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REVIEW ARTICLE

Recently Approved and Upcoming Treatments for Narcolepsy

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Abstract

Narcolepsy is a chronic, disabling neurologic disorder characterised by excessive daytime sleepiness (EDS) and, in up to 60% of patients, cataplexy. Treatments for narcolepsy are aimed at improving wakefulness (e.g. modafinil, armodafinil, stimulants), reducing cataplexy attacks (e.g. sodium oxybate, venlafaxine), and treating the symptoms of disturbed nocturnal sleep, sleep paralysis and sleep-related hallucinations (e.g. sodium oxybate). In general, medications that increase the release, or inhibit the reuptake, of norepinephrine or dopamine have wake-promoting effects and are useful in managing EDS, whereas medications that inhibit serotonin or norepinephrine reuptake have anticataplectic effects. Modulation of γ-aminobutyric acid B ($GABA_B$) receptors or histamine H_3 receptors (H3Rs) has effects on both EDS and cataplexy. Pitolisant, an H3R antagonist, and solriamfetol, a dopamine and norepinephrine reuptake inhibitor, are the most recently approved treatments for EDS associated with narcolepsy in the European Union (pitolisant) and the USA (pitolisant and solriamfetol). Several new agents are being developed and tested as potential treatments for EDS and cataplexy associated with narcolepsy; these agents include novel oxybate formulations (once-nightly [FT218]; low sodium [JZP-258]), a selective norepinephrine reuptake inhibitor (AXS-12), and a product combining modafinil and an astroglial connexin inhibitor (THN102). This review summarises the mechanisms of action, pharmacokinetics, efficacy, and safety/tolerability of recently approved and emerging treatments for narcolepsy.

Key Points

Excessive daytime sleepiness and cataplexy are common and disabling symptoms associated with narcolepsy.

Emerging treatments, including two recently approved medications (pitolisant and solriamfetol) and several medications still in development (FT218, JZP-258, AXS-12, THN102, SUVN-G3031, TAK-925), provide new options for the treatment of narcolepsy.

1 Introduction

Narcolepsy, a chronic, disabling neurologic disorder of hypersomnolence [1, 2], affects an estimated 20–67 people per 100,000 worldwide [3]. The onset of narcolepsy most commonly occurs in the second decade of life, though diagnosis is often delayed by several years [1, 4, 5].

Symptoms of narcolepsy include excessive daytime sleepiness (EDS), which, although not specific to narcolepsy, is a characteristic of the disorder present in all patients, as it is a requirement for diagnosis [2]. Cataplexy, an involuntary loss of muscle tone during wakefulness that is typically evoked by strong emotions, occurs in up to 60% of patients [6]. Other symptoms are disturbed night-time sleep; hypnagogic and hypnopompic hallucinations, which occur while falling asleep and waking up, respectively; and sleep paralysis [1].

The *International Classification of Sleep Disorders–Third Edition* (ICSD-3) diagnostic criteria for narcolepsy include two types: narcolepsy type 1 (NT1) and type 2 (NT2) [7]. Criteria common to both types include (1) chronic daily excessive sleepiness lasting ≥ 3 months; and (2) mean sleep latency ≤ 8 min and two or more sleep-onset rapid eye-movement (REM) periods (SOREMPs) on the Multiple Sleep Latency Test (MSLT). (A nocturnal polysomnographic test finding of a SOREMP within < 15 min of sleep onset may replace one SOREMP on the MSLT.) NT1 diagnostic criteria also include presence of cataplexy, and/or reduced cerebrospinal fluid (CSF) levels of hypocretin 1 (orexin A). NT2

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criteria include absence of cataplexy; normal or unmeasured CSF levels of hypocretin 1; and no other condition (including the effect of medication or of its withdrawal) that better explains the EDS and/or MSLT findings.

The pathophysiologic mechanism underlying NT1 is deficiency of hypocretin signalling, caused by selective loss of hypocretin-producing neurons in the hypothalamus, likely a result of autoimmune-related destruction [1, 2]. Genetic factors (e.g. human leukocyte antigen [HLA] class II polymorphisms in closely linked loci *DQB1**06:02 and *DQA1**01:02, which together form the DQ0602 heterodimer) and environmental factors (e.g. infection) can contribute to the development of NT1 [1, 2].

In NT1, EDS is a consequence of the loss of hypocretin-producing cells and the resulting hypocretin deficiency. Lack of hypocretin reduces excitatory signalling to neurons involved in synthesis of the wake-promoting neurotransmitters norepinephrine (NE), dopamine (DA), serotonin (5-hydroxytryptamine [5-HT]) and histamine, and may lead to a subsequent reduction in activation of the cortex, basal forebrain, hypothalamus and brainstem [1, 2].

The pathophysiology of cataplexy is not well-established, but evidence suggests mechanisms that are common to cataplexy and REM sleep paralysis [1, 2]. Furthermore, because hypocretin-producing neurons stimulate brain areas that inhibit REM sleep, extensive loss of these neurons causes dissociated REM sleep, which may manifest as cataplexy [1, 2]. Another suggestion is that deficient hypocretin signalling causes more frequent sleep–wake transitions, including brief transitions to REM sleep and partial REM states during wakefulness [1].

The mechanisms underlying NT2 are less clear. Possibly, moderate hypocretin neuronal loss or insufficient release of hypocretin neuropeptides, without a detectable reduction in CSF, may be a factor [2].

Treatments for narcolepsy are aimed at improving wakefulness and reducing cataplexy attacks, sleep disruption, sleep paralysis and sleep-related hallucinations. The effect of medications on EDS and cataplexy is related to their mechanism of action (MOA), therapeutic targets and effects on neurotransmitters. For example, medications that increase the release or inhibit the reuptake of NE and DA (e.g. amphetamines, stimulants, wake-promoting agents) are useful in managing EDS [1, 2, 8]. Inhibition of 5-HT and/or NE reuptake has anticataplectic effects [1, 2, 8]. Modulation of γ-aminobutyric acid (GABA) B ($GABA_B$) receptors (sodium oxybate, baclofen) or histamine H_3 receptors (H3Rs) has effects on EDS, cataplexy and other REM dissociative symptoms (e.g. hypnagogic and hypnopompic hallucinations); in addition, $GABA_B$ receptor modulation affects symptoms of sleep disruption [1, 2, 8, 9]. Medications historically used for treatment of EDS (modafinil, armodafinil, stimulants, sodium oxybate) and cataplexy (sodium oxybate, venlafaxine) have demonstrated efficacy in managing these symptoms. However, some patients may not be able to tolerate certain medications, some may have symptoms that are initially or become refractory to these agents, or some may have comorbidities or use concomitant medications that preclude the use of these agents due to drug–disease or drug–drug interactions (DDIs). Advances in the understanding of the underlying mechanisms of narcolepsy have led to the development of new treatments for this disorder.

Recently approved and emerging treatments for narcolepsy are reviewed here. Table 1 (overview), Table 2 (pharmacokinetics [PKs], DDI potential), and Table 3 (efficacy) summarise key information. As these agents are recently approved and still in development, not all studies have been fully published in peer-reviewed publications. In several cases, particularly for investigational agents, data were reported in abstracts, congress presentations and other alternative sources; this information has been included to provide a comprehensive summary of available information, but the limitations associated with these publication types should be borne in mind when considering the data.

2 Recently Approved Treatments for Narcolepsy

2.1 Pitolisant

Pitolisant, an N-piperidyl derivative [10], is a first-in-class H3R antagonist/inverse agonist [11] with wake-promoting and anticataplectic effects. Pitolisant is approved in the European Union (EU) for the treatment of narcolepsy in adults with narcolepsy with or without cataplexy, with an approved dose range of 4.5–36 mg/day [12]. In August 2019, pitolisant was approved by the US Food and Drug Administration (FDA) for treatment of EDS in adult patients with narcolepsy; the recommended dose range is 17.8–35.6 mg/day [13, 14]. Table 1 summarises dose titration recommendations. Note that the European studies (and EU labelling) used a different method for calculating the dosing of pitolisant from that used in the USA; as such, in the European studies/labelling, doses of 4.5, 9, 18 and 36 mg are equivalent to the US doses of 4.45, 8.9, 17.8 and 35.6 mg, respectively.

