Sleep Research Review™

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Issue 14 - 2025

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Abbreviations used in this issue:

AHI = apnoea-hypopnoea index; **BMI** = body mass index; **CPAP** = continuous positive airway pressure; **ESS** = Epworth Sleepiness Scale; **GABA** = gamma-aminobutyric acid; **MWT** = Maintenance of Wakefulness Test; **OSA** = obstructive sleep apnoea.

Welcome to the latest issue of Sleep Research Review.

In this issue we review trials of medications aiming to reduce sleepiness in narcolepsy and idiopathic hypersomnia, and a meta-analysis looks at the efficacy of various wake-promoting agents for patients with OSA. A Canadian study finds that inappropriate prescribing for insomnia is common despite national guidelines, and the dual orexin receptor antagonist lemborexant has a positive impact on daytime functioning in patients with insomnia. Finally, analysis of the longitudinal SLEEP T2D study highlights the importance of adequate sleep in patients with type 2 diabetes, and a large meta-analysis confirms the positive impact of PAP for OSA on cardiac and all-cause mortality.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind regards,

Dr Elizabeth Veitch
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Oveporexton, an oral orexin receptor 2-selective agonist, in narcolepsy type 1

Authors: Dauvilliers Y et al.

Summary: This phase 2 randomised, double-blind trial investigated the efficacy and safety of oveporexton in patients with narcolepsy type 1. A total of 112 patients were randomised 1:1:1:1 to receive one of four oveporexton regimens (0.5mg twice daily; 2mg twice daily; 2mg increasing to 5mg daily; or 7mg once daily) or placebo for 8 weeks. Mean change from baseline to week 8 in average sleep latency on the MWT was 12.5 min, 23.5 min, 25.4 min, and 15.0 min in the respective oveporexton groups compared with –1.2 min in the placebo group ($p \leq 0.001$ for all oveporexton regimens vs placebo). Mean change from baseline to week 8 in ESS total score was –8.9, –13.8, –12.8, and –11.3 in the respective oveporexton groups compared with –2.5 in the placebo group ($p \leq 0.004$). The most common adverse events reported with oveporexton were insomnia (48%), urinary urgency (33%), and urinary frequency (32%). No hepatotoxic effects were reported.

Comment: Patients with narcolepsy type 1 experience excessive daytime sleepiness, disrupted nighttime sleep, cataplexy, hypnagogic hallucinations and sleep paralysis due to a loss of orexin-producing neurones in the hypothalamus. Orexin acts in the brain through two receptors, with receptor 2 being involved in regulating wakefulness, rapid eye movement (REM) sleep and preventing cataplexy in animal models of narcolepsy. Current narcolepsy treatments do not target the pathophysiological defect. This trial compared oveporexton, a selective agonist of the orexin receptor 2, with placebo. The primary endpoint was an objective one (increase in mean sleep latency on the MWT), and there were additional patient-reported outcomes, including change in ESS score. Significant improvements in primary and secondary outcomes were seen. Impressively, these benefits were greater than those reported with existing treatments. A phase 3 trial is planned.

Reference: N Engl J Med. 2025;392(19):1905–16
Abstract

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Efficacy and safety of sodium oxybate in adults with idiopathic hypersomnia

Authors: Dauvilliers Y et al.

Summary: This phase 3 study investigated the efficacy and safety of sodium oxybate in patients with idiopathic hypersomnia (IH). Forty-five patients aged 18–60 years with IH (ESS score ≥14) were randomised 1:1 to receive sodium oxybate or placebo. Patients in the sodium oxybate group started with a 6-week individual twice-nightly up-titration from 4.5g to a maximum of 9g. The dose was kept stable for 2 weeks, then tapered for 2 weeks. The primary endpoint was the between-group difference in ESS scores at week 8. Sodium oxybate significantly decreased the mean ESS score at week 8 compared with placebo (least square mean difference: –6.86; p<0.0001). Significant between-group differences at week 8 were also observed for the Idiopathic Hypersomnia Severity Scale (IHSS) score and MWT latency. Treatment-emergent adverse events (mainly nausea, headache, and dizziness) were reported in 81.8% of sodium oxybate recipients and 26.1% of placebo recipients.

