Management of excessive daytime sleepiness in patients with obstructive sleep apnea or narcolepsy: A common link for separate conditions

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Current treatment strategies for the management of excessive daytime sleepiness

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Why is it important to manage excessive daytime sleepiness in people living with obstructive sleep apnea or narcolepsy?

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Goals for the effective management of EDS

Desired clinical outcomes include improvements in:[1–5]

- Daytime sleepiness
- Clinical measures related to the underlying cause, e.g. AHI and ODI in OSA
- Patient-reported QoL
- Cardiovascular outcomes
- Weight loss (when indicated)

Meaningful patient treatment goals include improvements in:[5–7]

- Wakefulness and alertness
- Safety
- Cognitive functioning
- Productivity in work and daily life
- Mood
- Social and financial health

- Guidelines for the management of common underlying conditions of EDS are available from international bodies such as AASM,[8,9] ACP[1] and ERS[10]
- COVID-19 updates for patients with OSA have been provided by AASM, including advice on the use of CPAP machines and attending in-lab vs at-home testing[11,12]

AASM, American Academy of Sleep Medicine; ACP, American College of Physicians; AHI, Apnea-Hypopnea Index; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ; ERS, European Respiratory Society; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; QoL, quality of life.

1. Qaseem A, et al. *Ann Intern Med*. 2013;159:471–83; 2. Karhu T, et al. *Front Neurosci*. 2021;15:657126; 3. Isidoro SI, et al. *Health Qual Life Outcomes*. 2015;13:68; 4. Drager LF, et al. *Circulation*. 2017;136:1840–50; 5. Sahni AS, et al. *Nat Sci Sleep*. 2019;11:241–52; 6. Waldman LT, et al. *Health Qual Life Outcomes.* 2020;18:128; 7. Lal C, et al. *Ann Am Thorac Soc*. 2021;18:757–68; 8. Epstein LJ, et al. *J Clin Sleep Med*. 2009;5:263-76; 9. Maski K, et al. *J Clin Sleep Med.* 2021;17:1895–945; 10. Randerath WJ, et al. *Eur Resp J*. 2011;37:1000–28; 11. AASM. Coronavirus FAQs: CPAP tips for sleep apnea patients. 2020. Available at: www.aasm.org/coronavirus-covid-19-faqs-cpap-sleep-apnea-patients/ (accessed 22 October 2021). 12. AASM. Considerations for the practice of sleep medicine during COVID-19. 2021. Available at: www.aasm.org/covid-19-resources/considerations-practice-sleep-medicine (accessed October 2021).

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What role do non-pharmacological measures currently play in the management of excessive daytime sleepiness?

Non-pharmacological therapy for EDS

OSA[1,2]

CPAP is recommended for patients with all severities of OSA

Weight loss is recommended if patients are overweight or obese

Positional therapy is recommended for management of exclusively positional sleep apnea and supplemental to primary therapies

Oral appliances to improve upper airway patency during sleep

Hypoglossal nerve stimulator

Surgery to the upper airway

Narcolepsy[3,4]

Non-pharmacological treatments are considered adjunctive

Scheduled daytime naps

Patient education on managing symptoms and optimizing sleep hygiene

Self-report assessments and sleep logs

Weight loss is encouraged if patients are overweight or obese

Comorbid OSA and narcolepsy

CPAP in patients with comorbid OSA and narcolepsy should be second-line, adjunctive therapy to standard pharmacological therapy for narcolepsy[2]

CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea.

1. Epstein LJ, et al. *J Clin Sleep Med*. 2009;5:263–76; 2. Kent DT, et al. *JAMA Otolaryngol Head Neck Surg.* 2019;145:1044–52;
3. Sahni AS, et al. *Nat Sci Sleep*. 2019;11:241–52; 4. Bhattarai J, Sumerall S. *Sleep Sci*. 2017;10:19–27.

How and when should pharmacotherapies be deployed in the management of excessive daytime sleepiness?

