks and 300 mg \times 8 weeks showed significant improvements in MWT SL, ESS, and CGIC in treated patients ($n=44$) compared to placebo ($n=49$). Figures 1–3 are from the Ruoff et al's⁵¹ study demonstrating the effects of JZP-110 on MWT, ESS, and CGIC. The results from these two studies are encouraging and demonstrate JZP-110 may be a new effective treatment for daytime somnolence. JZP-110 is currently recruiting for a Phase III Safety and Efficacy trial (NCT02348593) of 75, 150, and 300 mg of JZP-110 compared to placebo.⁴⁷

GABA modulation

GABA is an inhibitory neurotransmitter that binds to specific receptors in the plasma membrane of both pre- and postsynaptic neurons causing an influx of chloride ions intracellularly or an efflux of potassium extracellularly. There are two general classes of GABA receptors: GABA_A receptors are part of a ligand-gated ion channel complex while GABA_B receptors are G-protein-coupled receptors that open or close ion channels via G proteins.

GABA_B receptor agonists

At pharmacological doses, γ hydroxybutyric acid (GHB) binds to GABA_B receptors. GHB is a GABA_B receptor agonist; its sodium salt, sodium oxybate, is used to treat the various symptoms of narcolepsy. Baclofen is another GABA_B receptor agonist. A parallel group study in teenagers with narcolepsy Type 1 compared SXB 3–6 g/night ($n=13$) treatment to baclofen at 5–20 mg/night ($n=13$); each medicine was added to the patients' usual dose of modafinil (300 mg/d). Both SXB and baclofen increased delta sleep and total sleep time. However, baclofen had no significant effect on daytime sleepiness nor on cataplexy, while SXB improved both daytime sleepiness and cataplexy, suggesting that another mechanism other than GABA_B may be at work.⁵² Renewed interest in other GABA_B agonists as potential

therapy for narcolepsy was fueled by different findings in narcoleptic mice using R-baclofen. R-baclofen has a much higher affinity (three-fold) for GABA_B receptor than the racemic version. In murine narcolepsy, R-baclofen increased NREM sleep time and deepened sleep intensity and consolidation during the light period; wake-bout duration increased and cataplexy decreased during the subsequent dark period to a greater extent than with GHB.⁵³ These results are only positive in narcolepsy-rodent models, and further studies in human narcolepsy are needed. Several preparations of R-baclofen (arbaclofen, STX209) have already been studied in other conditions such as multiple sclerosis, autism, and gastroesophageal reflux disease; results from these studies could help in designing studies to test R-baclofen's efficacy and safety in narcolepsy.

GABA_A receptor modulators

In some patients with hypersomnia, CSF examination showed potentiation of GABA_A receptors. On this basis, clinical trials using GABA_A receptor antagonists (clarithromycin, flumazenil) have been undertaken to determine whether somnolence is improved.

Clarithromycin is an antibiotic as well as a negative allosteric modulator of GABA_A receptors. Clarithromycin 500 mg twice a day for 5 weeks significantly reduced daytime sleepiness with a four-point reduction in ESS, significantly improved Functional Outcomes of Sleep Questionnaire scores, and significantly improved SF-36 energy section scores in 20 hypersomnolent nonnarcoleptic-cataplectic patients, 4 of whom had Type 2 narcolepsy, when compared to the placebo group. There was no difference in median reaction time on the psychomotor vigilance task between the two groups.⁵⁴ The improvements seen with clarithromycin therapy appear modest, and chronic use of an antibiotic with possible emergence of drug-resistant bacteria does not appear warranted.

Flumazenil is another GABA_A receptor antagonist. A trial (NCT01183312) utilized retrospective chart review of 153 patients treated with flumazenil transdermal cream and/or sublingual flumazenil titrated up to 12 mg 4 \times /d.⁵⁵ The study showed symptomatic reduction in sleepiness in 62.8% of patients, with mean reduction of ESS by 4.7 ± 4.7 . Patients in this study either had previously used or were using wake-promoting drugs. Female sex and the presence of sleep inertia differentiated responders from nonresponders.⁵⁵ Flumazenil may be useful for recalcitrant somnolence in female narcoleptics who do not respond to standard stimulant therapy.

BTD-001 (NCT02512588) is currently recruiting for a Phase II multicenter dose-finding study (ARISE 201) of a