2.1.1 Mechanism of Action (MOA)

The key effects of pitolisant are thought to be mediated presynaptically through effects on histaminergic neurons in the brain [11]. As an H3R competitive antagonist and inverse

Table 1 Overview of recently approved and emerging treatments for narcolepsy

Medication	Class	Mechanism of action	EDS/cataplexy	Development/approval status in narcolepsy	Standard dosing
Pitolisant [12, 13]	Histamine H_3 receptor antagonist/inverse agonist	H_3 receptor antagonist/inverse agonist	EDS	Approved in EU Indication: treatment of narcolepsy with or without cataplexy Approved in USA Indication: treatment of EDS in adult patients with narcolepsy	EU[a] Approved dose range: 4.5–36 mg once daily in morning Starting dose: 9 mg/day; can be increased to 18 mg/day after 1 week and to 36 mg/day after 2 weeks; can be titrated down to 4.5 mg/day at any time USA: Approved dose range: 8.9–35.6 mg once daily in morning Starting dose: 8.9 mg/day; increase to 17.8 mg/day after 1 week and to 35.6 mg/day after 2 weeks; dose may be adjusted based on tolerability
Solriamfetol [26]	Monoamine reuptake inhibitor	Dopamine and norepinephrine reuptake inhibitor	EDS	Approved in USA Under review in EU Indication: improve wakefulness in adults with EDS associated with narcolepsy	75–150 mg once daily in morning
FT218 (long-acting sodium oxybate) [37, 38, 43]	$GABA_B$ receptor agonist	$GABA_B$ receptor agonist	EDS Cataplexy	Phase III FDA-designated orphan drug	4.5, 6, 7.5 or 9 g once nightly
JZP-258 (low-sodium oxybate formulation) [44]	$GABA_B$ receptor agonist	$GABA_B$ receptor modulator	EDS Cataplexy	Phase III	Not available
AXS-12 (reboxetine) [50, 51, 54, 78]	Monoamine reuptake inhibitor	Norepinephrine reuptake inhibitor	EDS Cataplexy	Phase II FDA-designated orphan drug	Twice-daily dosing
THN102 (modafinil/flecainide) [35, 62, 64]	Non-amphetamine wake-promoting agent/anti-connexin agent	Dopamine reuptake inhibitor/astroglial connexin inhibitor	EDS	Phase II	300 mg/3 mg or 300 mg/27 mg once daily

EDS excessive daytime sleepiness, EU European Union, *FDA* US Food and Drug Administration, *$GABA_B$* γ-aminobutyric acid B

[a]EU doses of 4.5, 9, 18 and 36 mg are equivalent to US doses of 4.45, 8.9, 17.8 and 35.6 mg, respectively

Table 2 Pharmacokinetics of recently approved and emerging treatments for narcolepsy

Medication[a]	Pharmacokinetics	t_{max}	$t_{½}$	Metabolism/clearance	Drug–drug interaction potential
Pitolisant [12, 13]	Approximately proportional	Median (range): 3.5 h (2–5 h)	Median (range): ~20 h (7.5–24.2 h)	CYP3A4 CYP2D6	CYP3A4 inducers decrease C_{max} and AUC; CYP2D6 inhibitors increase C_{max} and AUC; in vitro data suggest pitolisant and its main metabolites may induce CYP3A4 and CYP2B6 at therapeutic concentrations and, by extension, CYP2C, UGTs and P-glycoprotein; pitolisant dose adjustments recommended with concomitant use of strong CYP2D6 inhibitors or strong CYP3A4 inducers Not recommended for use with oral contraceptives; an alternative, non-hormonal contraceptive method should be used during treatment and for ≥ 21 days after discontinuation
Solriamfetol [26]	Linear over dose range of 42–1008 mg	Median (range): 2 h (1.25–3.0 h)	Mean: ~7.1 h	Minimal metabolism Renal clearance, 18.2 L/h Apparent total clearance, 19.5 L/h	Contraindicated in combination with or 14 days after discontinuing MAOIs CYP- and transporter-mediated interactions not expected based on in vitro data Potential for pharmacodynamic interactions when solriamfetol is used concomitantly with other drugs that increase BP and/or heart rate or drugs that increase levels of dopamine or that bind directly to dopamine receptors
FT218 (long-acting sodium oxybate) [39, 41]	Non-linear[b] [39]	Median: 1.5–2 h [41]	Not reported	Metabolised through Krebs cycle and β-oxidation Excretion by biotransformation to CO_2[b] [39]	Divalproex sodium increases sodium oxybate exposure[b] [39]
AXS-12 (reboxetine) [54]	Linear up to dose of 4.5 mg	Mean ± SD: 2.4 ± 1.8 h	Mean ± SD: 12.5 ± 2.9 h	CYP3A4 Renal clearance, 2.21 ± 0.87 L/h	Lack of effect on activity of CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 Strong CYP3A4 inhibitors increase AUC, decrease oral clearance and prolong $t_{½}$ Avoid coadministration with drugs known to inhibit CYP3A4 and with MAOIs Low serum concentrations reported with concurrent administration of CYP3A4 inducers Potential for increased BP with concomitant use of ergot derivatives and for hypokalaemia with concomitant use of potassium-losing diuretics

AUC area under the plasma drug concentration–time curve, *BP* blood pressure, C_{max} maximum plasma concentration, CO_2 carbon dioxide, *CYP* cytochrome P450, *MAOIs* monoamine oxidase inhibitors, *SD* standard deviation, $t_{½}$ elimination half-life, t_{max} time to maximum plasma concentration, *UGT* uridine 5'-diphospho (UDP)-glucuronosyltransferase

[a]Data not available for JZP-258 and THN102

[b]Based on currently available formulation of sodium oxybate (Xyrem®)

agonist, pitolisant blocks the inhibitory effect of histamine (or H3R agonists) on endogenous histamine release, and enhances histamine release throughout the central nervous system (CNS) [10, 15]. Pitolisant modulates other neurotransmitter systems as well, leading to increased release of acetylcholine and DA in the cerebral cortex without increased release of DA in the striatal complex [15].

2.1.2 Pharmacokinetic (PK) and Drug–Drug Interaction (DDI) Potential

The PKs of pitolisant are approximately proportional (Table 2) [13]. Doubling the dose to 54 mg from 27 mg led to a 2.3-fold increase in exposure (area under the plasma drug concentration–time curve [AUC] from time zero to infinity [AUC_{∞}]) [12]. Pitolisant is rapidly absorbed, with a median time to maximum plasma concentration (t_{max}) of 3.5 h [13]; administration with food delays but does not change the extent of absorption [12, 13, 16]. Pitolisant is highly protein bound (> 90%), with approximately equal distribution in plasma and red blood cells [12, 13, 16]. Pitolisant has a median elimination half-life ($t_{½}$) of approximately 20 h (range 7.5–24.2 h); it is metabolised through cytochrome P450 (CYP) 3A4 and CYP2D6 and eliminated primarily in the urine as inactive metabolites [12, 13].

In stage 2–4 renal failure, pitolisant exposure (maximum plasma concentration [C_{max}], AUC) was increased, but $t_{½}$ was not affected; 17.8 mg/day is the recommended maximum dose for individuals with moderate-to-severe renal impairment, but pitolisant is not recommended in patients with end-stage renal disease (ESRD) [13]. Mild hepatic impairment (Child-Pugh A) did not affect pitolisant PKs, whereas moderate (Child-Pugh B) hepatic impairment was associated with a 2.4-fold increase in AUC and a doubling of $t_{½}$ [12]. Pitolisant dose adjustments are not required in mild hepatic impairment; in moderate hepatic impairment, 17.8 mg/day is the maximum recommended dose; pitolisant is contraindicated in severe hepatic impairment (Child-Pugh C) [13]. Pitolisant exposure is increased (C_{max} and AUC to the end of the dosing period [AUC_{τ}] increased ~ 2.7- and 3.2-fold, respectively, after a single dose and 2.1- and 2.4-fold at steady state) and $t_{½}$ is longer in CYP2D6 poor metabolisers compared with extensive metabolisers [12]; the maximum recommended dose for known CYP2D6 poor metabolisers is 17.8 mg/day [13].

DDI studies demonstrated that CYP3A4 inducers reduce pitolisant exposure (C_{max} decreased ~ 39% and AUC ~ 50%) and CYP2D6 inhibitors increase pitolisant exposure (C_{max} increased ~ 47% and AUC 105%) [12]. Pitolisant dose reductions are recommended with concomitant use of strong CYP2D6 inhibitors and dose increases with strong CYP3A4 inducers [13]. In vitro data suggest pitolisant and its main metabolites may induce CYP3A4 and CYP2B6 at therapeutic concentrations and, by extension, CYP2C, uridine 5'-diphospho (UDP)-glucuronosyltransferases (UGTs), and P-glycoprotein [12]. Although clinical data are limited, evaluations of in vivo CYP3A4 induction in healthy volunteers receiving pitolisant at therapeutic doses (18–45 mg/day) for 7–28 days indicated a lack of CYP3A4 induction activity [17]. However, caution is advised when using pitolisant in combination with substrates of these enzymes; use in combination with substrates that have a narrow therapeutic margin (e.g. immunosuppressants, docetaxel, kinase inhibitors, cisapride, pimozide, halofantrine) should be avoided [12]. Pitolisant product information indicates that patients using hormonal contraceptives should be advised to use an alternative, non-hormonal method of contraception during treatment and for ≥ 21 days after discontinuing pitolisant [12, 13]. A study in healthy volunteers demonstrated that pitolisant had no effect on PK profiles of sodium oxybate or modafinil and that sodium oxybate has no clinically relevant effect on pitolisant PKs; modafinil decreases pitolisant exposure, though dose adjustment is not required [18].