Approved pharmacological agents for the treatment of EDS in OSA and narcolepsy[1]

- **Pharmacological therapy is the mainstay of treatment for narcolepsy**
- **CPAP is the gold-standard therapy for OSA and pharmacological therapy is adjunctive**

Indicated for OSA and narcolepsy	
Modafinil	Non-amphetamine stimulant; considered the 1L treatment for EDS by the AASM
Armodafinil	R-enantiomer of modafinil that acts as a dopamine-2 receptor partial agonist
Solriamfetol	Dopamine and norepinephrine reuptake inhibitor

Indicated for narcolepsy only	
Pitolisant	Antagonist of the histamine H_3 autoreceptor
Na oxybate; Ca/Mg/K/Na oxybates	CNS depressant indicated for EDS with or without cataplexy; caution required due to its contraindication with other CNS depressants and abuse potential. A low-sodium oxybate treatment option has recently been approved in the USA[2]
Amphetamines	Methylphenidate and dextroamphetamines sulphate; considered 2/3L therapies due to their abuse potential

Key considerations for pharmacological therapy

- Patients should be counselled on contraindications, side effects and potential for abuse and dependency
- Patients may become tolerant to treatments and require regular review

AASM, American Academy of Sleep Medicine; CNS, central nervous system; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; L, line; OSA, obstructive sleep apnea.

1. Sahni AS, et al. *Nat Sci Sleep*. 2019;11:241–52; 2. Bogan RK, et al. *Sleep.* 2021;44:zsaa206.

What more is needed to optimize quality of life and address ongoing unmet needs for people living with excessive daytime sleepiness?

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How can we optimize the management of EDS in a way that makes a meaningful difference to patients?

~12% of patients with narcolepsy report adequate symptom control[1]

9–22% patients with OSA continue to experience EDS despite adequate primary therapy[2]

Patients and physicians agree there is a need for better treatment options[1,3,4]

New non-stimulant wake-promoting agents

Improved patient–physician education and engagement

Improved psychosocial and holistic support to enhance behaviour modification strategies, sleep hygiene and routines

Improved awareness of potential tolerance and misuse of therapeutic agents

EDS, excessive daytime sleepiness.

1. Thorpy MJ, et al. *Neurology.* 2019;92(Suppl. 15):P3.6-036; 2. Lal C, et al. *Ann Am Thorac Soc.* 2021;18:757–68; 3. Maski K, et al. *J Clin Sleep Med.* 2021;17:1895–945; 4. Gandhi KD, et al. *Mayo Clin Proc.* 2021;96:1288–301.

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What's on the horizon for the optimal management of excessive daytime sleepiness in patients with obstructive sleep apnea or narcolepsy?

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- How might new and emerging agents impact future approaches to the management of excessive daytime sleepiness in people living with obstructive sleep apnea or narcolepsy?

Addressing unmet needs remaining in EDS management

Psychological, emotional and cognitive challenges remain a significant burden for people living with EDS in OSA or narcolepsy[1–4]

How will new and emerging therapies address treatment needs in EDS beyond sleep attacks?

- Psychiatric comorbidity (e.g. depression)
- Sustained attention and cognitive function
- Improve nocturnal sleep
- Psychosocial and role function
- Reduce side effects including long-term CV risks
- Improve daily functionality and better support overall QoL

Development, validation and wider adoption of clinically relevant and meaningful PROMs are imperative to optimize management of EDS tailored to individual needs and life circumstances[5,6]

CV, cardiovascular; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea; PROM, patient-reported outcome measure; QoL, quality of life.

1. Thorpy MJ, et al. *CNS Drugs.* 2020;34:9–27; 2. Waldman LT, et al. *Health Qual Life Outcomes.* 2020;18:128; 3; Lal C, et al. *Ann Am Thorac Soc.* 2021;18:757–68; 4. Gandhi KD, et al. *Mayo Clin Proc.* 2021;96:1288–301; 5. Abmer IL, et al. *Sleep Med Rev.* 2016;28:18–31; 6. Kallweit U, et al. *J Clin Sleep Med.* 2017;13:737–44.