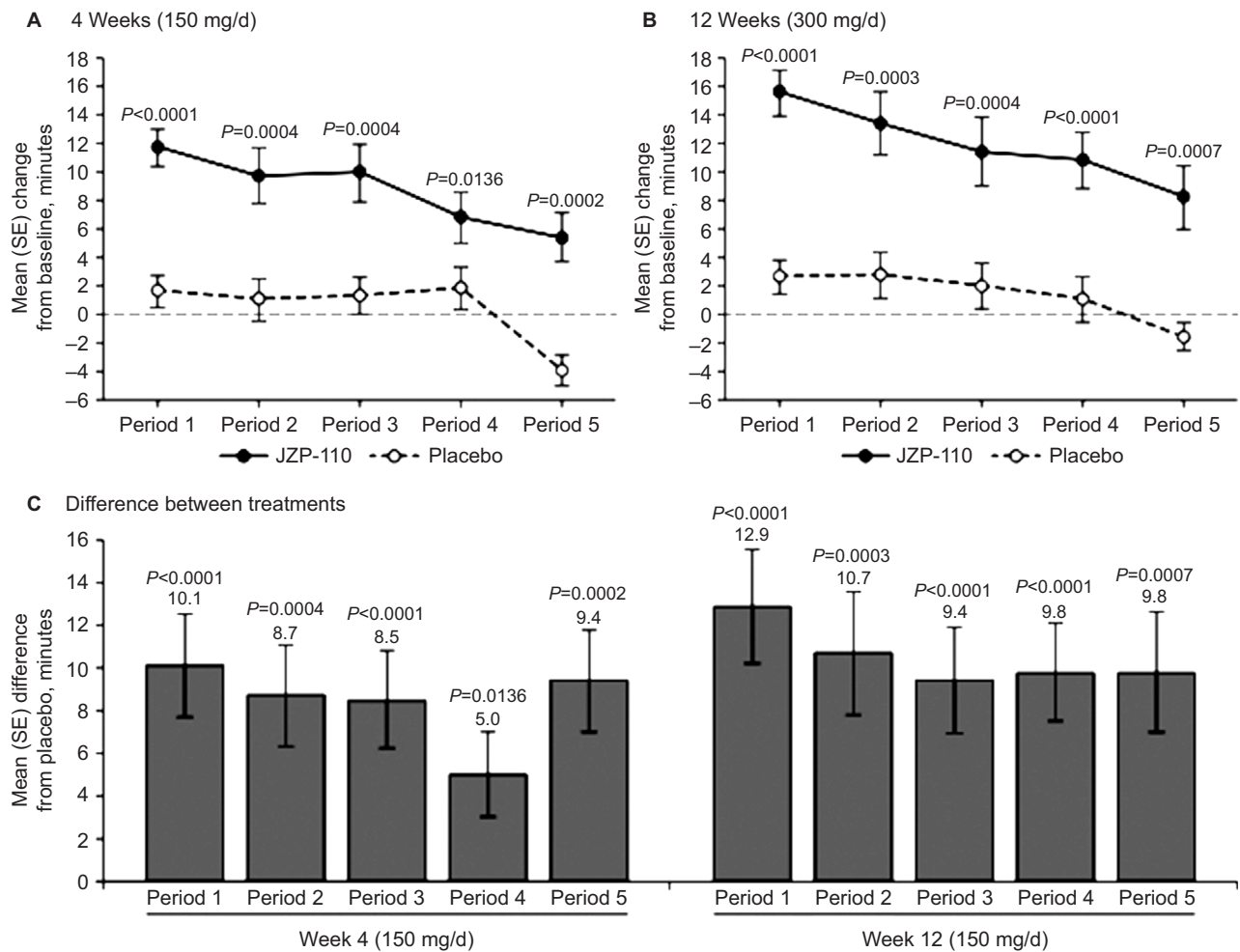


Figure 1 Mean change from baseline in sleep latency on MWT for each of the individual periods at 4 weeks on 150 mg/day (A) and 12 weeks on 300 mg/day of JZP-110 (B) and mean difference in change from baseline between JZP-110 and placebo at 4 weeks and 8 weeks (C).

Note: Reproduced from Ruoff C, Swick TJ, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016;39(7):1379–1387, by permission of Oxford University Press.⁵¹

Abbreviations: MWT, maintenance of wakefulness test; d, day; SE, standard error.

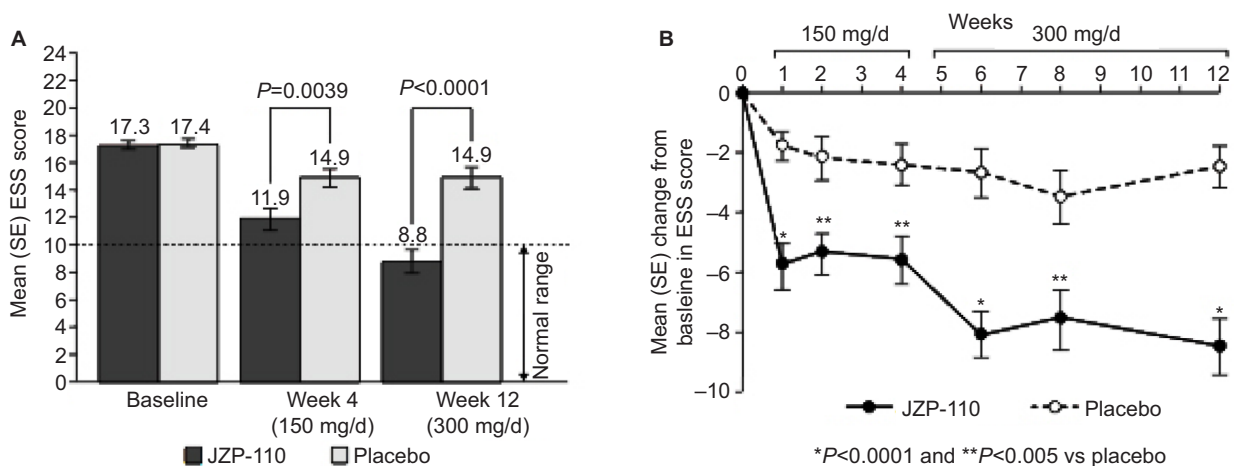


Figure 2 Change in ESS scores with JZP-110 compared to placebo

Notes: Change in ESS scores (A) absolute ESS scores at weeks 4 and 12 compared to baseline. Horizontal broken line represents the threshold for normal ESS score (B) represents the change in score with JZP-110 at doses of 150 mg/d for 4 weeks and 300 mg/d for 8 weeks. Reproduced from Ruoff C, Swick TJ, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016;39(7):1379–1387, by permission of Oxford University Press.⁵¹

Abbreviations: ESS, Epworth Sleepiness Scale; SE, standard error; d, day.

