

Treatment of Narcolepsy

15th - 18th September | Newcastle

Ivana Rosenzweig • BSS ISMC 2026 • Thursday 17 September • 10:30–11:00



British Sleep Society



UK Multidisciplinary Sleep Professionals



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ORIENTATION

Treat the person's symptom architecture — not the label alone

Daytime sleepiness, cataplexy and disrupted night-time sleep may need different levers

The best regimen fits phenotype, comorbidity, reproductive plans, work, driving and patient preference.

EDS

Cataplexy

Night sleep

Function

This lecture maps primarily to ESRS Textbook chapter E4, updated with the 2021 European/AASM guidelines and the August 2026 FDA approval of ovexorexton.

Sources: <https://esrs.eu/wp-content/uploads/2021/07/Table-of-Contents-and-Preface-Sleep-Medicine-Textbook-2nd-edition-2021-ESRS.pdf>;
<https://doi.org/10.1111/ene.14888>; <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-full-range-narcolepsy-type-1-symptoms>

CASE

A common treatment problem is partial success

CASE

A 32-year-old with NT1 takes modafinil. Morning alertness improved, but afternoon sleep attacks persist; cataplexy occurs weekly; night sleep is fragmented.

BP normal • planning pregnancy in 18 months • drives to work

What should drive the next choice?

Target symptoms

Safety constraints

Patient priorities

Ask for a plan, not a favourite drug. The answer will require explicit priorities, contraception/pregnancy counselling and driving risk review.

FOUNDATION

Medication sits on a behavioural and social foundation

Planned naps

Short, strategically timed naps can provide immediate benefit and complement medication.

Regular sleep–wake schedule

Protect adequate nocturnal sleep and reduce avoidable variability.

Work / education adjustments

Scheduled breaks, flexible timing, safe travel and occupational review.

Driving plan

No driving when sleepy; follow local licensing rules and document response.

Comorbidities

Treat OSA, mood disorders, obesity, RLS/PLMS and medication burden.

Shared outcomes

Track function and patient goals—not ESS alone.

European guideline strongly recommends scheduled naps for EDS; AASM did not make a recommendation because of evidence methodology, not because naps are clinically useless.

European 2021 recommendations: remember the symptom columns

ADULT EDS — STRONG

Five first-line-capable options

Scheduled naps

Modafinil

Pitolisant

Sodium oxybate

Solriamfetol

ADULT CATAPLEXY

Strong evidence / consensus

Sodium oxybate

Venlafaxine

Clomipramine

Pitolisant: weak recommendation

These are not a mandated rank order. European recommendations are symptom-specific; choice remains individualised.

MECHANISMS

Six levers — each solves a different part of the problem

Modafinil

Wake promotion; dopamine transporter effects among multiple mechanisms.

Solriamfetol

Dopamine/noradrenaline reuptake inhibition; potent wake effect.

Pitolisant

Histamine H3 inverse agonist/antagonist; wake and some cataplexy benefit.

Oxybates

Night-time GABA-B-related action; improves EDS, cataplexy and disrupted night sleep.

Stimulants

Methylphenidate or amphetamine derivatives; useful but greater CV/abuse considerations.

Antidepressants

REM suppression for cataplexy; evidence and withdrawal considerations vary.

Keep mechanisms tied to phenotype. There is no simplistic potency league table because head-to-head data are sparse.

Existing agents modulate downstream arousal, REM or nocturnal consolidation. OX2R agonism is different because it replaces a missing upstream signal in NT1.