Comment: Idiopathic hypersomnia is a rare, disabling condition. Its diagnosis relies on confirming hypersomnia and excluding other causes for this (such as sleep-disordered breathing, narcolepsy, periodic limb movement disorder, sedating medications). Treatment is mainly extrapolated from studies in narcolepsy, and there are no medications registered in Australia specifically for IH. This trial, from the National Reference Center for Rare Hypersomnias in France, assessed sodium oxybate against placebo using both subjective and objective measures. Only 45 patients were randomised over a 5-year period and only 40 completed the trial, highlighting the difficulties in studying very rare conditions. While sodium oxybate was effective in reducing hypersomnolence, it was poorly tolerated and the dosing schedule is difficult (half at bedtime and half 2–4 hours later). The search for a better treatment for IH continues.

Reference: Neurology 2025;104(11):e213690
Abstract

Pitolisant 40 mg for excessive daytime sleepiness in obstructive sleep apnea treated or not by CPAP

Authors: Dauvilliers Y et al., for the HAROSA III Study Group

Summary: The phase 3 HAROSA III study investigated the effects of the selective histamine-3 receptor antagonist pitolisant on excessive daytime sleepiness (EDS) in patients with moderate to severe OSA. A total of 361 patients (mean age 52.4 years, 77.3% male; mean AHI 27.0 events/h) were randomised 2:1 to receive pitolisant or placebo; approximately half of the patients in each group were also using CPAP therapy. The primary end-point was change in ESS score from baseline to week 12. After the 3-week dose-adjustment phase, most (88.8%) patients were taking pitolisant 40mg. Pitolisant significantly reduced ESS scores at week 12 compared with placebo (least square mean difference: –2.6; p<0.001) irrespective of CPAP use. The drug was well tolerated, and no new safety signals were identified.

Comment: OSA is effectively treated by using a nocturnal positive airway pressure (PAP) device, however a significant percentage of patients do not accept PAP or are unable to tolerate it, and 5–10% of patients who use PAP still experience EDS. Thus, there is an unmet symptomatic need in these patients. Pitolisant is approved in some countries for the treatment of narcolepsy. It showed improved EDS in OSA patients in two prior phase 3 randomised controlled trials (HAROSA I – patients on CPAP, and HAROSA II – no CPAP use), in doses up to 20mg. The current study examined a dose of 40mg in OSA patients, pitolisant led to a significant reduction in daytime sleepiness, as measured by ESS scores.

Reference: J Sleep Res. 2025;34(3):e14373
Abstract

Comparative efficacy and safety of multiple wake-promoting agents for the treatment of residual sleepiness in obstructive sleep apnea despite continuous positive airway pressure

Authors: Tanayapong P et al.

Summary: This systematic review and network meta-analysis compared the efficacies of various wake-promoting agents (WPAs) in patients with OSA who had residual sleepiness despite CPAP use. A search of MEDLINE, Scopus, and ClinicalTrials.gov identified 14 randomised controlled trials (n=2969) that were suitable for inclusion. The trials evaluated four WPAs: modafinil 200–400 mg/day (six trials), armodafinil 150–250 mg/day (four trials), solriamfetol 37.5–300 mg/day (two trials), and pitolisant 5–40 mg/day (two trials). Solriamfetol, modafinil, and armodafinil effectively reduced sleepiness within 4 weeks as measured by the ESS, as well as the objective MWT. Pitolisant showed later improvements in ESS (after >4 weeks), but there was limited data on MWT.