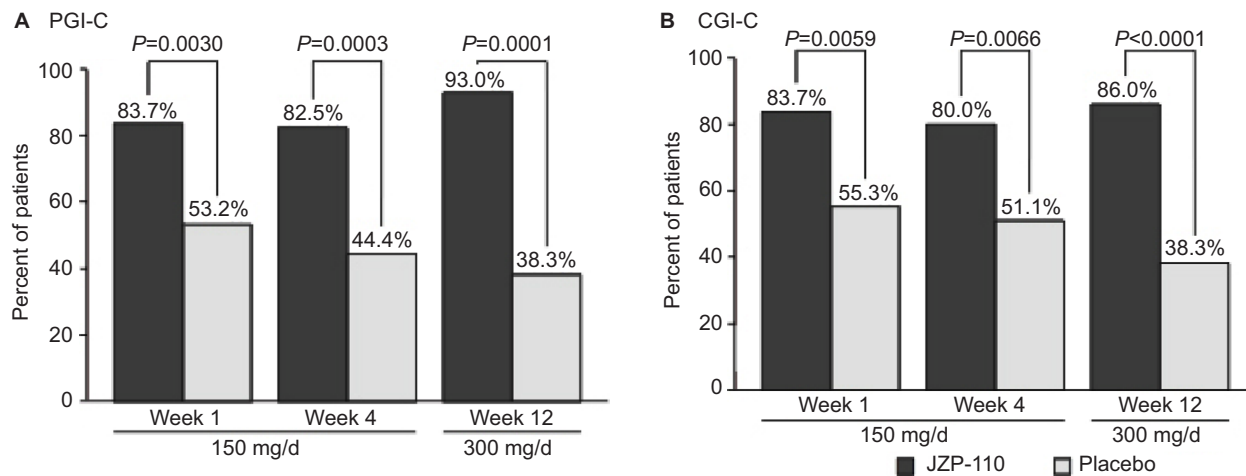


Figure 3 Percentages of patients who achieved improvement on global impression of change measures at weeks 1, 4, and 12 from the patient and clinician's perspective.

Notes: (A) PGI-C (B) CGI-C. Reproduced from Ruoff C, Swick TJ, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep*. 2016;39(7):1379–1387, by permission of Oxford University Press.⁵¹

Abbreviations: CGI-C, clinical global impression of change; d, day; PGI-C, patient global impression of change.

pentylene tetrazole medication to treat somnolent patients with narcolepsy or idiopathic hypersomnia. Pentylene tetrazole is a GABA_A receptor antagonist.⁴⁷

Slow-wave sleep enhancers

Narcolepsy is associated with sleep fragmentation, frequent awakenings, and stage shifts; disrupted nocturnal sleep may add to daytime fatigue. Theoretically, drugs that promote slow-wave sleep could be helpful, but they have not undergone clinical trials for this indication, except for SXB. Tiagabine is an inhibitor of GAT-1, a transporter protein that promotes GABA reuptake into the presynaptic terminals; GAT-1 inhibition results in increased synaptic levels of GABA. In sleep-deprived normal subjects, tiagabine increased slow-wave sleep by 41% and improved ratings of the restorative nature of sleep.⁵⁶ Other potential SWS enhancers include gaboxadol, a selective extrasynaptic GABA_A agonist, gabapentin and pregabalin, both of which act on $\alpha 2$ - δ voltage-gated calcium channels, and trazodone, which acts on multiple receptors including 5 HT₂ antagonist.⁵⁶ More research is needed to determine the usefulness of these drugs in consolidating nocturnal sleep in narcolepsy patients.

“Standard Drugs for Narcolepsy, new indications, and new formulations” provide other avenues to pursue treatment modalities.

A recent hypothesis based on animal studies is that modafinil acts as a cellular-coupling enhancer in glial cells through modulation of gap junctions constituted by connexins.⁵⁷ Connexins are gap junction proteins expressed by glial cells. In mice, flecainide is an astroglial connexin inhibitor that enhances the awakening and procognitive effects of modafinil.⁵⁷ Modafinil combined with flecainide reduced the cataplexy-like phenotype in orexin knockout mice.⁵⁷ A Phase II trial of THN

102 (NCT02821715) is not yet open for recruitment; it is a randomized, placebo-controlled, three-way crossover trial that will compare a combination drug (300 mg modafinil/3 mg flecainide) to 300 mg modafinil in narcoleptic patients.⁴⁷

A Phase III open-label, flexible-dose trial of the safety and effectiveness of modafinil treatment for excessive sleepiness (dose of 100 mg titrated to maximum of 400 mg/d) in children 6–16 years of age has concluded, but results have not been posted. (NCT00214968).⁴⁷