2.1.3 Efficacy

Several clinical trials, including four completed phase III studies, have evaluated the efficacy of pitolisant in participants with narcolepsy.

Harmony 1 was a phase III, 8-week, randomised, double-blind, placebo-controlled trial of pitolisant (10–40 mg/day) in adults with narcolepsy with or without cataplexy, with modafinil (100–400 mg/day) as an active comparator [19]. Stimulants were not permitted during or for ≥ 14 days before the trial; anticataplectic medications (including antidepressants and sodium oxybate) could be continued at a stable dose. The primary endpoint was the difference between pitolisant and placebo in change in Epworth Sleepiness Scale (ESS) scores at week 8. Of 94 participants in the intention-to-treat (ITT) group, 76 (81%) had cataplexy and 33 (35%) continued anticataplectics. At week 8, improvements from baseline were found in all groups on ESS and Maintenance of Wakefulness Test (MWT) sleep latency; the results demonstrated the efficacy of pitolisant over placebo but did not demonstrate non-inferiority with respect to modafinil (Table 3). Additional secondary efficacy measures included percentage of participants rated as improved on the Patient Global Impression of Change (PGI-C) scale (pitolisant, 81%; modafinil, 86%; placebo, 56%) and the Clinician Global Impression of Change (CGI-C) scale (pitolisant, 73%; modafinil, 86%, placebo, 56%). A post hoc analysis of response (final ESS score ≤ 10) found rates of 45%, 46% and 13% for pitolisant, modafinil and placebo, respectively; based on these response rates, the treatment effect for pitolisant compared with placebo was 4.4 (95%

Table 3 Efficacy of recently approved and emerging treatments for narcolepsy in clinical trials

Trial	Treatment groups (number analysed for efficacy, unless otherwise noted)	Design, duration	ESS score	MWT (or MSLT) sleep latency, minutes	Cataplexy attacks
Recently approved					
Pitolisant					
Harmony 1 [19]	Pitolisant 10–40 mg/day ($n=31$) Modafinil 100–400 mg/day ($n=33$) Placebo ($n=30$)	Phase III, randomised, double-blind, placebo-controlled trial 8 weeks	Mean baseline values, 17.8–18.9 across groups Mean (SD) change from baseline: Pitolisant, − 5.8 (6.2) Modafinil, − 6.9 (6.2) Placebo, − 3.4 (4.2) Mean difference between pitolisant and placebo, − 3.0 (95% CI − 5.6 to − 0.4; $p=0.024$) Mean difference between pitolisant and modafinil, 0.12 (95% CI − 2.5 to 2.7; $p=0.250$)	MWT mean baseline values, 7.4–8.8 across groups Change from baseline (calculated as final/baseline): Pitolisant, 1.32 Modafinil, 1.72 Placebo, 0.88 Mean difference between pitolisant and placebo, 1.47 (95% CI 1.01–2.14; $p=0.044$) Mean difference between pitolisant and modafinil, 0.77 (95% CI 0.52–1.13; $p=0.173$)	Mean daily cataplexy rates, 0.4–0.52 at baseline Mean change from baseline (calculated as final/baseline): Pitolisant, 0.38 Modafinil, 0.64 Placebo, 0.92 Mean difference between pitolisant and placebo, 0.38 (95% CI 0.16–0.93; $p=0.034$) Mean difference between pitolisant and modafinil, 0.54 (95% CI 0.24–1.23; $p=0.138$)
Harmony Ibis [12, 16]	Pitolisant 5–20 mg/day ($n=66$) Modafinil 100–400 mg/day ($n=65$) Placebo ($n=32$)	Phase III, randomised, double-blind, placebo-controlled trial 8 weeks	Mean baseline value, 18 Mean (SD) reduction from baseline: Pitolisant, − 4.6 (4.6) Modafinil, − 7.8 (5.9) Placebo, − 3.6 (5.6) Mean difference between pitolisant and placebo, − 1.94 (95% CI − 4.05 to 0.07; $p=0.065$) Mean difference between pitolisant and modafinil, − 2.75 (95% CI − 4.48 to − 1.02)	MWT increase from baseline: Pitolisant, 1.14 Placebo, −1.39 Difference between pitolisant and placebo, 1.57 (95% CI 1.12–2.20; $p=0.009$) Difference between pitolisant and modafinil, 1.05 (95% CI 0.80–1.38; $p=0.713$)	Daily cataplexy rate Change from baseline: Pitolisant, + 0.85 Modafinil, − 0.33 Placebo, not stated Difference between pitolisant and placebo, − 1.00 (95% CI − 2.12 to 0.128; $p=0.077$) Difference between pitolisant and modafinil, 0.05 (95% CI − 0.55 to 0.65; $p=0.865$)
Harmony CTP [20]	Pitolisant 5–40 mg/day ($n=54$) Placebo ($n=51$) Adults with high-frequency cataplexy	Phase III, randomised, double-blind, placebo-controlled trial 7 weeks	Mean baseline values, 17.3–17.4 across groups Mean change from baseline: Pitolisant, –5.4 Placebo, –1.9 Mean difference between pitolisant and placebo, − 3.48 (95% CI − 5.03 to − 1.92; $p=0.0001$)	Mean baseline values (geometric means): Pitolisant, 3.54 Placebo, 4.08 Final values (geometric means): Pitolisant, 6.91 Placebo, 4.32 Geometric mean of ratios (final/baseline) for pitolisant and placebo, 1.85 (95% CI 1.24–2.74; $p=0.003$)	Mean baseline weekly cataplexy rate (geometric means): Pitolisant, 9.15 Placebo, 7.31 Final values (geometric means): Pitolisant, 2.27 Placebo, 4.52 Geometric mean of ratios (final/baseline) for pitolisant and placebo, 0.51 (95% CI 0.43–0.60; $p<0.0001$)

Table 3 (continued)

Trial	Treatment groups (number analysed for efficacy, unless otherwise noted)	Design, duration	ESS score	MWT (or MSLT) sleep latency, minutes	Cataplexy attacks
Harmony 3 (long-term [9])	Pitolisant up to 40 mg/day (safety population) Previously untreated with pitolisant ($n=73$) Previously treated with pitolisant ($n=29$)	Pragmatic, open-label, multicentre study 12 months	Mean (SE) baseline values Previously untreated, 17.6 (0.35) Previously treated, 15.6 (0.54) Mean (SE) reduction from baseline Overall (LOCF; $n=98$), −4.0 (0.46) Completers ($n=68$), − 4.6 (0.6) Previously untreated, − 4.9 (0.7) ($p<0.001$) Previously treated, − 4.2 (1.1) ($p=0.001$)	MSLT mean (SE) baseline values Previously untreated, 5.3 (0.32) Previously treated, 4.8 (0.53) Change from baseline, not reported	Reduction in [mean (SE)]: Total cataplexy attacks/day (completers with cataplexy data, $n=44$): 68%, from 1.09 (0.53) at baseline to 0.35 (0.10) at month 12 ($p=0.055$)
Solriamfetol					
Phase IIb [30]	Solriamfetol 150 mg/day × 4 weeks, then 300 mg/day × 8 weeks ($n=43$) Placebo ($n=47$)	Phase IIb, randomised, double-blind, placebo-controlled trial 12 weeks	Mean baseline scores, 17.3–17.4 across groups Mean change from baseline: Solriamfetol, − 8.5 Placebo, − 2.5 ($p<0.0001$)	MWT mean baseline values, 5.7 (both groups) Mean (SE) change from baseline: Solriamfetol, 12.8 (1.6) Placebo, 2.1 (1.2) ($p<0.0001$)	Weekly cataplexy attacks at baseline: Mean ± SE, 19.2 ± 45.3 Median, 4.0 Median change from baseline: Solriamfetol ($n=17$), −1.0 Placebo ($n=16$), 0
Phase III [31]	Solriamfetol 75 mg/day ($n=59$) Solriamfetol 150 mg/day ($n=55$) Solriamfetol 300 mg/day ($n=59$) Placebo ($n=58$)	Phase III, randomised, double-blind, placebo-controlled trial 12 weeks	Mean baseline scores, 16.9–17.3 across groups Mean (SE) change from baseline, LS mean: Solriamfetol 75 mg, − 3.8 (0.7) Solriamfetol 150 mg, − 5.4 (0.7) Solriamfetol 300 mg, − 6.4 (0.7) Placebo, − 1.6 (0.7) Difference from placebo, LS mean difference: Solriamfetol 75 mg, − 2.2 (95% CI −4.0 to − 0.3; $p=0.0211$) Solriamfetol 150 mg, − 3.8 (95% CI −5.6 to − 2.0; $p<0.0001$) Solriamfetol 300 mg, − 4.7 (95% CI −6.6 to − 2.9; $p<0.0001$)	MWT mean baseline values, 6.1–8.7 across groups Mean (SE) change from baseline, LS mean: Solriamfetol 75 mg, 4.7 (1.3) ($p=0.1595$) Solriamfetol 150 mg, 9.8 (1.3) Solriamfetol 300 mg, 12.3 (1.4) Placebo, 2.1 (1.3) Difference from placebo, LS mean difference: Solriamfetol 75 mg, 2.6 (95% CI −1.0 to 6.3; $p=0.1595$) Solriamfetol 150 mg, 7.7 (95% CI 4.0–11.3; $p<0.0001$) Solriamfetol 300 mg, 10.1 (95% CI 6.4–13.9; $p<0.0001$)	No clear effect of solriamfetol on number of cataplexy attacks per week among participants with cataplexy (study was not powered or designed to rigorously evaluate effects of solriamfetol on cataplexy)