How are new and emerging agents targeting our current understanding of the pathophysiology of excessive daytime sleepiness?

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Understanding and targeting sleep-wake control mechanisms in EDS

Greater understanding of sleep-wake control mechanisms is driving development of new pharmacotherapies for the management of EDS in OSA and narcolepsy[1–6]

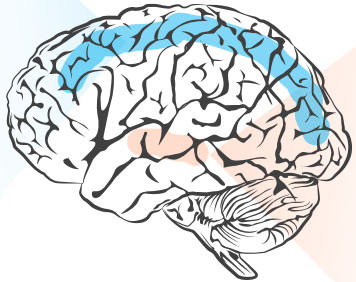
Sleep-promoting

$GABA_B$ agonists

Valiloxybate *NCE* (XW10172-MR)

Mixed (Ca/Mg/K/Na) oxybates (JZP-258)

Controlled-release Na oxybate (FT218)



Other arousal pathways

A_{2A}-R antagonists

Wake-promoting

DNRI

Solriamfetol (JZP-110)

NRI

Reboxetine (AXS-12)

H_3R antagonist

Pitolisant

Samelisant *NCE* (SUVN-G3031)

Sympathomimetic amine (SNDRI, H_1R, ORX_2R)

Mazindol extended release (NLS2)

ORX-R agonist

ORX_2R-selective agonists (YNT-185; TAK-925)

A_{2A}-R, adenosine A_{2A} receptor; DNRI, dopamine and norepinephrine reuptake inhibitor;
EDS, excessive daytime sleepiness; GABA, γ-aminobutyric acid; H1R, histamine H_1 receptor; H3R, histamine H_3 receptor; ORX-R, orexin receptor;
OSA, obstructive sleep apnea; NCE, new chemical entity; NRI, norepinephrine reuptake inhibitor; SNDRI, serotonin-, noradrenaline- and dopamine-reuptake inhibitor.

1. Murray BJ. *Canadian Resp J.* 2016:4215938; 2. Thorpy MJ, et al. *CNS Drugs.* 2020;34:9–27; 3. Sahni AS, et al. *Nat Sci Sleep.* 2019;11:241–52;
4. Lal C, et al. *Ann Am Thorac Soc.* 2021;18:757–68; 5. Thorpy, MJ Bogan RK. *Sleep Med.* 2020;68:97–109; 6 Wigal TL, et al. *CNS Drugs.* 2018;32:289–301.