Sodium oxybate use in pediatric patients has been investigated. A retrospective study of tolerance and efficacy of SXB in childhood narcolepsy with cataplexy (n=27, mean age: 10.3±3.2) showed that 18/27 had been prescribed SXB as their first anticataplectic drug. SXB treatment allowed withdrawal from other medications (7/10 patients were on venlafaxine, 5/24 patients on modafinil). A large majority of SXB-treated patients reported improvements in cataplexy, daytime sleepiness, and nocturnal sleep. Three patients reported improved attention and learning in school. Main side effects were weight loss, headache, nausea, disturbed nocturnal sleep, irritability, parasomnias (sleep walking, sleep talking, enuresis), and/or daily episodes of sleep drunkenness. About 15% (n=4) required complete SXB withdrawal because of sleep loss and persistent nausea.⁵⁸ The Xyrem Pediatric Narcolepsy Study (NCT02221869) is a 52-week, Phase III randomized, double-blind open-label multicenter (US and EU) clinical trial that will evaluate safety and efficacy and pharmacokinetics in pediatric patients (ages 7–17) with narcolepsy with cataplexy. This trial is active but not currently enrolling.⁴⁷ JZP 13-005 (CT2014-001389-93) is an open label Xyrem pharmacokinetic evaluation and safety extension in children and adolescents under 18 years of age

and is ongoing. JZP-386 is deuterium-modified analog of sodium oxybate; it is a dopamine receptor agonist. Results from a Phase I clinical trial in 30 subjects showed a higher serum concentration and increased pharmacodynamics effect when compared to SXB-Xyrem. A Phase IV open-label study (NCT00345800) to evaluate the effects of SXB-Xyrem on the endocrine system has completed, but results have neither been posted nor published.⁴⁷

A new formulation of SXB that will allow single dosing at night is being tested. This study (NCT02720744, FT218) conducted by Flamel Ireland is not yet open for recruitment. It is a double-blind, randomized, placebo-controlled, two-arm, multicenter study to assess the efficacy and safety of a once-nightly formulation of sodium oxybate for extended-release oral suspension using micropump technology (doses of 4.5, 6.0, 7.5, and 9.0 g) with regard to daytime somnolence and cataplexy.⁴⁷ If effective and safe, this formulation may simplify administration and mask the taste of SXB. Flamel also has “trigger-lock technology” (although not in this study) that can alleviate abuse potential concerns.

TRH and its analogs

TRH is a tripeptide that has endocrinologic and neuromodulatory actions. It stimulates cholinergic turnover, increases neurotransmission of dopamine and norepinephrine, depolarizes spinal motor neurons, promotes CNS arousal, modulates pain perception and locomotor activity, regulates respiration, and modulates seizure threshold.^{59–61} Hypocretin cells are modulated by TRH. Two receptors that are targets for TRH are TRH-R1 and TRH-R2. TRH-R2 is believed to be responsible for neuropharmacological actions, while TRH-R1 is responsible for endocrinologic effects.⁶² Clinical applications for TRH are limited due to its short plasma half-life of 5 minutes, low intestinal and CSF permeability, and endocrine side effects.⁶¹ Modifications of the C or N terminals have yielded several TRH analogs of varying potencies (CG-3703, CG-3509, and TA-0910) that have been used intravenously in canine narcolepsy; these TRH analogs increased wakefulness, suppressed both slow-wave sleep and REM sleep, and significantly reduced cataplexy.^{60,61} Drug tolerance was noted with CG-3703 usage after a week of therapy, requiring dose adjustment.⁶¹ Although studies in canine narcolepsy have been somewhat successful, we are not aware of any clinical trials of these drugs in human narcolepsy. Researchers have synthesized metabolically stable and more potent selective TRH prodrugs and analogs – taltirelin [TA-0910], montirelin [CG-3703], azetirelin [YM-14673], JTP-2942, DN 1417, MK-771, and posatirelin [RGH-2202] – which have potential applications in various diseases, such as depression,

epilepsy, spinocerebellar degeneration, amyotrophic lateral sclerosis, Parkinson’s disease, schizophrenia, Alzheimer’s disease, and cancer-related fatigue.⁶² Rovatirelin is another TRH analog that binds to TRH receptor with greater affinity than taltirelin (a drug approved for spinocerebellar degeneration treatment) and has increased noradrenergic activity and increased locomotor activity.⁶³ JAK4D binds to a new TRH receptor subtype in human hippocampal tissue and reduced cognitive defects in rat model of neurodegeneration; it also protected against neuronal damage.⁶⁴ TRH analogs potentially represent new therapies for narcolepsy, but further studies need to be undertaken to determine their safety and efficacy.

Melanin-concentrating hormone (MCH) receptor modulation

MCH is a 19-amino acid neuropeptide that results from the cleavage of a precursor preproMCH. MCH neurons intermingle with hypocretin neurons in the lateral hypothalamus and project widely throughout the CNS where MCH receptors (MCHR-1 and MCHR-2) are widely distributed. MCH cells play a central role in sleep promotion – they express c-Fos during sleep, discharge action potentials during both NREM and REM sleep, but are preferentially active during REM sleep.⁶⁵ MCH neurons innervate arousal-promoting regions such as histaminergic TMN cells and the noradrenergic locus coeruleus cells. MCH cells release GABA, thereby inhibiting wake-promoting circuits.⁶⁵ Optogenetic stimulation of MCH cells triggers rapid onset of sleep; MCH neurons also promote and stabilize REM sleep by inhibiting wake-promoting circuits.^{65,66} Whether MCH agonists will reduce insomnia and disrupted nocturnal sleep in narcolepsy has not been determined. Meanwhile, MCHR1 antagonists are being investigated as treatments for depression, anxiety, and obesity.