Comment: With an increasing number of WPAs being developed, clinicians may be unsure which medication is the most efficacious, and which is best suited to an individual patient. This paper sought to provide guidance in this area. The medications assessed have different mechanisms of action – modafinil (acts on central dopamine and GABA), armodafinil (R-isomer of modafinil), solriamfetol (norepinephrine and dopamine reuptake inhibitor) and pitolisant (selective histamin-3 receptor antagonist). As with all systematic reviews, not all trials had measured the same outcomes, or tested medication over the same time-frame. Only studies of OSA patients who were compliant with nocturnal PAP were included. Ultimately all four drugs were found to be effective out to 12 weeks, with favourable safety profiles. In the Australian context our decision is currently simpler, as neither solriamfetol or pitolisant are registered here (both have been available in the US and Europe for over 5 years).

Reference: CNS Drugs 2025;39(6):527–44
Abstract

Positive airway pressure therapy and all-cause and cardiovascular mortality in people with obstructive sleep apnoea

Authors: Benjafield AV et al., for the medXcloud Group

Summary: This systematic review and meta-analysis investigated the effects of positive airway pressure (PAP) therapy on all-cause and cardiovascular mortality in patients with OSA. A search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials identified 30 outpatient studies (10 randomised controlled trials and 20 confounder-adjusted, non-randomised controlled studies) that assessed the incidence of all-cause mortality, cardiovascular mortality, or both in adults with OSA who were using PAP versus not using PAP. The studies included a total of 1,175,615 participants (mean age 59.5 years, 77% male); mean follow up was 5.1 years. Meta-analysis of the data showed that the PAP group had a significantly reduced risk of all-cause mortality (hazard ratio [HR] 0.63, 95% CI 0.56–0.72; p<0.0001) and cardiovascular mortality (HR 0.45, 95% CI 0.29–0.72; p<0.0001) than the no-PAP group.

Comment: The adverse impact of untreated OSA on cardiovascular morbidity and mortality are well-established, with relative risks for severe OSA ranging between 1.5 and 4.0 depending on the outcome examined. To what degree treatment with nocturnal PAP modifies this risk is less well established. This ambitious systematic review and meta-analysis of the trial evidence to date sought to provide clarity. Ultimately 30 studies encompassing over a million subjects showed significant reductions in all-cause mortality and cardiovascular mortality in patients who used PAP compared with those who did not. Clinicians may wish to factor this into their discussions regarding the goals of PAP therapy with patients.

Reference: Lancet Respir Med. 2025;13(5):403–13
Abstract

References: 1. MOUNJARO® Approved Product Information. **2.** Malhotra A *et al. N Engl J Med* 2024; 391(13): 1193–205 (including supplement). **3.** Chang JL *et al. Int Forum Allergy Rhinol* 2023; 13(7): 1061–482.

The relationship between obesity and obstructive sleep apnea in four community-based cohorts: An individual participant data meta-analysis of 12,860 adults

Authors: Esmaeili N et al.

Summary: This meta-analysis of four community-based cohort studies (n=12,860) investigated the relationship between obesity and OSA. Mean age of the participants was 66.6 years, 56.2% had OSA, and 25.7% had obesity (BMI ≥30 kg/m^2). Individual participant data meta-analysis showed that 31.5% of individuals with OSA had obesity and 44.4% were overweight (25 ≤ BMI < 30). Among overweight or obese participants, 59.8% and 74.3%, respectively, had OSA. Obesity was more common in females than males with OSA, and in younger (<65 years) versus older individuals. Compared to individuals with BMI <25 kg/m^2, overweight individuals were twice as likely to have OSA (odds ratio 2.18, 95% CI 1.73–2.76) and obese individuals were more than four times as likely to have OSA (odds ratio 4.84, 95% CI 3.09–6.00).

Comment: Obesity is rising, with the most recent Australian Bureau of Statistics 2022 data revealing that 34.0% of people are overweight and 31.7% are obese. Obesity is a major risk factor for OSA, but not all patients with OSA are obese. By analysing four large community-based studies (three in the US and one from Switzerland) the authors hoped to examine more closely the relationship between obesity and OSA. Their perhaps surprising finding was that most adults with OSA do not have obesity (44.4% were overweight and 23.5% were of normal weight or underweight). Hence, further studies are needed to consider the importance of other anatomical factors in OSA, such as narrow bone structure and increased soft palate size, and non-anatomical endotypes, such as ventilatory control instability, low arousal threshold and low upper airway dilator muscle responsiveness.