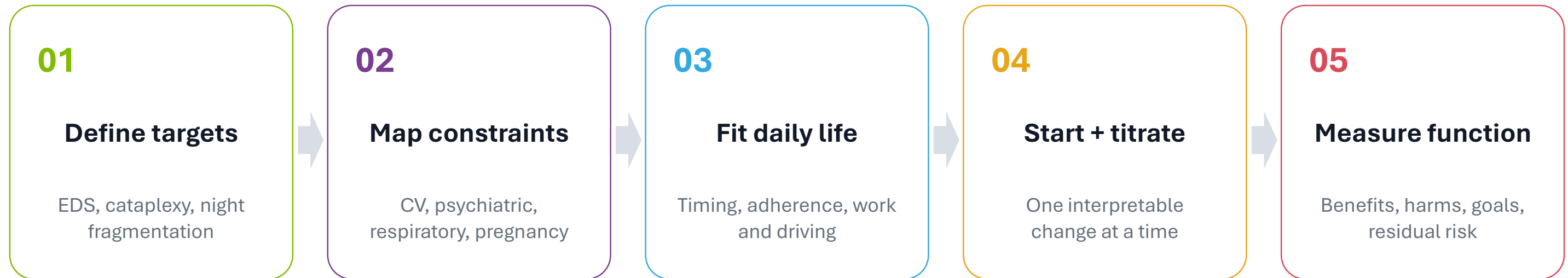


Mechanistic synthesis aligned with Bassetti et al. Eur J Neurol 2021 and ESRS Textbook chapter E4.

DAT blockade • DA/NA reuptake • H3 inverse agonism • GABA-B • REM suppression • OX2R agonism

SELECTION

Choose by phenotype, then subtract contraindications



The practical algorithm is iterative. Combination therapy is reasonable when different symptom domains remain uncontrolled, but keep each addition interpretable.

COMPARISON

A compact treatment matrix for the exam

Treatment	EDS	Cataplexy	Night sleep	High-yield caution
Modafinil	✓✓	—	—	Pregnancy risk; reduces steroidal contraception effectiveness
Solriamfetol	✓✓	—	—	BP/heart rate; MAOI interaction
Pitolisant	✓	✓	—	QT / interactions; slower titration
Sodium oxybate	✓✓	✓✓	✓✓	CNS/respiratory depression; alcohol/sedatives
Stimulants	✓✓	—	—	CV, psychiatric and misuse risk
Venlafaxine / clomipramine	—	✓	variable	Withdrawal may trigger rebound cataplexy

Symbols communicate typical symptom targets, not comparative efficacy. Licensing and availability vary by jurisdiction.

Oxybate is a night treatment with daytime consequences

Best fit

EDS + frequent cataplexy + disrupted nocturnal sleep.

Practical burden

Night dosing regimen, preparation, adherence and controlled-drug procedures.

Safety screen

Respiratory disease, sedatives/alcohol, falls, parasomnias and psychiatric context.

Emphasise strict avoidance of alcohol and other CNS depressants. Assess sleep-disordered breathing and medication interactions.

WAKE PROMOTION

Wake-promoters differ more in risk profile than in slogans

Modafinil

Long clinical experience; rash, headache, psychiatric effects, CYP interactions and reproductive safety.

Solriamfetol

Strong alerting effect; monitor BP/heart rate and avoid with MAO inhibitors.

Pitolisant

Histaminergic; useful when stimulant/controlled-drug concerns matter; review QT and interactions.

Cataplexy therapy must survive missed doses and life changes

MULTI-SYMPTOM

Oxybate or pitolisant

- Can address more than cataplexy
- Choose around night symptoms and safety
- Titrate and track attack burden

REM-SUPPRESSING

Venlafaxine or clomipramine

- Useful anti-cataplectic options
- Do not stop abruptly
- Plan pregnancy and interaction review

Rebound cataplexy can follow abrupt withdrawal of antidepressants; build discontinuation plans before starting.

SAFETY

Four red flags change the prescription

Pregnancy or conception plans

Review all drugs early. Avoid modafinil in pregnancy; ensure effective contraception and account for enzyme induction.

Cardiovascular disease

BP, heart rate, arrhythmia risk and interacting medicines shape wake-promoter choice.