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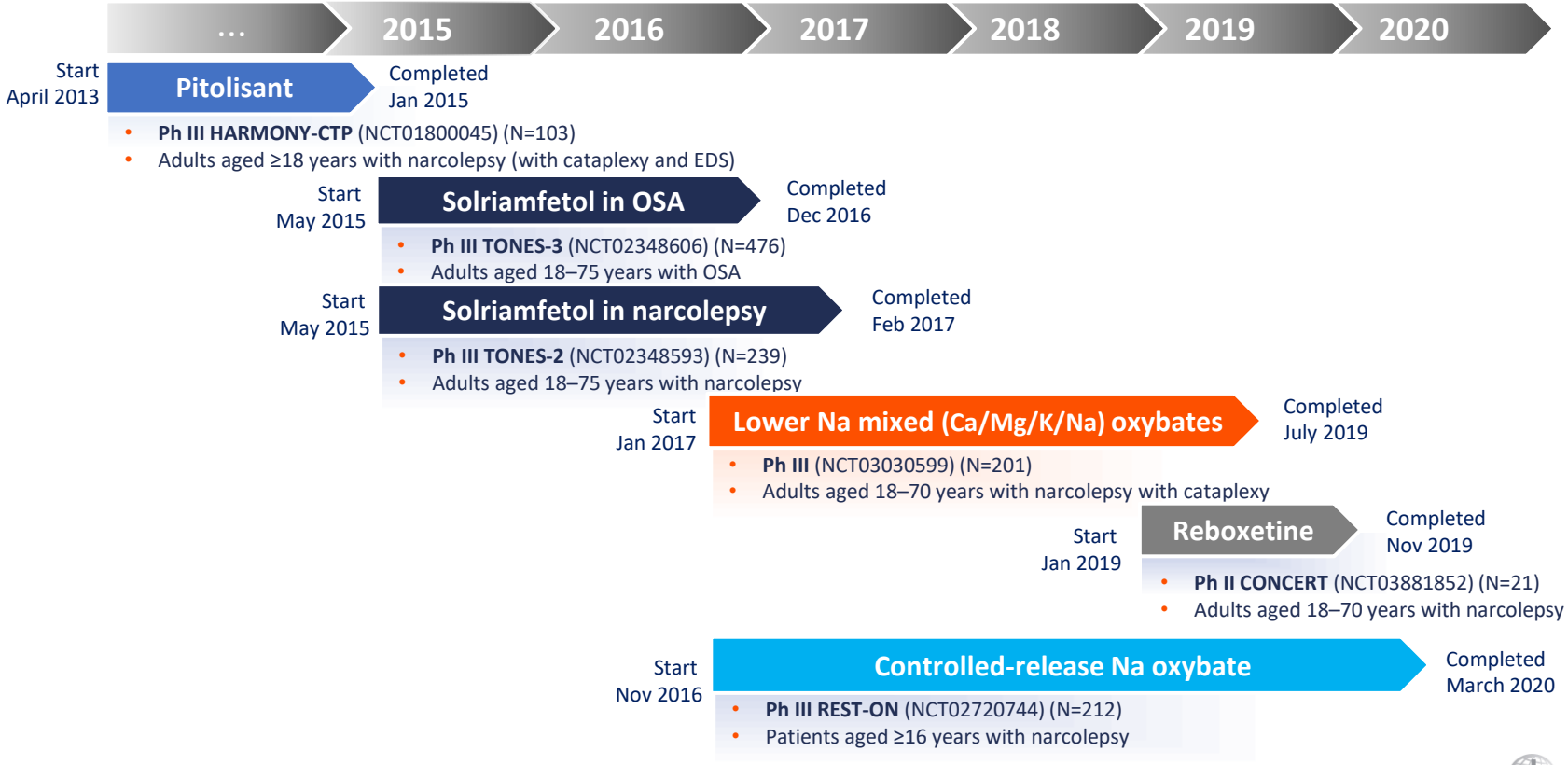
What are we learning from clinical trial data about the efficacy of these new and emerging agents in the management of excessive daytime sleepiness?

Pharmacotherapies for EDS in OSA or narcolepsy: Completed trials



EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea.
Clinical trials listed by their ClinicalTrials.gov identifiers. Trial information available at https://clinicaltrials.gov/ (accessed October 2021).

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Efficacy of pharmacotherapies for EDS in OSA or narcolepsy

Solriamfetol[1]

37.5 (OSA ONLY) / **75** / **150** / **300 mg** vs **PBO**

ESS ≤10 at Week 12
(% participants)

Narcolepsy	OSA
N=231	N=459
30.5–49.2% vs 15.5%	51.8–73.0% vs 37.7%

≥ 25% Δ ESS from baseline at Week 12
(% participants)

Narcolepsy	OSA
44.1–62.7% vs 27.6%	50.0–81.9% vs 36.8%

- Responses mostly dose dependent
- More patients receiving solriamfetol achieved normal ESS score (≤10) or clinically meaningful improvement in ESS compared with PBO

Lower Na mixed (Ca/Mg/K/Na) oxybates[2]

Narcolepsy with CTX
N=134
LXB vs PBO

Δ mESS score

0.0 vs 2.0

Significant worsening of symptoms with PBO compared with LXB

Pitolisant[4]