Reference: EClinicalMedicine 2025;83:103221
Abstract

Predictors of sleep-disordered breathing and chronic hypoventilation in obese women and men

Authors: Mollet M et al.

Summary: This cross-sectional observational study evaluated the impact of obesity on lung volumes and the prevalence of sleep-disordered breathing (SDB) and obesity hypoventilation syndrome (OHS). A total of 1065 patients (39% female) with obesity (BMI ≥30 kg/m^2) who underwent an in-laboratory sleep study, arterial blood gas analysis and pulmonary function tests in 2018–2023 were included. Overall, 48% of patients had WHO stage I obesity, 24% had WHO stage II obesity, and 28% had WHO stage III obesity. The prevalence of OSA (AHI ≥5/h), severe OSA (AHI ≥30/h), sleep hypoventilation and OHS in the overall group was 77%, 29%, 21% and 8%, respectively. The likelihood of OSA, severe OSA and sleep hypoventilation increased with obesity class, but the presence of OHS did not. Multivariate regression models showed that bicarbonate and forced vital capacity were independent predictors of both sleep hypoventilation and OHS, and neck circumference was an independent predictor of severe OSA.

Comment: Obesity is now the most common metabolic disease associated with adverse health outcomes. SDB is closely associated with obesity, but why some patients develop chronic hypoventilation when others do not is unknown. This study from a single centre sleep laboratory in Zurich sought to tease out the relationship between obesity, lung volumes and SDB. The prevalence of SDB (OSA and sleep hypoventilation) was high and increased with obesity class, while the prevalence of OHS was similar across all grades of obesity. Different independent predictors were identified for the various forms of SDB. Several study limitations were evident, including the lack of overweight and normal weight patients, and study site (a tertiary referral centre for obesity and bariatric surgery). However, with rising rates of obesity, a proactive approach to SDB detection and management is crucial.

Reference: BMJ Open Respir Res. 2025;12(1):e002632
Abstract

Association between sleep duration and obesity in patients with type 2 diabetes

Authors: Makhdom EA et al.

Summary: This analysis of the longitudinal SLEEP T2D study investigated the association between sleep duration and adiposity in patients with type 2 diabetes (T2D). A total of 229 patients (mean age 61.2 years, 61% male) were enrolled in the study from 13 UK NHS Trusts; 63.7% of patients had BMI ≥30 kg/m^2. Sleep duration was self-reported using the Pittsburgh Sleep Quality Index, and categorised as short (≤6h per night), long (>9h) or normal (6–9h). At baseline, sleep duration negatively correlated with BMI and waist circumference. In models adjusted for potential confounders, short sleep duration was associated with higher BMI (p=0.006) and higher waist circumference (p=0.01). After a median follow-up of 26.5 months, short sleep at baseline was associated with a ≥5% increase in BMI (adjusted odds ratio 10.03, 95% CI 1.55–64.84; p=0.01).

Comment: Over 90% of patients with T2D are overweight or obese, and excess weight impacts on individuals' health and survival, plus imposes significant costs on healthcare systems. Thus, identification of modifiable factors that impact on weight in T2D is important. The large SLEEP T2D study reported in 2024 that short sleep duration was significantly associated with the development of T2D. The current study examined the impact of sleep duration on weight in patients with existing T2D. Short sleep duration was common (54.9% of patients) and was associated with a higher BMI and waist circumference at baseline, and with greater weight gain over time. Although study weaknesses include a smaller sample size than planned due to the COVID-19 pandemic, and the fact that sleep duration was self-reported, it suggests that clinicians managing T2D should deliver clear messages about the importance of adequate sleep.

Reference: Diabet Med. 2025;42(6):e70051
Abstract

Independent commentary by Dr Elizabeth Veitch, MBBS FRACP

Dr Elizabeth Veitch is Head of Respiratory and Sleep Medicine at Concord General Hospital in Sydney. She has broad clinical practice and interests, with particular focus on airways diseases, interstitial lung diseases, pulmonary embolism and respiratory failure in neuromuscular disease. Over the last 20 years she has been a principal investigator on multiple international, multi-centre trials of novel medications for COPD, bronchiectasis and interstitial lung diseases.