Respiratory / sedative burden

Oxybate requires special caution with OSA, opioids, alcohol and CNS depressants.

Psychiatric vulnerability

Screen for anxiety, mood, psychosis, impulsivity and misuse risk; monitor after changes.

SPECIAL SITUATIONS

Children and pregnancy are not small versions of routine adult care

CHILDREN

Protect development

Scheduled naps and educational plan

Sodium oxybate: strong European recommendation

Other agents: weaker paediatric evidence

Monitor growth, weight and mental health

PREGNANCY

Pre-conception review

Minimise fetal exposure where possible

Balance maternal safety and function

Non-pharmacological strategies become central

Coordinate sleep, obstetric and primary care teams

European guideline separates adult and paediatric recommendations and provides expert statements for pregnancy.

2026 UPDATE

Orexin agonism moves treatment closer to the disease biology

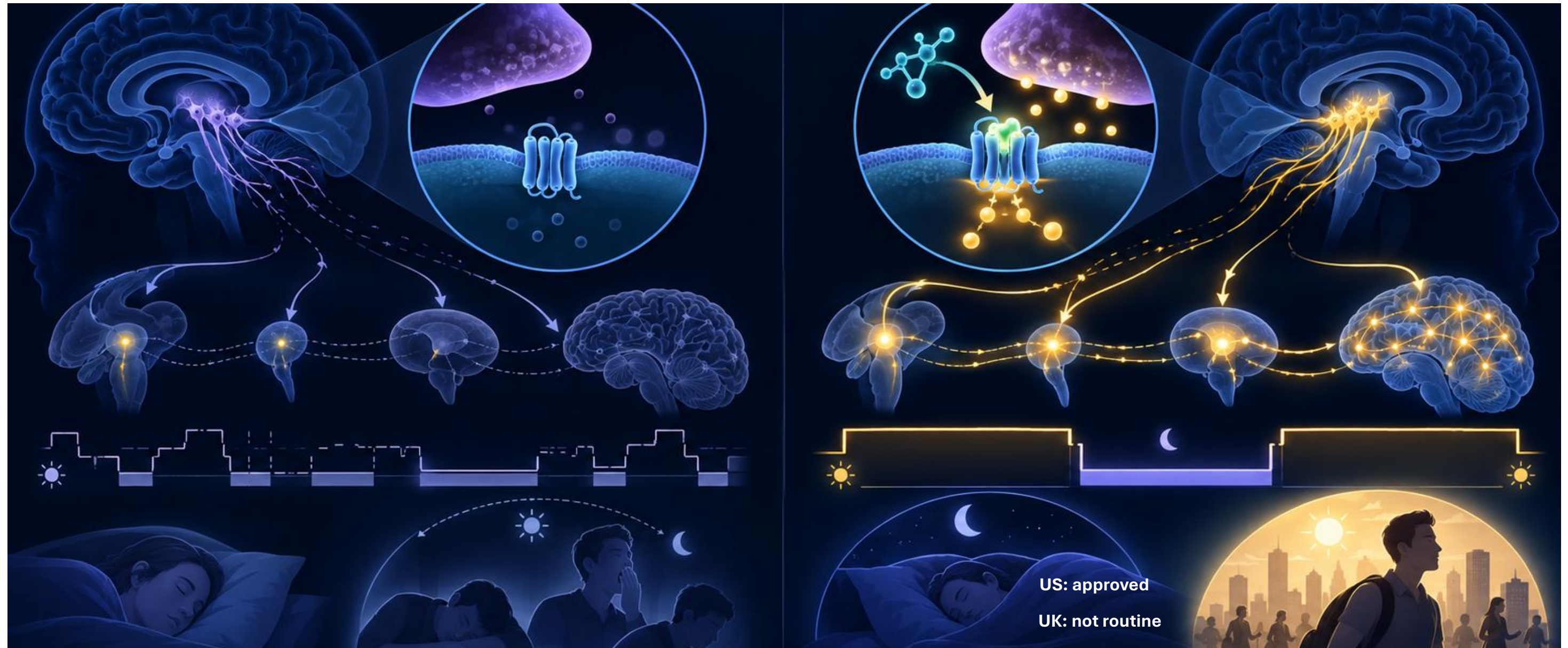


Oveporexton (Orzeyful) is an oral selective OX2R agonist and was FDA-approved 5 August 2026 for adult NT1. This is a major scientific milestone, but it is not yet routine UK/NHS treatment; do not transplant US availability into European exam answers.