≤35.6 mg daily vs **PBO**

HARMONY-1	HARMONY-CTP
EDS treatment response (% participants)	
67.7% vs 43.3%	68.6% vs 34.0%

Post-hoc analyses confirm treatment benefit of pitolisant for EDS in patients with narcolepsy and CTX

Controlled-release Na oxybate[3]

Narcolepsy
N=222
ON-SXB vs PBO

Δ mESS score at Week 13

-6.52 vs -2.66

ON-SXB significantly improved narcolepsy symptoms compared with PBO

Reboxetine[5]

Narcolepsy
N=21
REBOX vs PBO

Δ ESS score

-6.0 vs -3.1

REBOX also improved cognition, sleep quality and reduced inadvertent naps and night awakenings

Δ , change at specified time point from baseline; CTX, cataplexy; EDS, excessive daytime sleepiness; ESS, Epsworth Sleep Scale; LXB, lower-sodium mixed oxybates; m, mean; ON-SXB, once-nightly sodium oxybate; OSA, obstructive sleep apnea; PBO, placebo; REBOX, reboxetine.

1. Rosenberg R, et al. *J Clin Sleep Med*. 2021;17:711–17; 2. Bogan RK, et al. *Sleep.* 2021;44:zsaa206; 3. Kushida CA, et al. *Sleep.* 2021; zsab200; 4. Meskill G, et al. *Sleep.* 2021;44 (Suppl. 2):A198–9; 5. O'Gorman C, et al. *Sleep.* 2020;43(Suppl. 1):A281.

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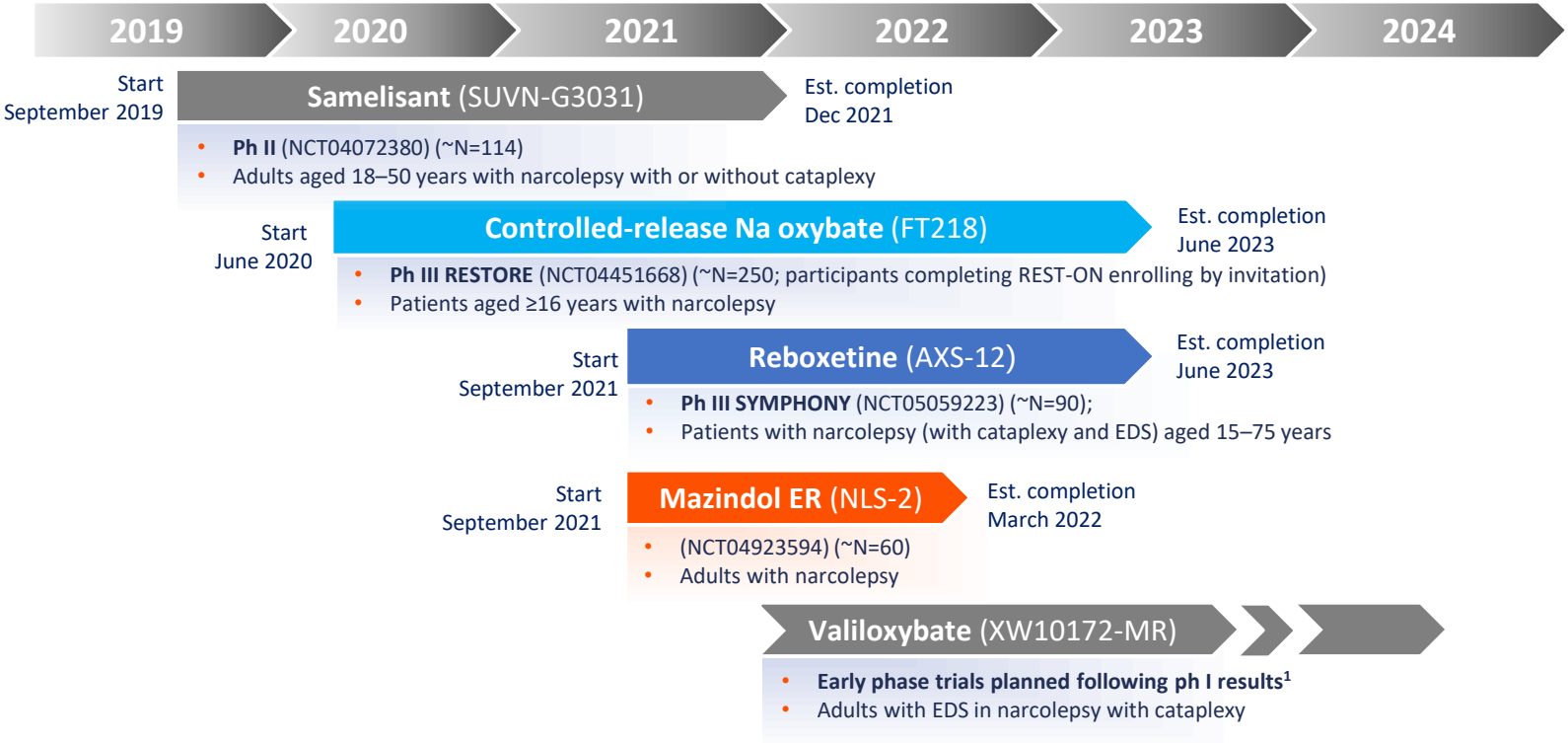
Pharmacotherapies for EDS in narcolepsy: Ongoing trials