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A retrospective observational study to understand medication utilization and lines of treatment in patients with insomnia disorder

Authors: Kamboj L et al.

Summary: This Canadian study assessed real-world prescribing practices among patients with insomnia. Longitudinal drug claims data for 2018–2020 from the Canadian IQVIA National Private Drug Plan and Ontario Drug Benefit databases were analysed to identify patients prescribed medications for insomnia. Inappropriate medication usage was categorised as elevated daily doses, an extended duration of use for benzodiazepines and/or Z-drugs, use of drug combinations, and opioid overlap with Z-drugs and/or benzodiazepines. In 2019, a total of 597,222 patients (mean age 55 years, 64% female) received treatment for insomnia. Overall, 52.5% of patients aged <65 years and 69.5% of older patients had inappropriate medication usage (mostly extended duration of use). Inappropriate medication use accounted for more than half (55.2%) of the total annual cost of medications for insomnia ($54.8 million).

Comment: Insomnia affects around 10% of Canadian adults and is associated with poor quality of life, increased risk of disease, and increased mortality. The economic burden is significant, with costs estimated to range between 26% and 46% higher than in those without insomnia. In recent years new pharmacotherapies have become available in the form of dual orexin receptor antagonists (lemborexant, daridorexant), but non-benzodiazepine Z-drugs (zopiclone, zolpidem, zaleplon), benzodiazepines, antidepressants and antipsychotic medications are all used for insomnia, at times inappropriately. This retrospective observational study used claims data from a large private insurer and the Ontario publicly-funded programme to interrogate insomnia treatments over 3 years. More than 500,000 patients were examined each year. Unfortunately, inappropriate prescribing was common, particularly in those over 65 years, and more prevalent in publicly-funded patients. This study highlights the fact that inappropriate prescribing is common and new strategies to combat it are required.

Reference: J Clin Psychiatry 2024;85(4):23m15015
Abstract

Effect of lemborexant on daytime functioning in adults with insomnia: Patient-reported outcomes from a phase 3 clinical trial

Authors: Chepke C et al.

Summary: This post hoc analysis of patient-reported outcomes from a phase 3 trial assessed the impact of the dual orexin receptor antagonist lemborexant on daytime functioning in patients with insomnia. Adults with insomnia were randomised 1:1:1 to receive placebo, lemborexant 5mg or lemborexant 10mg for 6 months. Patients' perceptions of their insomnia symptoms and daytime functioning was assessed using the Insomnia Severity Index (ISI) and Fatigue Severity Scale (FSS) questionnaires. Compared with placebo, lemborexant 5mg and 10mg significantly improved ISI Total Score (ISI-TS) and ISI Daytime Functioning Score (ISI-DFS) at 1 month, and maintained the improvements for 6 months. FSS score also improved with lemborexant at 3 and 6 months compared with placebo. Both dosages of lemborexant were well tolerated.

Comment: Individuals with insomnia often experience daytime symptoms leading to impaired quality of life. Existing drugs acting on GABA type A receptors (benzodiazepines and non-benzodiazepine Z-drugs) shorten sleep latency and improve sleep efficiency, but are associated with adverse daytime symptoms, such as impaired memory and cognition. SUNRISE 2, a phase 3 double-blind randomised placebo-controlled trial reported in 2020, showed that lemborexant, a competitive dual orexin receptor antagonist (DORA), significantly improved sleep latency and sleep efficiency out to 12 months. The current study examined the patient-reported outcomes from the first 6 months of SUNRISE 2. Significant improvements were reported in patients' daytime functioning which were maintained at 6 months. Two doses of lemborexant were examined, 5 and 10mg, with headache and somnolence the most common adverse events.

Reference: Prim Care Companion CNS Disord. 2025;27(1):24m03810
Abstract