Table 3 (continued)

Trial	Treatment groups (number analysed for efficacy, unless otherwise noted)	Design, duration	ESS score	MWT (or MSLT) sleep latency, minutes	Cataplexy attacks
Long-term [32]	Open-label solriamfetol (75 mg/day, 150 mg/day, or 300 mg/day) Total ($n=643$) With narcolepsy ($n=226$) Randomised withdrawal Solriamfetol ($n=139$) Placebo ($n=141$)	Long-term open-label extension study (2-week titration; up to 50 weeks of maintenance) with 2-week randomised-withdrawal period	Open-label period Participants with narcolepsy ($n=226$) Enrolled directly from previous study ($n=186$) Baseline, 17.3 Final, 11.4 Not enrolled from previous study ($n=40$) Baseline, 17.9 Final, 10.3 Randomised-withdrawal period LS mean change: Solriamfetol, 1.6 Placebo, 5.3 LS mean difference, − 3.7 (95% CI −4.80 to − 2.65; $p<0.0001$)	Not reported	Not reported
Investigational					
JZP-258 (low-sodium oxybate formulation) [44, 47, 79]	Total enrolled/safety population ($n=201$) Randomised withdrawal ($n=134$) JZP-258 ($n=69$) Placebo ($n=65$) Adults with narcolepsy with cataplexy	Phase III randomised, double-blind, placebo-controlled, randomised-withdrawal trial Titration, up to 12 weeks Stable dose, 2 weeks Randomised withdrawal, 2 weeks	Change in median ESS score in randomised withdrawal period (key secondary endpoint), median (Q1, Q3) JZP-258, 0.0 (−1.0, 1.0) Placebo, 2.0 (0.0, 5.0) Treatment difference, $p<0.0001$	Not reported	Change in average weekly cataplexy attacks in randomised withdrawal period (primary endpoint), median (Q1, Q3) Placebo, 2.35 (0.00, 11.61) JZP-258, 0.00 (−0.49, 1.75), treatment difference, $p<0.0001$
AXS-12 (reboxetine) [55]	Reboxetine 10 mg/day (divided doses; titrated over 9 days) ($n=12$)	Pilot study 2 weeks	Decrease from (mean ± SD) 20.58 ± 2.93 at baseline to 10.58 ± 7.21 on day 14 ($p<0.01$)	MSLT mean (± SD) values: Baseline, 4.86 ± 4.01 Day 14, 7.52 ± 4.97 ($p<0.05$)	UNS cataplexy score (mean ± SD): Baseline, 5.85 ± 2.67 Day 7, 1.71 ± 1.60 ($p<0.05$)
THN102 [59, 64]	Modafinil/flecainide 300 mg/3 mg daily Modafinil/flecainide 300 mg/27 mg daily Modafinil 300 mg/placebo daily Estimated enrolment ($n=48$)	Phase II double-blind, randomised, placebo-controlled, 3-way crossover trial 3 × 2 weeks	Preliminary results do not indicate any difference in efficacy between THN102 and modafinil alone	Not reported	Not reported

All trials enrolled adults with narcolepsy with or without cataplexy, unless otherwise noted. Changes from baseline to end of study. Phase II trials are ongoing for FT218 (long-acting sodium oxybate; NCT02720744) [43] and AXS-12 (reboxetine; NCT03881852)[78]; results have not yet been reported

CI confidence interval, *ESS* Epworth Sleepiness Scale, *LOCF* last observation carried forward, *LS* least squares, *MSLT* Multiple Sleep Latency Test, *MWT* Maintenance of Wakefulness Test, *Q* quartile, *SD* standard deviation, *SE* standard error, *UNS* Ullanlinna Narcolepsy Scale

confidence interval [CI] 2.1–9.2; $p < 0.0006$) and compared with modafinil was 1.0 (95% CI 0.68–1.6; $p = 0.908$). Another post hoc analysis found a greater reduction from baseline in daily cataplexy frequency with pitolisant compared with placebo; pitolisant and modafinil did not differ significantly (Table 3).

Harmony Ibis, a phase III, 8-week, randomised controlled trial with a design similar to that of Harmony 1, used a lower dose range for pitolisant (5–20 mg/day) [16]. Across treatment groups (ITT, $n = 163$), 75–81% of participants had a history of cataplexy. At week 8, changes from baseline in ESS scores did not demonstrate superiority of pitolisant relative to placebo or non-inferiority of pitolisant with respect to modafinil; change in MWT sleep latency with pitolisant was greater than with placebo and similar to modafinil (Table 3). The change in daily cataplexy rate in the pitolisant group did not differ significantly from the placebo or modafinil groups (Table 3). In a post hoc analysis of responder rates (ESS scores ≤ 10 or decrease ≥ 3), the risk ratio for pitolisant was 0.60 versus placebo (95% CI 0.41–0.88; $p = 0.008$) and 0.9 versus modafinil (95% CI 0.74–1.10; $p = 0.306$).

Harmony CTP was a phase III, 7-week, randomised, double-blind, placebo-controlled trial in adults with narcolepsy and three or more cataplexy episodes/week (ITT, $n = 105$) [20]. After a 2-week screening/baseline period, participants were randomised to pitolisant or placebo. A 3-week flexible-dose period (pitolisant doses, 5–20 mg/day) was followed by a 4-week stable-dose period (pitolisant doses, 5–40 mg/day). The primary outcome was change in weekly cataplexy rate between the 2-week baseline period and the 4-week stable-dose period. Pitolisant was associated with significant improvement versus placebo in cataplexy rates and secondary outcomes, including ESS and MWT (Table 3).

A 12-month, pragmatic, open-label, multicentre study (Harmony 3) evaluated the safety and efficacy of pitolisant (up to 40 mg/day, after a titration period) in adults with narcolepsy ($\pm$ cataplexy) and persistent EDS (ESS ≥ 12) despite established treatments [9]. A total of 102 participants received pitolisant (29 previously treated with pitolisant [23 with cataplexy], 73 not previously treated with pitolisant [52 with cataplexy]). At baseline, 35% of participants were taking other narcolepsy medications (e.g. stimulants, sodium oxybate, antidepressants), and these co-medications increased (or new treatment was added) in 50%. Sixty-eight participants completed ≥ 12 months of treatment. Most discontinuations (31/34) occurred during the first 3 months; the most common reasons for discontinuation were perceived insufficient efficacy ($n = 20$) and adverse events (AEs) ($n = 11$). Mean change in ESS scores from baseline to end of study among all participants (using last observation carried forward) was -4.0 and among participants who completed 12 months of treatment was -4.6 (Table 3). Among those who completed 12 months of treatment, the 1-year response rate (final ESS score ≤ 10 and/or decrease ≥ 3) was 64.7% (44/68), and ESS scores had normalised (≤ 10) in 36.8% (25/68); in participants whose scores had normalised, mean (standard error [SE]) final ESS score was 6.6 (0.6), a decrease from 15.3 (0.6) at baseline. Among completers with cataplexy data ($n = 44$), mean total cataplexy episodes/day decreased by 68% (Table 3). Among 44 participants with completed sleep diaries, at month 12, mean (SE) hypnagogic hallucinations/day decreased by 54%, from 0.13 (0.06) to 0.06 (0.03) (change, -0.06; 95% CI -0.14 to 0.01), and mean (SE) frequency of sleep paralysis decreased by 63%, from 0.16 (0.06) to 0.06 (0.04) per day (change, –0.10; 95% CI -0.21 to 0.00; $p = 0.023$).