EDS, excessive daytime sleepiness; ER, extended release; Est., estimated; ~N, estimated enrolment; OSA, obstructive sleep apnea.

1. Canafax D, et al. *Sleep.* 2021;44(Suppl. 2):A197–8.

Clinical trials listed by their ClinicalTrials.gov identifiers. Trial information available at https://clinicaltrials.gov/ (accessed September 2021).

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What safety aspects should we consider when evaluating use of these agents to manage excessive daytime sleepiness in people living with obstructive sleep apnea or narcolepsy?

Safety of pharmacotherapies for EDS in OSA or narcolepsy

DNRI — Solriamfetol[1]

Common TRAEs

(≥5% solriamfetol-treated participants)

- Headache (11.0%)
- Nausea (8.9%)
- Nasopharyngitis (8.4%)
- Insomnia (7.9%)
- Dry mouth (7.3%)
- Anxiety (7.2%)
- Appetite loss (5.0%)
- Upper respiratory infection (5.0%)

Similar safety profiles in narcolepsy and OSA cohorts

Oxybates

LXB[2]

Common TRAEs in patients receiving LXB

Headache (20.4%) | Nausea (12.9%) | Dizziness (10.4%)

ON-SXB[3]

Common TRAEs in patients receiving ON-SXB

Nausea (22.4%)	Headache (18.7%)	Vomiting (17.8%)	Dizziness (15.9%)	Enuresis (15.9%)	Appetite loss (12.1%)

H_3RA — Pitolisant[4,5]

Most commonly reported AEs

Headache (9.8%) | Nausea (6.6%) | Anxiety (5.6%) | Insomnia (4.7%)

16.7% discontinued treatment due to AE

Dose titration of some agents may be required to optimize efficacy and manage side effects[†5]

†Check local guidance on controlled substance status of agents. AE, adverse event; DNRI, dopamine and norepinephrine reuptake inhibitor; EDS, excessive daytime sleepiness; H_3RA, histamine H_3 receptor antagonist; LXB, lower-sodium mixed (Ca/Mg/K/Na) oxybates; NRI, norepinephrine reuptake inhibitor; ON-SXB, once-nightly sodium oxybate; OSA, obstructive sleep apnea; TRAE, treatment-related AE.