Hypocretin-based therapies

A messenger RNA encodes prepro-hypocretin (orexin). This precursor is cleaved to form two hypothalamic neuropeptides. Hypocretin-1 (orexin A) is a 33-amino acid peptide with an *N*-terminal pyroglutamyl residue, two intrachain disulfide bonds, and C-terminal amidation, while hypocretin-2 (orexin B) is a 28-amino acid C-terminally amidated linear peptide.⁶⁷ Hypocretin actions are mediated by 2 orphan G-protein coupled receptors: HCRT1 and HCRT2. HCRT1 has higher affinity for hypocretin-1 than hypocretin-2, while HCRT2 binds both hypocretin-1 and hypocretin-2 with similar affinities. Low or undetectable hypocretin peptides are found in almost 95% of patients with narcolepsy Type 1.¹⁰ The hypocretin ligand deficiency is probably due to postnatal cell death of hypocretin neurons.⁶⁸

Various hypocretin ligand replacement therapies have been pursued including cell transplantation, peptide replacement, and gene therapy.

Cell transplantation and stem cells

With enhanced transplant media, cells from the posterior hypothalamus of rat pups that were transplanted into the midline pons of adult rats at the level of the locus coeruleus survived up to day 36 (n=9).⁶⁹ Narcoleptic rats that received transplant grafts showed reduced somnolence.⁷⁰ However, survival rate of the grafts was poor (~5% of implanted cells).⁷⁰ Poor graft survival fueled interest in stem cells to produce hypocretin neuroblasts for transplantation.

Merkle et al⁷¹ reported the differentiation of both human embryonic stem cells and human-induced pluripotent stem cells into hypothalamic neurons using complementary self-patterning and directed differentiation approaches. This research lays the foundation for in vitro generation of human hypothalamic neurons, which can then enable further investigation into disease modeling, cell transplantation, and efficient drug screening for narcolepsy.

Hypocretin peptide replacement

Hypocretin-1 replacement in ligand-deficient narcoleptic dogs via intracerebroventricular or intravenous methods (up to 6 µg/kg) had no effect on cataplexy or wakefulness. Only very high intravenous doses (96–384 µg/kg) penetrated the blood–brain barrier for a short-lasting anticataplectic effect.⁷² Intracerebroventricular hypocretin-1 infusion in ligand-deficient mice improved cataplexy and wakefulness for 3 hours.⁷³ These results and the impracticability of intracerebroventricular administration highlight the need to develop hypocretin analogs that can penetrate centrally more effectively, preferably through noninvasive routes of administration.

Hypocretin-1 was applied intranasally to Type I narcolepsy subjects in two studies (n=8, n=14)^{74,75} – there was no statistically significant effect on wakefulness, although REM sleep quantity was reduced and REM was more stable with fewer wake-REM sleep transition. Participants committed fewer false reactions in the test of divided attention performed the next day.⁷⁵ The addition of 1% phenylephrine into formulations containing hypocretin-1 applied intranasally significantly reduced absorption of hcr-1 into the blood by 65%, increased deposition into the olfactory epithelium about threefold, and reduced concentration in the trigeminal nerve by 65%. Brain-to-blood concentrations were increased 16–6.8-fold.⁷⁶ At this time, intranasal hypocretin replacement is not yet a viable treatment.

Gene replacement therapy

Diffuse expression of ligand (transgene with β-actin promoter) improved cataplexy and consolidated REM sleep in ligand-deficient narcoleptic mice.⁷⁷ Using herpes simplex virus-1 amplicon-based vector, a gene for prepro-hypocretin was transferred into the lateral hypothalamus of narcoleptic mice: this reduced cataplexy by 60%, and REM sleep levels increased.⁷⁷ Recombinant adeno-associated virus (rAAV)-orexin gene transfer into the zona incerta neurons suppressed cataplexy while rAAV gene transfer into the striatum did not, suggesting site-specific effects of gene transfer.⁷⁸ rAAV-orexin gene transfer into the dorsolateral pons improved wake maintenance (wake bouts lasting longer than 32.2 minutes significantly increased to 23% [+180% vs no rAAV; $P < 0.001$]), but overall wake time did not change; cataplexy was also significantly reduced.⁷⁹ More studies are needed to establish safety and efficacy, but these may be therapies for the future.

Immunotherapy

Since autoimmunity is believed to underlie hypocretin cell destruction, clinical trials have tested immunotherapy as a potential disease modifying therapy. Plasmapheresis,⁸⁰ corticosteroids,^{81,82} and intravenous immunoglobulin infusions⁸³ have been used in case reports and small studies with mixed results (plasmapheresis did not improve narcolepsy; corticosteroids helped daytime somnolence in two cases, did not help in one case; intravenous immunoglobulin (IVIG) infusions helped cataplexy but not other symptoms in ¼ of the cases, but not the other symptoms). Plasmapheresis and steroids were utilized close to onset of symptoms, while IVIG was used within 6 months of diagnosis. Immunotherapy is believed to be helpful when administered close to disease onset to prevent neuronal death. Surprisingly, cataplexy but not other narcoleptic symptoms resolved when a patient who developed lymphoma was treated with alemtuzumab, even though his narcolepsy had started 52 years ago.⁸⁴ Alemtuzumab is a humanized monoclonal antibody that binds to CD52 and causes lysis of lymphocytes and subsequently a differential recovery of lymphocyte subsets with prolonged suppression of CD4⁺ T cells.⁸⁴ We are not aware of any other immunosuppressant therapies utilized in narcolepsy patients. The small numbers and the uncontrolled nature of these various studies as well as differing treatment regimens used do not provide enough bases for guidelines. More controlled studies are indicated.