2.1.4 Safety/Tolerability

The most common AEs reported with pitolisant include insomnia (8.4%), headache (7.7%), nausea (4.8%), anxiety (2.1%), irritability (1.8%), dizziness (1.4%), depression (1.3%), tremor (1.2%), sleep disorders (1.1%), fatigue (1.1%), vomiting (1.0%), vertigo (1.0%), dyspepsia (1.0%), weight increase (0.9%) and abdominal pain upper (0.9%). The most serious AEs (SAEs) associated with pitolisant were abnormal weight decrease (0.09%) and abortion spontaneous (0.09%) [12].

An integrated safety analysis of pooled data from four short-term (7- to 8-week) pitolisant randomised controlled trials that used flexible dosing up to 35.6 mg (three studies) or 17.8 mg (one study) evaluated AEs, vital signs, laboratory assessments and electrocardiogram (ECG) data [21]. The analysis population included 303 participants (pitolisant, $n = 172$; placebo, $n = 131$). Treatment discontinuation due to AEs was reported for 3.5% of participants who received pitolisant and 3.8% who received placebo. No clinically relevant effects on vital signs, laboratory findings or ECG measurements were reported.

In the 1-year Harmony 3 long-term study ($n = 102$), 57% of participants reported treatment-emergent AEs (TEAEs); the majority of TEAEs (55%) occurred during the first 3 months. The percentage of participants with TEAEs was greater among those receiving concomitant narcolepsy treatment than among those receiving pitolisant alone (any TEAE, 70% vs. 42%, $p = 0.003$; treatment-related TEAEs, 54% vs. 29%, $p = 0.012$). The most commonly reported TEAEs included headaches (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%) and nausea (4.9%). Serious TEAEs were reported for seven participants (6.9%); all were considered unrelated to treatment with pitolisant, except for one miscarriage, which was considered possibly related [9].

In a US-based expanded-access programme, adults with narcolepsy can receive treatment with pitolisant [22].

Pitolisant is titrated over 3 weeks to 35.6 mg/day (or the highest tolerable dose) and may be adjusted at the discretion of the treating physician. Interim data are available for 208 participants (59% with NT1), the majority of whom (91%) were titrated to pitolisant 35.6 mg/day; 60% of participants treated with pitolisant were also receiving treatment with one or more concomitant narcolepsy medication (e.g. stimulant, sodium oxybate, modafinil, armodafinil, antidepressant) [22]. Overall, the safety/tolerability profile of pitolisant is consistent with what was found in clinical trials. The most common AEs were headache (8.1%), anxiety (3.8%) and nausea (3.4%). AEs were generally mild to moderate and often occurred early in treatment; 5.3% of participants discontinued because of an AE.

The effects of pitolisant on night-time sleep were evaluated using real-world data from a sleep centre database [23]. Fourteen individuals with narcolepsy (64% NT1) were treated with pitolisant 17.8 mg/day (21.4%), 26.7 mg/day (14.3%) or 35.6 mg/day (64.3%) for 6–12 months (mean, 10.2 months). Overnight polysomnographic data suggested no meaningful changes in sleep architecture or quality based on mean total sleep time, sleep efficiency or arousal index. There generally were no changes in subjective sleep quality based on the Pittsburgh Sleep Quality Index (PSQI), with the exception of its sleep efficiency component (increase from 1.2 at baseline to 1.6 at endpoint; $p < 0.05$).

The effects of pitolisant on the corrected QT (QTc) interval were evaluated in a randomised, double-blind, active-control (moxifloxacin), four-period, crossover, thorough QTc study ($n = 58$ healthy volunteers) [16]. Single doses of pitolisant at therapeutic (40 mg) and supratherapeutic (120 mg) levels were compared with moxifloxacin (400 mg) and placebo. Mean observed QTc using Fridericia's formula (QTcF) variation was 3.7 ms (upper bound of 90% CI 5.9) with pitolisant 40 mg and ~ 10 ms (upper bound of 90% CI 12.2 ms) with pitolisant 120 mg, suggesting a risk of QT/QTc prolongation at the supratherapeutic dose. In a phase I study ($n = 25$ healthy male volunteers) of single doses of pitolisant at supratherapeutic levels of 160, 200 and 240 mg, the placebo-corrected increase from baseline (ΔΔQTcF) was > 5 ms at all doses, and the 95% upper bound of predicted effect was 11.9, 13.3 and 9.9 ms, respectively [16]. No specific cardiac safety signal was identified in clinical trials using therapeutic doses of pitolisant; however, caution is advised when pitolisant is used in patients who receive other medications known to prolong QT intervals, or who receive medications that increase pitolisant exposure, as well as in those with severe renal or moderate hepatic impairment [12, 13].

Preclinical data suggested pitolisant has a low potential for abuse [24]. The abuse potential of pitolisant was evaluated in a randomised, double-blind, active- and placebo-controlled four-period crossover study in non-dependent recreational stimulant users ($n = 43$) [25]. Single therapeutic (35.6 mg) and supratherapeutic (213.6 mg) doses of pitolisant were compared with phentermine 60 mg and placebo. Drug liking (peak effect and overall) and willingness to take the drug again for both doses of pitolisant were significantly lower than for phentermine and were similar to placebo, consistent with a minimal risk of abuse.

2.1.5 Place in Therapy

The lack of effect on DA release in the nucleus accumbens differentiates pitolisant from other wake-promoting agents (amphetamine-like psychostimulants) [16], and its tolerability profile, with low rates of TEAEs, is advantageous. Pitolisant is likely to be used both as first- or second-line treatment for narcolepsy with or without cataplexy and as add-on treatment with other narcolepsy medications.

Potential DDIs with antidepressants (which may be used off-label for treatment of narcolepsy) that are metabolised by or affect the activity of CYP enzymes should be considered.

2.2 Solriamfetol

Solriamfetol (formerly JZP-110), a phenylalanine derivative, is a DA and NE reuptake inhibitor indicated to improve wakefulness in adults with EDS associated with narcolepsy or obstructive sleep apnoea [26]. In March 2019, the FDA approved solriamfetol at doses of 75–150 mg/day for the treatment of EDS in narcolepsy [26]. A Marketing Authorisation Application for these indications is under review with the European Medicines Agency.

2.2.1 MOA

Solriamfetol inhibits DA and NE reuptake through DA and NE transporters (DAT, NET), respectively, without significant effects on other targets, including 5-HT, histamine H_1, histamine H_3, α_2-adrenergic and orexin 2 receptors [27]. In vivo, solriamfetol increases extracellular concentrations of DA and NE in the striatum and prefrontal cortex; it does not have substantial monoamine-releasing effects [27]. The wake-promoting effects of solriamfetol are thought to be attributable to its actions at DAT and NET, not to other neurotransmitter receptors involved in regulating sleep (e.g. histamine, orexin) [27].

2.2.2 PK/DDI Potential

Solriamfetol exhibits linear PKs over a dose range of 42–1008 mg (Table 2) [26]. It is rapidly absorbed after oral administration (median t_{max}, 2 h); administration with food delays absorption by ~ 1 h but does not affect overall

exposure (minimal changes in C_{max} and AUC_{∞}) [28]. It is not extensively protein bound (13–19%) and has a mean $t_{½}$ of ~ 7 h [26]. Solriamfetol is minimally metabolised and is excreted primarily in the urine as unchanged drug; renal clearance (18.2 L/h) accounts for the majority of apparent total clearance (19.5 L/h) [26].

Solriamfetol C_{max} and t_{max} values are not substantially affected by mild to severe renal impairment [29]. However, there are incremental decreases in clearance with worsening renal function, and these correspond to increases in AUC_{∞} (53%, 129%, 339%) and $t_{½}$ (1.2-, 1.9-, 3.9-fold) in mild, moderate and severe renal impairment, respectively, relative to no renal impairment. Exposure (AUC_t) was 4- or 5-fold higher (with or without dialysis) in ESRD than in normal renal function, and the $t_{½}$ was over 100 h (regardless of dialysis). Dosage adjustments are recommended for patients with moderate and severe renal impairment (initial dose for both, 37.5 mg/day; maximum doses, 75 and 37.5 mg/day, respectively); use of solriamfetol is not recommended for patients with ESRD [26]. Because solriamfetol undergoes minimal metabolism [26], hepatic impairment is not expected to affect its PKs.

Clinically significant DDIs involving major CYPs and transporters are not expected with solriamfetol, based on in vitro data [26]. Because of the potential for pharmacodynamic interactions when solriamfetol is used concomitantly with other drugs that increase blood pressure (BP) and/or heart rate (HR) or drugs that increase levels of DA or that bind directly to DA receptors, such combinations should be used with caution. Solriamfetol should not be used concomitantly with or within 14 days after discontinuing monoamine oxidase inhibitors (MAOIs) [26].