1. Malhotra A, et al. *Sleep.* 2020;43:zsz220; 2. Bogan RK, et al. *Sleep.* 2021;44:zsaa206; 3. Kushida CA, et al. *Sleep.* 2021; doi: 10.1093/sleep/zsab200; 4. Bauer ED, et al. *Sleep.* 2020;43(Suppl. 1):A291; 5. Thorpy MJ, Bogan RK. *Sleep Med.* 2020;68:97–109.

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Safety of pharmacotherapies for EDS in OSA or narcolepsy

Headaches, irritability and agitation are the main side effects of stimulants due to sympathetic stimulation and may limit use[1]

Caution should be exercised in patients with uncontrolled hypertension or cardiovascular disease[1–3]

~1/3 patients develop tolerance and dose increases may be needed[1]

Although effective, the potential for addiction (and/or abuse) alongside negative side effects with these medications needs to be recognized[1]

Dose titration of some agents may be required to optimize efficacy and manage side effects[†5]

Check local guidance on controlled substance status of agents. EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea.

1. Sahni AS, et al. *Nat Sci Sleep.* 2019;11:241–52; 2. Gandhi KD, et al. *Mayo Clin Proc.* 2021;96:1288–301;
3. Abad VC. *Nat Sci Sleep.* 2021;13:75–91.

Challenges evaluating excessive daytime sleepiness and its primary underlying cause

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Why is it important to recognize excessive daytime sleepiness, and how does it impact people living with obstructive sleep apnea or narcolepsy?

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Early recognition of EDS is essential to optimize management

ICSD-3 definition of EDS: *"Daily episodes of an irrepressible need to sleep or daytime lapses into sleep"* [1,2]

- **EDS is often confused with fatigue, exhaustion, lethargy, tiredness and lassitude**[1]
- **EDS affects 10–20% of the population, and impacts daily function and QoL**[3]
- **Important to distinguish between EDS and fatigue, and identify underlying cause**[4]

Fatigue

- Often caused by psychological, physical or lifestyle factors
- Lack of energy (physical and/or mental) and inability to initiate/maintain activities that would usually be easy
- Difficulty with memory, concentration and emotional control
- Not generally associated with inappropriate episodes of sleep during the day

EDS

- Common symptom of multiple sleep (e.g. OSA) and hypersomnolence (e.g. narcolepsy) disorders
- Varies in severity from excessive sleepiness to episodes of inadvertently falling asleep, incl. sleep attacks
- Unrefreshing sleep, recurrent naps and sleep inertia
- Safety implications (e.g. driving, tasks requiring alertness)

Early recognition and assessment of EDS through thorough history, physical examination and objective testing (PSG and MSLT as needed) is essential to optimize individualized management

EDS, excessive daytime sleepiness; ICSD-3, International Classification of Sleep disorders (3rd edition); MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; PSG, polysomnography; QoL, quality of life.

1. American Academy of Sleep Medicine. *International classification of sleep disorders, 3rd ed*. Darien, IL, USA: American Academy of Sleep Medicine, 2014;
2. Sateia MJ, et al. *CHEST*. 2014;146:1387–94; 3. Wang H, et al. *Nat Commun.* 2019:10:3503; 4. Gandhi KD, et al. *Mayo Clin Proc.* 2021;96:1288–301.

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What assessments are needed to meaningfully evaluate excessive daytime sleepiness?

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Accurate and meaningful assessment of EDS is imperative

Thorough patient history is the first step in the EDS assessment journey

Patient history

- Sleep schedule
- Brain lesions/head trauma
- Neurodegenerative disorders
- Medication reconciliation
- Recreational substance abuse
- Co-morbidities (CV, renal, hepatic, hypothyroidism, diabetes)

Metabolic work-up

- Anaemia
- Thyroid dysfunction
- Vitamin deficiencies (D, B12)
- Hepatic dysfunction

Routine metabolic work-up not always indicated

Sleepiness screening tools[1]

Patient-completed questionnaires
e.g. Epworth Sleepiness Scale

ESS score >10 consistent with EDS

Physical examination

- Drooping eyelids
- Wide neck circumference
- Crowded posterior pharynx
- Yawning throughout encounter

Psychiatric disorders

- Consider psychiatric disorders that may also present with EDS
  e.g. depression and bipolar disorder

Effective and empathetic patient–physician conversations, which offer recognition and encouragement surrounding the challenges faced by people living with EDS, are important to support clinical and QoL outcomes

CV, cardiovascular; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; QoL, quality of life.