Conclusion

Narcolepsy remains a complex disease whose cure remains elusive despite our expanding knowledge about its pathophysiology. Disease-specific therapies need further development

and testing before they can be clinically relevant. The ability to generate hypothalamic neurons from stem cells should facilitate drug screening for narcolepsy. Symptomatic therapy may make a difference in functionality and quality of life. Historically, clinicians choose medications empirically based upon practice guidelines, experience, and personal and patient preferences. As the cost of genotyping becomes more affordable, personalized medicine will come to the foreground. Pharmacogenomics will play a greater role clinically in choosing the best drugs for patients, using documented genetic variation to guide medication selection and dosing.⁸⁵

Disclosure

The authors report no conflicts of interest in this work.

References

- Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep*. 2007;30:13–26.
- Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA). The Voice of the Patient. A series of reports from the US Food and Drug Administration's (FDA's) Patient Focused Drug Development Initiative. Narcolepsy Public Meeting: September 24, 2013. Report date: June 2014. Available from <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM402907.pdf>. Accessed October 15, 2016.
- Rosenberg R, Kim AY. The AWAKEN survey: knowledge of narcolepsy among physicians and the general population. *Postgrad Med*. 2014;126:78–86.
- Dauvilliers Y, Montplaisir J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology*. 2001;57:2029–2033.
- Guilleminault C, Abad VC. Narcolepsy. In: Chokroverty S, editor. *Sleep Disorders Medicine. Basic Science, Technical Considerations, and Clinical Aspects*. Philadelphia, PA: Saunders Elsevier; 2009:377–396.
- Roth T, Dauvilliers Y, Mignot E, et al. Disrupted nighttime sleep in narcolepsy. *J Clin Sleep Med*. 2013;9(9):955–965.
- Pizza F, Franceschini C, Peltola H, et al. Clinical and polysomnographic course of childhood narcolepsy with cataplexy. *Brain*. 2013;136:3787–3795.
- Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. 2014;15:502–507.
- American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
- Nishino S, Ripley B, Overeem S, et al. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy. *Ann Neurol*. 2001;50:381–388.
- Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. *Sleep*. 2014;37:1035–1042.
- Mahljos J, De la Herran-Arita AK, Mignot E. The autoimmune basis of narcolepsy. *Curr Opin Neurobiol*. 2013;23:767–773.
- Luca G, Haba-Rubio J, Dauvilliers Y, et al. Clinical, polysomnographic, and genome-wide association analyses of narcolepsy with cataplexy: a European Network study. *J Sleep Res*. 2013;22(5):482–495.
- Yamasaki M, Miyagawa T, Toyoda H, et al. Evaluation of polygenic risks for narcolepsy and essential hypersomnia. *J Hum Genet*. 2016;61(10):873–878.
- Fontana A, Gast H, Reith W, Recher M, Birchler T, Bassetti CL. Narcolepsy: autoimmunity, effector T cell activation due to infection, or T cell independent, major histocompatibility complex class II induced neuronal loss? *Brain*. 2010;133(Pt 5):1300–1311.
- Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep*. 2007;30:1705–1711.
- Krahn LE, Hershner S, Loeding LD, et al. Quality measures for the care of patients with narcolepsy. *J Clin Sleep Med*. 2015;11:335–355.
- Billiard M, Bassetti C, Dauvilliers Y, et al; EFNS Task Force. EFNS guidelines on management of narcolepsy. *Eur J Neurol*. 2006;13:1035–1048.
- Wise MS, Arand DL, Auger RR, Brooks SN, Watson NF; American Academy of Sleep Medicine. Treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30:1712–1727.
- Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. *Neurotherapeutics*. 2012;9(4):739–752.
- Scammell T. Treatment of narcolepsy in adults. Benca R, Eichler AF (Eds), UpToDate, Waltham, MA. Accessed October 23, 2016.
- Kotagal S. Narcolepsy in children. Scammell T, Eichler AF (Eds), UpToDate, Waltham, MA. Accessed October 23, 2016.
- Thorpy M, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med*. 2015;16:9–18.
- PDR.net [homepage on the Internet]. Available from: <http://www.pdr.net>. Accessed April 11, 2016.
- Drugs.com [homepage on the Internet]. Available from: <http://www.drugs.com>. Accessed October 31, 2016.
- Scammell TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci*. 2000;20(22):8620–8628.
- Wisor J. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. *Front Neurol*. 2013;4:139.
- Schwartz JR, Feldman NT, Bogan RK. Dose effects of modafinil in sustaining wakefulness in narcolepsy patients with residual evening sleepiness. *J Neuropsychiatry Clin Neurosci*. 2005;17:405–412.
- Schwartz JR, Feldman NT, Bogan RK, Nelson MT, Hughes RJ. Dosing regimen effects of modafinil for improving daytime wakefulness in patients with narcolepsy. *Clin Neuropharmacol*. 2003;26:252–257.
- Schwartz JR, Nelson MT, Schwartz ER, Hughes RJ. Effects of modafinil on wakefulness and executive function in patients with narcolepsy experiencing late-day sleepiness. *Clin Neuropharmacol*. 2004;27:74–79.
- Black JE, Hull SG, Tiller J, Yang R, Harsh JR. The long-term tolerability and efficacy of armodafinil in patients with excessive sleepiness associated with treated obstructive sleep apnea, shift work disorder, or narcolepsy: an open-label extension study. *J Clin Sleep Med*. 2010;6(5):458–466.
- Carlton R, Lunacek O, Regan T, Carroll CA. Healthcare costs among patients with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, or narcolepsy. *Am Health Drug Benefits*. 2014;7(6):334–340.
- Alshaiikh MK, Tricco AC, Tashkandi M, Mamdani M, Straus SE, BaHammam AS. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. *J Clin Sleep Med*. 2012;8(4):451–458.
- US Xyrem Multi-Center Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep*. 2002;25:42–49.
- Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med*. 2005;1:391–397.
- Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29:939–946.
- Mayer G, Meier KE, Hephata K. Selegiline hydrochloride treatment in narcolepsy. A double-blind, placebo-controlled study. *Clin Neuropharmacol*. 1995;18(4):306–319.
- Droogleever Fortuyn HA, Fronczek R, Smitshoek M, et al. Severe fatigue in narcolepsy with cataplexy. *J Sleep Res*. 2012;21(2):163–169.
- Ohayon M. Narcolepsy is complicated by high medical and psychiatric co-morbidities; a comparison with the general population. *Sleep Med*. 2013;14:488–492.