2.2.3 Efficacy

A phase IIb, 12-week, randomised, double-blind, placebo-controlled trial evaluated the efficacy of solriamfetol in adults with narcolepsy with or without cataplexy [30]. Participants were randomly assigned to receive placebo or solriamfetol (150 mg/day for 4 weeks, then 300 mg/day for 8 weeks). Co-primary endpoints were change from baseline in mean MWT sleep latency and percentage of patients rated as improved on CGI-C at week 12. The safety population had 93 participants (solriamfetol, 44; placebo, 49); 33 (35.5%) had cataplexy. Solriamfetol demonstrated efficacy compared with placebo on MWT sleep latency (Table 3) and percentage of participants improved on CGI-C (86.0% vs. 38.3%; $p < 0.0001$). Improvement in ESS scores (Table 3) and the percentage of participants with improvement on PGI-C (93% vs. 38.3%; $p < 0.0001$) were also greater with solriamfetol than with placebo. On the exploratory endpoint of number of weekly attacks, median change from baseline to week 12 was − 1.0 for solriamfetol and 0 for placebo (Table 3).

The efficacy and safety of solriamfetol were also evaluated in a phase III, 12-week randomised, double-blind, placebo-controlled trial from the TONES (Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness) phase III programme—the TONES 2 study [31]. Adults with narcolepsy with or without cataplexy were randomly assigned to fixed doses of solriamfetol (75, 150, 300 mg/day) or placebo. Co-primary endpoints were change from baseline in mean MWT sleep latency and ESS score. The safety population had 236 participants; 120 (51%) reported having cataplexy. Efficacy was evaluated in the ITT population ($n = 231$). At week 12, solriamfetol was associated with greater improvement than placebo on MWT sleep latency (150 and 300 mg doses) and ESS scores (all doses; Table 3). Improvement on PGI-C was reported by 67.8%, 78.2% and 84.7% in the 75, 150 and 300 mg groups, respectively, and 39.7% in the placebo group ($p < 0.0001$ for 150 and 300 mg vs. placebo). Improvement on CGI-C was reported for 69.5%, 83.6% and 83.1% in the 75, 150 and 300 mg groups, respectively, and 41.4% in the placebo group ($p < 0.05$ for 75 mg and $p < 0.0001$ for 150 and 300 mg vs. placebo). There was no clear effect of solriamfetol on number of weekly cataplexy attacks (the study was not designed or powered to evaluate this outcome).

A long-term open-label extension study evaluated the safety and maintenance of efficacy of solriamfetol in participants with narcolepsy or obstructive sleep apnoea [32]. Adults who completed an earlier solriamfetol study ($n = 643$; 226 with narcolepsy) received solriamfetol (2-week titration, up to 50 weeks of maintenance treatment at doses of 75 mg/day, 150 mg/day, or 300 mg/day). The study included a 2-week randomised-withdrawal phase after 6 months of treatment in which participants were randomly assigned to solriamfetol ($n = 139$) or placebo ($n = 141$). Of participants with narcolepsy, 66.4% completed the full study; TEAEs (10.2%) and lack of efficacy (17.3%) were the most frequent reasons for withdrawal. In the open-label phase, solriamfetol was associated with sustained reductions in mean ESS scores (Table 3). At the end of open-label treatment, approximately 87% of participants with narcolepsy (previously treated and previously untreated subgroups) reported improvement on PGI-C; improvement on CGI-C was reported for 88.2% of previously treated and 89.5% of previously untreated participants with narcolepsy. In the randomised-withdrawal phase (data not reported by diagnosis subgroups), significant increases in ESS scores were found with placebo versus solriamfetol (Table 3) and participants who received placebo were worse than those who received solriamfetol on both PGI-C (64.5% vs. 28.2%; $p < 0.0001$) and CGI-C (63.8% vs. 28.7%; $p < 0.0001$); similar results were observed by indication across endpoints ($p < 0.05$).

2.2.4 Safety

The most common TEAEs with solriamfetol (incidence ≥ 2% and greater than placebo) in the narcolepsy studies at the FDA-approved doses were headache, decreased appetite, nausea, anxiety, insomnia, dry mouth, constipation and palpitations [26].

Discontinuations due to AEs were reported for 7% of solriamfetol-treated participants in the short-term phase IIb study and for 5.1% of solriamfetol-treated participants (1.7%, 5.1% and 8.5% for the 75, 150 and 300 mg groups) in the short-term phase III study, compared with 4% and 2% in placebo-treated participants, respectively [30, 31]. SAEs were reported for 4.5% (2/44) and 0.6% (1/177) of solriamfetol-treated participants in the phase IIb and III studies, respectively (no SAEs with placebo in either study) [30, 31].

Solriamfetol has been associated with dose-dependent increases in BP and HR [26]. In the phase III study, based on 24-h ambulatory BP monitoring, mean changes from baseline to week 8 in systolic BP (SBP) were − 0.5–2.4 mmHg with solriamfetol (across doses 75–300 mg) and − 0.4 mmHg with placebo; in diastolic BP (DBP) were 0.8–3.0 mmHg with solriamfetol and − 0.2 mmHg with placebo; and in HR they were 0.2–4.8 beats per min (bpm) with solriamfetol and 0.0 bpm with placebo.

In the long-term study [32], common AEs (≥ 5%) included headache (incidence in narcolepsy subgroup, 13.7%), nausea (11.5%), nasopharyngitis (8.4%), insomnia (7.1%), dry mouth (6.2%), anxiety (9.3%), decreased appetite (8.0%) and upper respiratory tract infection (4.4%). SAEs were reported for six (2.7%) participants with narcolepsy.

Effects on QTc were evaluated in a randomised, double-blind, four-period, placebo- and positive-controlled crossover study comparing single doses of solriamfetol (300, 900 mg), moxifloxacin 400 mg and placebo in healthy volunteers ($n = 60$) [33]. The upper bounds of two-sided 90% CIs for the mean differences in mean pre-dose-adjusted QTcF between both doses of solriamfetol (300 and 900 mg) and placebo were < 10 ms at all post-dose timepoints, suggesting minimal risk of QTc prolongation. Small mean dose-dependent increases in HR (from 2 through 12 h after dosing), SBP and DBP were found after administration of solriamfetol 300 or 900 mg, and absolute values remained within normal ranges.

The abuse potential of solriamfetol was evaluated in a randomised, double-blind, placebo-controlled crossover study in adults with recent history of recreational polydrug use from two or more illicit drug classes including a stimulant ($n = 43$) [34]. Solriamfetol (300, 600, 1200 mg) was compared with phentermine (45 and 90 mg) and placebo. Peak drug liking was significantly higher with solriamfetol (all doses) than with placebo but was lower than with phentermine 90 mg. Overall drug liking with solriamfetol 600 and 1200 mg was not significantly different from that with placebo and was significantly lower than that with both doses of phentermine; with solriamfetol 300 mg, overall drug liking was significantly higher than that with placebo but was not significantly different from that with phentermine 45 mg. Participants were significantly less willing to take solriamfetol (all doses) again than to take phentermine (both doses) again. In addition, positive medication effects were consistently lower and negative effects consistently higher with solriamfetol than with phentermine. Overall, the data suggest the abuse potential of solriamfetol may be similar to or lower than that of phentermine. Accordingly, solriamfetol has received a Schedule IV designation in the USA [26].

2.2.5 Place in Therapy

Available data suggest solriamfetol may have efficacy advantages over existing agents in improving alertness. The safety and tolerability profile of solriamfetol, including cardiovascular effects (BP, HR), is acceptable. Further, compared with other wake-promoting agents, solriamfetol has lower potential for DDIs and no need for use of a secondary method of birth control in patients using oral/hormonal contraceptives (as recommended for modafinil [35] and pitolisant [12, 13]). Although head-to-head studies have not compared solriamfetol and other agents, an indirect treatment comparison analysis suggested that the magnitude of effects of solriamfetol on ESS and MWT may be greater than that of modafinil or armodafinil [36]. However, currently available data suggest that solriamfetol does not significantly affect cataplexy, in contrast to sodium oxybate and pitolisant.

3 Investigational Drugs

Table 1 provides an overview of emerging treatments for narcolepsy.

3.1 FT218 (Controlled-Release Sodium Oxybate)

FT218 is a novel controlled-release formulation of sodium oxybate [37]. This formulation involves proprietary Micropump® technology, a microparticulate platform that can be used to achieve either extended delivery or both delayed and extended delivery of orally administered small-molecule medications [38]. FT218 is in phase III development for treatment of EDS associated with narcolepsy and cataplexy, and has been designated an orphan drug by the FDA [37].

