Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis
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CRD summary
The authors concluded that sodium oxybate significantly reduced cataplexy, significantly improved daytime sleepiness, and was well tolerated. This was a generally well-conducted review, but given the limited evidence base and uncertain long-term effects of sodium oxybate, the authors’ conclusions should be interpreted with caution as the findings may not be reliable.

Authors’ objectives
To assess the efficacy and safety of sodium oxybate in adults with excessive daytime sleeping and sudden loss of muscle tone (narcolepsy-cataplexy).

Searching
Five electronic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE were searched up to October 2010 without restrictions on language or publication status. A search strategy was presented. In addition, ClinicalTrials.gov was scanned, along with reference lists of included studies, and authors’ personal files. Experts in the field and relevant manufacturers were also contacted to find additional studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared the safety and efficacy of sodium oxybate to any comparator in adults with narcolepsy and cataplexy. The primary outcome of interest was elimination of excessive daytime sleeping, assessed according to subjective or objective measures (as stated in the review). Secondary outcomes included quality of life and adverse events.

Included trials were conducted in clinics in the USA, Canada and Europe (where reported), and were published after 2002. The proportion of females ranged from 46% to 65% and the mean age ranged from 36 to 48 years. Where reported, the mean weight of participants ranged between 80.5 and 87.5kg. None of the patients had concurrent sleep disordered breathing. The occurrence of narcolepsy/cataplexy varied between studies. Various assessment methods were used to measure some outcomes, while others were based on diaries. The duration of most interventions ranged from four to eight weeks, and the dose of sodium oxybate in most studies ranged between 4.5 and 9g per night.

Two reviewers independently screened studies for inclusion. Discrepancies were resolved through discussion or referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed study quality based on the Cochrane risk of bias tool criteria. Discrepancies were resolved through discussion or referral to a third reviewer.

Data extraction
Two reviewers independently extracted outcome data to calculate relative risks or mean differences and their 95% confidence intervals. Any discrepancies were resolved through discussion or referral to a third reviewer.

Methods of synthesis
Where possible, a random-effects model was used to combine relative risks, mean differences and their 95% confidence intervals. Where it was not possible to combine studies in meta-analysis, data were briefly discussed narratively.

Statistical heterogeneity was assessed through visual inspection of forest plots and using $I^2$ and $X^2$. The authors planned to assess publication bias using funnel plots.

Results of the review
Six RCTs (741 participants; range 20 to 278) were included in the review. All studies were blinded, and all reported that
incomplete outcome data had been addressed. Five studies reported freedom from selective reporting, but all other criteria were not addressed or it was unclear whether they had been addressed.

Compared to placebo, sodium oxybate (4.5g per night) statistically significantly reduced cataplexy attacks (MD -8.5, 95% CI -15.3 to -1.6; two of four trials) measured using diaries. Compared to placebo, sodium oxybate (9g per night) statistically significantly increased wakefulness (MD 5.18, 95% CI 2.59 to 7.78; two trials), significantly decreased mean number of sleep attacks (MD -9.65, 95% CI -17.72 to -1.59; two trials), and significantly increased the proportion of patients who were much improved or very much improved as measured on the Clinical Global Impression of Change (MD 2.42, 95% CI 1.77 to 3.32; three trials).

There were no statistically significant differences between treatment groups in the percentage of restful eye movement sleep before and after sodium oxybate. Sodium oxybate (9g per night) statistically significantly increased the number of adverse events compared to placebo, including nausea, vomiting and dizziness.

There was no evidence of statistical heterogeneity for any outcomes. Other results were reported in the review.

**Authors' conclusions**

Sodium oxybate significantly reduced cataplexy (based on diaries) and significantly improved daytime sleepiness, as measured using objective and subjective assessment methods. Sodium oxybate was well tolerated and most adverse events were mild-to-moderate in severity.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. A number of sources were searched to identify relevant articles. The authors could not formally assess publication bias due to the small number of studies involved. Trial risk of bias was assessed using appropriate criteria, but this indicated potential for some risk of bias. Each stage of the review process was performed in duplicate, which reduced potential for reviewer error and bias.

There was some variability in the methods used to measure outcomes, some of which were subjective, which reduced the robustness of the findings. Meta-analyses were generally based on two small trials and confidence intervals were wide for some outcomes, which again reduced the reliability of the findings.

This was a generally well-conducted review, but given the limitations of the evidence and uncertain long-term effects of sodium oxybate, the authors' conclusions should be interpreted with caution as the findings may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that caution was advised when treating narcoleptics with concurrent sleep disordered breathing, and health care professionals should confirm that these patients were compliant with positive airway pressure therapy before starting sodium oxybate.

**Research:** The authors stated that future research should explore the long-term efficacy and tolerability of sodium oxybate, the effect of sodium oxybate in patients with concurrent sleep disordered breathing, and the effect of different dosages on patients with milder narcolepsy.

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