40. Inocente CO, Lavault S, Lecendreux M, et al. Impact of obesity on children with narcolepsy. *CNS Neurosci Ther.* 2013;19:521–528.
41. Thorpy M, Zhao CG, Dauvilliers Y. Management of narcolepsy during pregnancy. *Sleep Med.* 2013;14(4):367–376.
42. Baronio D, Ganchorski T, Castro K, Zanatta G, Gottfried, Riesgo R. Histaminergic system in brain disorders: lessons from the translational approach and future perspectives. *Ann Gen Psychiatry.* 2014;13(1):34.
43. Swick TJ. Treatment paradigms for cataplexy in narcolepsy: past, present, and future. *Nat Sci Sleep.* 2015;7:159–169.
44. Dauvilliers Y, Bassetti C, Lammers GJ, et al. HARMONY I study group. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double blind, randomized trial. *Lancet Neurol.* 2013;12(11):1068–1075.
45. *Summary of Product Characteristics.* Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf. Accessed November 30, 2016.
46. Syed YY. Pitolisant: first global approval. *Drugs.* 2016;76:1313.
47. ClinicalTrials.gov. Available from: <https://clinicaltrials.gov/ct2/results?term=narcolepsy&cond=%22Narcolepsy%22>. Accessed October 25, 2016.
48. Brioni JD, Esbenshade TA, Garrison TR, Bitner SR, Coward MD. Discovery of histamine H3 antagonists for the treatment of cognitive disorders and Alzheimer's disease. *J Pharmacol Exp Ther.* 2011;336:38–46.
49. Barbier AJ, Aluisio L, Lord B, et al. Pharmacological characterization of JNJ-28583867, a histamine H(3) receptor antagonist and serotonin reuptake inhibitor. *Eur J Pharmacol.* 2007;576(1–3):43–54.
50. Bogan RK, Feldman N, Emsellem HA, et al. Effect of oral JZP-110 (ADX-N05) treatment on wakefulness and sleepiness in adults with narcolepsy. *Sleep Med.* 2015;16(9):1102–1108.
51. Ruoff C, Swick TJ, Doekel R, et al. Effect of oral JZP-110 (ADX-N05) on wakefulness and sleepiness in adults with narcolepsy: a phase 2b study. *Sleep.* 2016;39(7):1379–1387.
52. Huang YS, Guilleminault C. Narcolepsy: action of two γ -aminobutyric acid type B agonists, baclofen and sodium oxybate. *Pediatr Neurol.* 2009;41(1):9–16.
53. Black SW, Morairty SR, Chen TM, et al. GABA_B agonism promotes sleep and reduces cataplexy in murine narcolepsy. *J Neurosci.* 2014;34(19):6485–6494.
54. Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in γ -aminobutyric acid-Related hypersomnolence: a randomized, crossover trial. *Ann Neurol.* 2015;78(3):454–465.
55. Trotti LM, Saini P, Koola C, LaBarbera V, Bliwise DL, Rye DB. Flumazenil for the treatment of refractory hypersomnolence: clinical experience with 153 patients. *J Clin Sleep Med.* 2016;12(10):1389–1394.
56. Walsh JK. Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med.* 2009;5(2 Suppl):S27–S32.
57. Duchêne A, Perier M, Zhao Y, et al. Impact of astroglial connexins on modafinil pharmacological properties. *Sleep.* 2016;39(6):1283–1292.
58. Lecendreux M, Poli F, Oudiette D, et al. Tolerance and efficacy of sodium oxybate in childhood narcolepsy with cataplexy: a retrospective study. *Sleep.* 2012;35(5):709–711.
59. Nicoll RA. Excitatory action of TRH on spinal motor neurons. *Nature.* 1977;265:242–243.
60. Nishino S, Arrigoni J, Shelton J, et al. Effects of thyrotropin-releasing hormone and its analogs on daytime sleepiness and cataplexy in canine narcolepsy. *J Neurosci.* 1997;17:6401–6408.
61. Riehl J, Honda K, Kwan M, et al. Chronic oral administration of CG-3703, a thyrotropin-releasing hormone analog, increase wake and decreases cataplexy in canine narcolepsy. *Neuropsychopharmacology.* 2000;23:34–45.
62. Khomane KS, Meena CL, Jain R, Bansal AK. Novel thyrotropin-releasing hormone analogs: a patent review. *Expert Opin Ther Pat.* 2011;21(11):1673–1691.
63. Ijiro T, Nakamura K, Ogata M, et al. Effect of rovatirelin, a novel thyrotropin-releasing hormone analog, on the central noradrenergic system. *Eur J Pharmacol.* 2015;761:413–422.
64. Kelly JA, Boyle NT, Cole N, et al. First-in-class thyrotropin-releasing hormone (TRH)-based compound binds to a pharmacologically distinct TRH receptor subtype in human brain and is effective in neurodegenerative models. *Neuropharmacology.* 2015;89:193–203.