3.1.1 MOA

Sodium oxybate, the sodium salt of γ-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA [39], acts as a $GABA_B$ receptor agonist [38]. The MOA of sodium oxybate in the treatment of narcolepsy is not known, but the therapeutic effects of sodium oxybate on cataplexy and EDS are hypothesised to be mediated through $GABA_B$ agonist actions at noradrenergic and dopaminergic neurons and thalamocortical neurons [39].

3.1.2 PK/DDI Potential

A pilot PK study in healthy volunteers ($n = 16$) evaluated three prototypes for FT218 (Table 2). For each prototype, the study compared a single 4.5 g dose with two 2.25 g doses (totalling 4.5 g) of immediate-release sodium oxybate [40]. All three prototypes showed a sustained-release profile, with C_{max} below the C_{max} of immediate-release sodium oxybate and concentration at 8 h (C_{8h}) close to reference values. Prototype 2 was selected for further study, as its C_{max} was higher than that of the other prototypes, and its AUC_∞ was closest to that of immediate-release sodium oxybate.

A phase I PK study (n not stated) evaluated dose proportionality of FT218 across the dosage range of 4.5, 7.5 and 9 g [41]. Single-dose administrations of each dose were separated by a ≥ 7-day washout period. Mean PK parameters reflected similar profiles across doses; median t_{max} was 1.5–2 h. The mean C_{max} increased in a dose-proportional manner (slope estimate, 1.02; 90% CI 0.84–1.21); dose proportionality for AUC_∞ was exceeded (1.34; 90% CI 1.17–1.46) but to a lesser extent than with immediate-release sodium oxybate (2.3- vs. 3.8-fold increase, respectively).

An ongoing phase III trial is evaluating the bioavailability of FT218 relative to immediate-release sodium oxybate (Xyrem®) in healthy volunteers [38, 42].

The potential for DDIs with FT218 would be expected to be similar to that with immediate-release sodium oxybate. Divalproex sodium increases exposure to sodium oxybate, necessitating a reduction in the dose of sodium oxybate, and concomitant use of other CNS depressants may potentiate the CNS-depressing effects of sodium oxybate [39].

3.1.3 Efficacy

The efficacy of FT218 is being evaluated in the phase III, 13-week, multinational, multicentre, double-blind, placebo-controlled REST-ON (Randomized study Evaluating the efficacy and SafeTy of a Once Nightly formulation of sodium oxybate; ClinicalTrials.gov identifier NCT02720744) trial (Table 3) [38, 43]. Participants (age, ≥ 16 years) with narcolepsy with or without cataplexy will receive FT218 (titrated to 4.5, 6.0, 7.5 or 9.0 g/day) or placebo [43].

Estimated target enrolment is 264 participants [43]; enrolment as of February 2019 was 149 participants [38]. Primary outcome measures include MWT sleep latency, CGI-C sleepiness scores and mean number of cataplexy attacks [43].

3.1.4 Safety

No safety or tolerability findings have been reported in published abstracts on studies in healthy volunteers [40, 41].

3.1.5 Place in Therapy

Once-nightly dosing with FT218 offers a potential advantage over the twice-nightly dosing required with the currently available formulation of sodium oxybate. (Note: for some patients, twice-nightly dosing is not bothersome and in some cases may be preferred.) Although it is reasonable to expect that the safety and tolerability of FT218 generally will be similar to those of the currently available formulation, the lower C_{max} compared with that of immediate-release sodium oxybate may confer improved tolerability for FT218.

3.2 JZP-258

JZP-258 is a novel low-sodium oxybate preparation in phase III development for treatment of cataplexy and EDS in patients with narcolepsy [44]. JZP-258 is a combination of sodium oxybate, potassium oxybate, calcium oxybate and magnesium oxybate [45] and has 92% less sodium than sodium oxybate [44].

3.2.1 MOA

As with sodium oxybate products, the MOA of JZP-258 is not fully understood. The therapeutic effects of JZP-258 on sleep–wake symptoms are hypothesised to be mediated through modulation of $GABA_B$ [44].

3.2.2 PK/DDI Potential

The PKs of JZP-258 were compared with sodium oxybate in two phase I studies [46]. JZP-258 had a lower C_{max}, longer t_{max}, and similar AUC compared with that of sodium oxybate. Food reduced the C_{max} for both agents, but to a lesser extent with JZP-258 than with sodium oxybate ($p < 0.05$) [46]. As with FT218, the potential for DDIs with JZP-258 generally would be expected to be similar to that of immediate-release sodium oxybate.

3.2.3 Efficacy

The efficacy and safety of JZP-258 in treating cataplexy in adults with narcolepsy was evaluated in a phase III

multicentre, randomised-withdrawal study (Table 3) [47]. This study included a titration period of up to 12 weeks and a 2-week stable-dose period, followed by 1:1 randomisation to either JZP-258 or placebo for 2 weeks. A 24-week, open-label safety extension period was optional for participants who completed the randomised-withdrawal period. The study population included participants previously treated with sodium oxybate, those naive to sodium oxybate, and those with or without other anticataplectic treatments [48]. Of 201 participants enrolled, 134 were randomly assigned to JZP-258 or placebo and assessed for efficacy [47]. Differences between JZP-258 and placebo were statistically significant for the primary endpoint (change in weekly number of cataplexy attacks) and key secondary endpoint (change in ESS score), indicating clinically meaningful maintenance of efficacy with JZP-258 and statistically significant worsening on both endpoints with placebo (Table 3). Additionally, the percentage of participants with worsening was higher for placebo than for JZP-258 on both PGI-C (44.6% vs. 4.3%) and CGI-C (60.0% vs. 5.9%; nominal $p < 0.0001$).

3.2.4 Safety

In the phase III randomised-withdrawal study, the most commonly reported TEAEs (≥ 5% of participants who received JZP-258) were headache (22.4%), nausea (13.4%) and dizziness (11.4%); treatment-related SAEs were reported in two participants [47]. A 24-week open-label safety study is ongoing.

3.2.5 Place in Therapy

The lower sodium formulation of JZP-258 may have advantages over sodium oxybate—it would be expected to be preferable for patients sensitive to sodium (e.g. those with hypertension, heart failure or renal impairment) and may be less likely to cause fluid accumulation/swelling, which can occur in some patients taking sodium oxybate [39, 49].

In addition, JZP-258 may be better tolerated than sodium oxybate (some patients associate the high sodium content of sodium oxybate with an unpleasant taste and gastrointestinal effects [39, 49]). JZP-258 has the potential to become a preferred approach for treating cataplexy and EDS, particularly if it is better tolerated than sodium oxybate.

3.3 AXS-12 (Reboxetine)

AXS-12 (reboxetine) is an NE reuptake inhibitor originally developed for the treatment of depression that is approved for that indication in more than 40 countries outside the USA [50]. AXS-12 is in development for the treatment of cataplexy and EDS associated with narcolepsy [50] and has been designated an orphan drug by the FDA [51].

3.3.1 MOA

AXS-12 selectively inhibits NE reuptake but has a weak effect on 5-HT reuptake and no effect on DA reuptake [52]. Preclinical data have demonstrated a reduction in narcoleptic episodes (~ 50% of which fulfil criteria for cataplexy; the remainder are sleep attacks) in orexin-deficient mice—an effect attributed to NE reuptake inhibition [53].

3.3.2 PK/DDI Potential

The PKs of AXS-12 are linear after single doses up to 4.5 mg and after multiple doses up to 12 mg/day (Table 2) [54]. AXS-12 is rapidly absorbed after oral administration (t_{max}, 2–4 h) and is highly protein bound (primarily α_1-acid glycoprotein). The mean $t_{½}$ of AXS-12 is ~ 12.5 h and mean plasma clearance is 2.21 L/h. Administration with food delays absorption and significantly reduces C_{max}, but AUC_{∞} is unaffected. AXS-12 is eliminated primarily through metabolism by CYP3A4. Systemic exposure (AUC_{∞}) and the $t_{½}$ are ~ twofold higher in patients with renal or hepatic impairment than in healthy volunteers. DDI studies in healthy volunteers have demonstrated that strong CYP3A4 inhibitors increase exposure (AUC), decrease clearance and prolong the $t_{½}$ of AXS-12. Based on information for the currently available reboxetine product, AXS-12 should not be coadministered with drugs known to inhibit CYP3A4; low reboxetine serum concentrations have been reported with concurrent administration of CYP3A4 inducers [52]. In vitro data suggest AXS-12 does not affect activity of CYP1A2, CYP2C9, CYP2D6, CYP2E1 or CYP3A4 [54]. Concomitant use with MAOIs should be avoided. There is a potential for increased BP with concomitant use of ergot derivatives and for hypokalaemia with concomitant use of potassium-losing diuretics [52].