Sources: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-full-range-narcolepsy-type-1-symptoms>; <https://www.narcolepsy.org.uk/major-oveporexton-milestones-reached/>

MECHANISM INTERLUDE

Selective OX2R agonism restores the missing wake signal



Dauvilliers Y et al. N Engl J Med. Published 9 September 2026. doi:10.1056/NEJMoa2601598.

Molecule → OX2 receptor → distributed wake network → more stable daytime wakefulness

NEW FINDING

Phase 3 moved OX2R agonism from concept to clinic

Two 12-week randomized trials • 273 participants with NT1 • all key comparisons $P < 0.001$

Maintenance of Wakefulness Test

+14.3 to +19.8 min

Placebo: -0.4 to -0.8 min

Change from baseline at week 12

Epworth Sleepiness Scale

-9.7 to -11.8

Placebo: -1.5 to -1.7

Change from baseline at week 12

Weekly cataplexy rate

79.0% to 88.8% ↓

Placebo: 27.7% to 39.1% ↓

Median percentage reduction

First Light enrolled 168 participants and Radiant Light 105. Oveporexton improved MWT, ESS and weekly cataplexy rate across tested doses. Adverse events occurred in 86–89% with active treatment versus 43–54% with placebo; urinary frequency and transient insomnia were most common. 12-week efficacy and the need for longer-term surveillance.

Sources: <https://www.nejm.org/doi/abs/10.1056/NEJMoa2601598>; <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-full-range-narcolepsy-type-1-symptoms>

CASE RESOLUTION

Case: build a plan, not a pile of drugs

1 • Clarify priorities

Afternoon EDS, weekly cataplexy, fragmented night sleep and pregnancy timeline.

2 • Revisit foundation

Planned nap, driving plan, sleep schedule, OSA screen and workplace adjustment.

3 • Select deliberately

Consider a multi-symptom option versus staged combination; address reproductive safety now.

There is no single mandatory answer. There has to be a coherent, safety-aware plan with documented goals and follow-up.

EXAM CHECKPOINT

Single best answer

Which adult treatment has strong European recommendations for both EDS and cataplexy?

A Solriamfetol

B Sodium oxybate

C Modafinil

D Methylphenidate

Correct answer: B — sodium oxybate. Modafinil and solriamfetol strongly address EDS; methylphenidate has a weaker recommendation.

TAKE-HOME

The treatment algorithm is a conversation with constraints

Target symptoms. Fit the patient. Re-measure function.

Foundation: planned naps, regular sleep and practical adjustments remain treatment.

Selection: match EDS, cataplexy and night symptoms to mechanism.

Safety: pregnancy, cardiovascular, respiratory and psychiatric context can dominate choice.

Follow-up: aim for function and safe wakefulness, not a perfect questionnaire score.

2026: orexin agonism is now FDA-approved for adult NT1, but UK access has not followed yet.

SOURCES

Core reading

ESRS Sleep Medicine Textbook, 2nd ed. (2021): chapter E4.

Bassetti CL et al. European narcolepsy guideline and expert statements. Eur J Neurol 2021.

Maski K et al. Treatment of central disorders of hypersomnolence. J Clin Sleep Med 2021.

MHRA. Modafinil: pregnancy and contraception safety update (2020).

US FDA. Oveporexton approval announcement, 5 August 2026.