65. Fraigne JJ, Peever JH. Melanin-concentrating hormone neurons promote and stabilize sleep. *Sleep.* 2013;36(12):1767–1768.
66. Pelluru D, Konadhode R, Shiromani PJ. MCH neurons are the primary sleep-promoting group. *Sleep.* 2013;36(12):1779–1781.
67. Sakurai T, Mieda M. Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal. *Trends Pharmacol Sci.* 2011;32(8):451–462.
68. Nishino S, Okuro M, Kotorii N, et al. Hypocretin/orexin and narcolepsy: new basic and clinical insights. *Acta Physiol.* 2000;198:209–222.
69. Arias-Carrión O, Murillo-Rodríguez E, Xu M, Blanco-Centurion C, Drucker-Colin R, Shiromani PJ. Transplantation of hypocretin neurons into the pontine reticular formation. *Sleep.* 2004;27(8):1465–1470.
70. Arias-Carreón O, Murillo-Rodríguez E. Effects of hypocretin/orexin cell transplantation on narcoleptic-like sleep behavior in rats. *PLoS One.* 2014. 9(4):e95342.
71. Merkle FT, Maroof A, Wataya T, et al. Generation of neuropeptidergic hypothalamic neurons from human pluripotent stem cells. *Development.* 2015;142(4):633–643.
72. Fujiki N, Yoshida Y, Ripley B, Mignot E, Nishino S. Effects of IV and ICV hypocretin-1 (orexin A) in hypocretin receptor-2 gene mutated narcoleptic dogs and IV hypocretin-1 replacement therapy in a hypocretin-ligand-deficient narcoleptic dog. *Sleep.* 2003;26(8):953–959.
73. Mieda M, Willie JT, Hara J, Sinton CM, Sakurai T, Yanagisawa M. Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. *Proc Natl Acad Sci U S A.* 2004;101(13):4649–4654.
74. Baier PC, Hallschmid M, Seeck-Hirschner M. Effects of intranasal hypocretin-1 (orexin A) on sleep in narcolepsy with cataplexy. *Sleep Med.* 2011;12(10):941–946.
75. Weinhold SL, Seeck-Hirschner M, Nowak A, Hallschmid M, Göder R, Baier PC. The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. *Behav Brain Res.* 2014;262:8–13.
76. Dhuria SV, Hanson LR, Frey WH 2nd. Novel vasoconstrictor formulation to enhance intranasal targeting of neuropeptide therapeutics to the central nervous system. *J Pharmacol Exp Ther.* 2009;328(1):312–320.
77. Liu M, Thankachan S, Kaur S, et al. Orexin (hypocretin) gene transfer diminishes narcoleptic sleep behavior in mice. *Eur J Neurosci.* 2008;28:1382–1393.
78. Liu M, Blanco-Centurion C, Konadhode R, et al. Orexin gene transfer into zona incerta neurons suppresses muscle paralysis in narcoleptic mice. *J Neurosci.* 2011;31:6028–6040.
79. Blanco-Centurion C, Liu M, Konadhode R, Pelluru D, Shiromani PJ. Effects of orexin gene transfer in the dorsolateral pons in orexin knock-out mice. *Sleep.* 2013;36(1):31–40.
80. Chen W, Black J, Call P, Mignot E. Late-onset narcolepsy presenting as rapidly progressing muscle weakness: response to plasmapheresis. *Ann Neurol.* 2005;58(3):489–490.
81. Hecht M, Lin L, Kushida CA, et al. Report of a case of Immunosuppression with Prednisone in an 8-year-old boy with an acute onset of hypocretin-deficiency narcolepsy. *Sleep.* 2003;26(7):809–810.
82. Coelho FM, Pradella-Hallinan MA, Rodrigues G, Bittencourt LR, Tufik S. Report of two narcoleptic patients with remission of hypersomnolence following use of prednisone. *Arq Neuropsiquiatr.* 2007;65(2A):336–337.
83. Plazzi G, Poli F, Franceschini C, et al. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. *J Neurol.* 2008;255(10):1549–1554.
84. Donjacour CE, Lammers GJ. A remarkable effect of alemtuzumab in a patient suffering from narcolepsy with cataplexy. *J Sleep Res.* 2012;21(4):479–480.
85. Mrazek DA. Psychiatric pharmacogenomics testing in clinical practice. *Dialogues Clin Neurosci.* 2010;12:69–76.

Nature and Science of Sleep

Dovepress

Publish your work in this journal

Nature and Science of Sleep is an international, peer-reviewed, open access journal covering all aspects of sleep science and sleep medicine, including the neurophysiology and functions of sleep, the genetics of sleep, sleep and society, biological rhythms, dreaming, sleep disorders and therapy, and strategies to optimize healthy sleep. The manuscript

management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/nature-and-science-of-sleep-journal>