3.3.3 Efficacy

A 2-week pilot study evaluated the stimulant and anticataplectic effects of AXS-12 in 12 consecutive participants (six men, six women with narcolepsy) who attended a sleep disorders clinic (Table 3) [55]. Mean (standard deviation [SD]) age was 36.6 (11.7) years. AXS-12 was titrated from a dose of 2 mg/day (single dose in the morning) on day 1 to 10 mg/day (6 mg in the morning, 4 mg at lunchtime) beginning on day 9. All 12 participants completed the 2-week treatment period. The mean (SD) ESS score decreased ~ 49%, from 20.58 (2.93) at baseline to 10.58 (7.21) on day 14 ($p < 0.01$), and mean (SD) MSLT sleep latency increased ~ 55%, from 4.86 (4.01) min at baseline to 7.52 (4.97) min on day 7 ($p < 0.05$). Significant improvement was found in the frequency of cataplexy attacks, based on a decrease in the mean (SD) Ullanlinna Narcolepsy Scale

cataplexy score, from 5.85 (2.67) at baseline to 1.71 (1.60) on day 7 ($p < 0.05$).

A phase II randomised, double-blind, placebo-controlled crossover study in participants with narcolepsy with cataplexy and EDS is underway (ClinicalTrials.gov identifier NCT03881852) [56]. This study includes two 3-week treatment periods (AXS-12, placebo); participants are randomly assigned to one of two sequences. Efficacy outcomes include change in number of cataplexy attacks, MWT and ESS.

3.3.4 Safety

AEs reported in the 2-week pilot study included dry mouth, hyperhidrosis, constipation and restlessness [55]. The most common AEs reported in clinical trials of AXS-12 for depression and in post-marketing experience include insomnia, dizziness, dry mouth, constipation, nausea and hyperhidrosis [52].

3.3.5 Place in Therapy

As noradrenergic reuptake inhibitors (e.g. venlafaxine) tend to be very effective in treating cataplexy, AXS-12 likely would be used as an anticataplectic. If AXS-12 also improves EDS, it could become an alternative for patients who cannot take sodium oxybate or pitolisant. Given that AXS-12 is approved outside the USA for treating major depressive disorder [52], it potentially could be well-suited for patients who have both narcolepsy and depression (up to 57% of narcolepsy patients report symptoms of depression [57, 58]).

3.4 THN102 (Modafinil/Flecainide)

THN102, a combination of modafinil and flecainide [59], reached phase II development for EDS associated with narcolepsy and is in phase II development for EDS and other symptoms in Parkinson's disease [59].

3.4.1 MOA

Modafinil is a non-amphetamine agent with wake-promoting effects thought to be mediated through DA reuptake inhibition [35]. The therapeutic effects of modafinil also may be related to modulation of connexins, as astrocytes and astroglial connexins are thought to be involved in sleep–wake regulation. Specifically, experimental data indicate that, in the cortex, modafinil increases messenger RNA (mRNA) expression and protein of connexin 30, a major astroglial connexin [60, 61].

Flecainide is an inhibitor of astroglial connexins [62]. In preclinical studies [63], flecainide enhanced the wake-promoting and pro-cognitive effects of modafinil in wild-type mice and modafinil/flecainide coadministration decreased the number and duration of direct transitions to REM sleep (characteristic of narcoleptic episodes) in orexin knockout mice. Modafinil also enhanced connexin-mediated astroglial cell coupling—an effect reversed with flecainide coadministration.

3.4.2 PK/DDI Potential

Data on PKs and potential DDIs have not been reported specifically for THN102. However, data from mouse models indicate that flecainide did not affect the PK parameters or bioavailability of modafinil [63]. The DDI profile of THN102 would be expected to be consistent with its individual components (modafinil and flecainide).

3.4.3 Efficacy

THN102 was evaluated in a phase II double-blind, randomised, placebo-controlled, three-way crossover trial [64] in ~48 adults with narcolepsy with or without cataplexy (Table 3) [64]. Participants received modafinil/flecainide 300 mg/3 mg, modafinil/flecainide 300 mg/27 mg and modafinil 300 mg/placebo in each of three 2-week treatment periods [64]. Preliminary results did not indicate any difference in efficacy between THN102 and modafinil alone. This finding might result from an overrepresentation of participants with severe narcolepsy who had a low response to modafinil [59, 65].

3.4.4 Safety

In a press release, the sponsor stated that the safety and tolerability profile of THN102 was "very satisfactory" based on phase II data [59]. Specific safety data have not been reported.

3.4.5 Place in Therapy

The potential role of THN102 in narcolepsy is unclear. Development in narcolepsy is on hold due to lack of efficacy in the phase II study; further development is pending results of a phase II study in Parkinson's disease [65].

3.5 Other Agents (Earlier Development Phases)

3.5.1 Histamine H_3 Receptor Inverse Agonists

SUVN-G3031 is an H3R inverse agonist in phase II development [66]. Preclinical data have demonstrated wake-promoting and anticataplectic effects in rodents [67].

In several species, SUVN-G3031 caused significant increases in acetylcholine, histamine, DA and NE levels in the cortex but did not alter DA levels in the striatum and nucleus accumbens, indicating it may not have abuse potential [68]. SUVN-G3031 did not inhibit or induce major CYP

isoforms and was not a substrate or an inhibitor of major uptake transporters. Preclinical studies indicated no negative effects on ECG parameters, fertility or embryofoetal development and no CNS safety issues [66].

Phase I data from single-dose (0.1, 1, 6, 12, 20 mg) and multiple ascending-dose (1, 3, 6 mg daily for 14 days) studies in healthy participants (*n* not stated) demonstrated rapid absorption of SUVN-G3031 with dose-proportional exposure [69]. Projected efficacy concentrations were achieved and steady state attained on day 5. No effects of food, gender or age on the PKs of SUVN-G3031 were found. Tolerability was considered acceptable up to the highest tested dose in single- and repeat-dose studies.

3.5.2 Hypocretin/Orexin 2 Receptor-Selective Agonists

Strategies being investigated for the treatment of narcolepsy include hypocretin/orexin-based strategies, such as hypocretin/orexin receptor agonists [70, 71]. For example, the hypocretin/orexin 2 receptor-selective agonist TAK-925 (administered subcutaneously) has demonstrated improved wakefulness, reduced cataplexy-like episodes and ameliorated weight gain in a mouse model of narcolepsy [72, 73]. A phase I study evaluated the safety, tolerability and PKs of single ascending doses of TAK-925 (7–240 mg, administered as a 9-h intravenous [IV] infusion) in healthy volunteers ($n = 36$) and evaluated the safety, PKs and efficacy (exploratory) of TAK-925 (5, 11.2 and 44.8 mg, administered as a 9-h IV infusion) in a placebo-controlled crossover study in patients with NT1 ($n = 14$) [74]. PK analyses showed that TAK-925 exposure was approximately dose-proportional over the dose range studied and $t_{½}$ was less than 2 h; PKs were similar in healthy volunteers and patients with NT1. The most common TEAEs observed in healthy volunteers were BP increase (at doses of 134.4 mg [two of six participants], 180 mg [two of six participants] and 240 mg [four of six participants]) and HR increase (two of six participants at 134.4 mg dose). In healthy volunteers and patients with NT1, TEAEs were generally mild in severity, with no SAEs reported. In patients with NT1, mean sleep latency on the 40-min MWT was 22.4, 37.6 and 40.0 min with TAK-925 5, 11.2 and 44.8 mg, respectively, compared with 2.9 min with placebo ($p < 0.001$ for difference in least squares means vs. placebo with all doses); scores on the Karolinska Sleepiness Scale were lower with all doses of TAK-925 than with placebo.

Another hypocretin/orexin 2 receptor-selective agonist, TAK-994 (administered orally), increased wakefulness and reduced cataplexy-like episodes in mouse models; TAK-994 also ameliorated fragmentation of wakefulness in these models [75, 76]. Additional hypocretin/orexin-based strategies under consideration include administration of orexin peptides, neuronal transplantation, stem cells and gene therapy [71].

3.5.3 Immune-Based Therapies

Immune-based therapies are a strategy of interest for NT1, based on the hypothesis that destruction of hypocretin neurons in NT1 is autoimmune mediated [71, 77]. A variety of immune therapies, including corticosteroids, intravenous immunoglobulin (IVIg), plasmapheresis, alemtuzumab and rituximab have been investigated; however, data are limited to case reports or small case series and results have been variable (see reviews in Barateau and Dauvilliers [71] and Barateau et al. [77]).

4 Summary

As research continues to provide insights into the mechanisms underlying narcolepsy, the development of new treatments continues to evolve, offering more options for optimising management of narcolepsy symptoms, particularly EDS and cataplexy. Additional data from ongoing and planned clinical trials, as well as real-world evidence from upcoming newly approved agents, will help determine the specific role or place in therapy for these new treatments.

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Compliance with Ethical Standards

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