1. Sahni AS, et al. *Nat Sci Sleep.* 2019;11:241–52.

How can we overcome the challenges associated with diagnosing the underlying cause of excessive daytime sleepiness?

Causes of EDS: Overcoming differential diagnostic challenges

Patient history in combination with PSG and MSLT data are often key to identifying the underlying cause of EDS[1,2]

Patient history

OSA[1]

- **EDS – common presenting symptom**
- **Does not occur universally and not diagnostic**
- **OSA may coexist with narcolepsy**

- Snoring
- Witnessed apneas
- Multiple wake ups
- Nocturia
- Morning headache
- Crowded airway on exam
- History of weight gain

Narcolepsy[1,3]

- **EDS – primary clinical symptom**
- **Typically first symptom to present**
- **Often has greatest impact on daily life**

- Poor nocturnal sleep
- Unrefreshing sleep
- Hallucinations (hypnagogic, hypnopompic)
- Sleep attacks
- Sleep paralysis
- Cataplexy episodes

Establish regular sleep schedule prior to PSG and MSLT to reduce false positives due to sleep deprivation[1,2]

Objective tests

- PSG – standard diagnostic test
- OSA may be an independent cause of EDS, decreased sleep latency and SOREMs, and should be treated prior to establishing a narcolepsy diagnosis

- O/N PSG with next-day MSLT is standard
- Diagnostic criteria include: mean MSLT ≤8 min and ≥2 SOREMs on MSLT
- Sleep diary and/or actigraphy completed 1–2 wks prior to PSG/MSLT to ensure studies performed during the patient's usual sleep times

EDS, excessive daytime sleepiness; MSLT, multiple sleep latency test; O/N, overnight; OSA, obstructive sleep apnea; PSG, polysomnography; SoC, standard of care; SOREM, sleep onset rapid eye movement [REM] period.

1. Sahni AS, et al. *Nat Sci Sleep.* 2019;11:241–52; 2. Arand DL, Bonnet MH. *Handb Clin Neurol.* 2019;160:393–403; 3. Sateia MJ, et al. *CHEST.* 2014;146:1387–94; 4.Gandhi KD, et al. *Mayo Clin Proc.* 2021;96:1288–301.

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How do excessive daytime sleepiness assessments help to guide medical management strategies for people with obstructive sleep apnea or narcolepsy?

Optimizing management through regular EDS assessments

Understanding individual patient needs[1–3]

- History taking is key to re-evaluate comorbidities and life circumstances
  - Use of validated screening tools and scales (e.g. ESS, KSS, SSS, PSQI)
  - Patient experience and self-assessment on functionality and QoL

Tailoring treatment regimens[1–3]

- Efficacy, tolerability, safety, abuse potential and financial considerations guide medication adjustments
  - Support individualized treatment goals
    - Improve quality/duration of nocturnal sleep
    - Improve role functioning (work/social)
    - Alleviate symptoms

Serial assessment of EDS, using validated tools, and evaluation of patient-reported experience of EDS (both at diagnosis and throughout follow-up) underpin optimized management of hypersomnolence associated with OSA or narcolepsy

EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; KSS, Karolinska Sleepiness Scale; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; SSS, Stanford Sleepiness Scale; QoL, quality of life.

1. Thorpy MJ, Bogan RK. *Sleep Medicine.* 2020;68:97–109; 2. Sahni AS, et al. *Nat Sci Sleep.* 2019;11:241–52; 3. Maski K, et al. *J Clin Sleep Med.* 2021;17:1895–945.