Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review found that gamma hydroxybutyrate provided statistically significant benefits in patients with narcolepsy. Limited quality assessment of the included trials and significant variation across the results make the reliability of the authors' conclusions uncertain.

Authors' objectives
To evaluate the effectiveness of gamma hydroxybutyrate on the clinical and neurological features of narcolepsy.

Searching
PubMed, EMBASE, Web of Science, Scirus, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched for relevant studies to August 2010; search terms were reported.

Study selection
Randomised controlled trials that evaluated oral administration of gamma hydroxybutyrate compared to orally administered placebo in patients with narcolepsy were eligible for inclusion. Eligible trials were required to report at least one outcomes: cataplexy attacks, excessive daytime sleepiness attacks, hypnagogic hallucinations, sleep paralysis, clinical global impression change, quality of life, neurophysiological outcomes on the multiple sleep latency test or the maintenance of wakefulness test, or nocturnal somnographic data. Studies that did not present sufficient data to enable calculation of summary estimates were excluded from the review.

The included studies were published between 1989 and 2009. Gamma hydroxybutyrate dose ranged from 3.0g to 9.0g. Treatment duration ranged from four to eight weeks. Concomitant medications were stimulants, antidepressants or hypnotics and low-dose propanolol.

It appeared that three reviewers performed the study selection; any discrepancies between reviewers were resolved by consensus.

Assessment of study quality
Methodological quality was assessed using the five-point Jadad scale of randomisation, blinding and treatment of withdrawals and drop-outs. An overall score of 3 points was indicative of a high quality study.

The authors did not state how many reviewers assessed study quality.

Data extraction
Odds ratios (OR) were calculated for dichotomous outcomes and mean differences were calculated for continuous outcomes, each with 95% confidence intervals (CI) for the estimates. Study authors were contacted for additional data.

Data were extracted by two reviewers and checked by a third. Any disagreements between reviewers were resolved by consensus.

Methods of synthesis
Pooled odds ratios, weighted mean differences (WMD) and 95% CIs for the summary estimates were calculated using a fixed-effect model. Statistical heterogeneity was assessed using $X^2$ and $I^2$. Where statistical heterogeneity was detected the results were combined using a random-effects model. Potential for publication bias was evaluated by visual appraisal of funnel plots.

Results of the review
Nine randomised controlled trials (1,154 participants) were included in the review. Seven studies scored 4 on the Jadad
scale and two studies scored 3.

Statistically significant benefits were observed with treatment with gamma hydroxybutyrate doses of 4g, with reductions in cataplexy attacks on a daily (WMD -1.10, 95% CI -1.29 to -0.90; I²=0%; two trials) and weekly basis (WMD -7.04, 95% CI -12.45 to -1.63; I²=93%; three trials) and daytime sleep attacks on a weekly basis (WMD -9.30, 95% CI -15.92 to -2.68; I²=15%; two trials). Statistically significant improvements were observed across doses that ranged from 3.0g to 9.0g in subjective daytime sleepiness (WMD -2.81, 95% CI -4.13 to -1.49; I²=94%; six comparisons) and on the clinical global impression changes scale (OR 3.45, 95% CI 2.47 to 4.80; I²=0%; seven comparisons).

There were statistically significant changes showing benefits of gamma hydroxybutyrate compared to placebo in stage 3 and 4 sleep (WMD 4.11, 95% CI 0.07 to 8.16; I²=0%; two trials), stage shifts in sleep (WMD -9.69, 95% CI -17.14 to -2.24; I²=0%; two trials) and in subjective nocturnal awakenings (WMD -1.33, 95% CI -1.78 to -0.88; I²=0%; two trials).

No statistically significant differences observed between gamma hydroxybutyrate and placebo in daytime sleep attacks on a daily basis, night-time sleep latency, total sleep time or percentages of stage 1 or stage 2 sleep or REM sleep (two trials for each outcome).

There was no evidence of publication bias observed in the appraisals of the funnel plots for the comparisons in the review.

**Authors' conclusions**
The results showed that gamma hydroxybutyrate was effective in the treatment of major clinically relevant symptoms of narcolepsy and sleep architecture abnormalities.

**CRD commentary**
The review addressed a clearly specified question. Study inclusion criteria were stipulated. Appropriate databases were searched for relevant studies. Attempts were made to identify unpublished studies. The authors used validated methods to examine potential for publication bias. Steps were taken to minimise reviewer error and bias during study selection and data extraction; methods were not reported for the assessment of methodological quality. Jadad scores indicated that the studies were of good quality. No data were presented on long term follow-up. Important quality criteria such as the reporting of allocation concealment were not evaluated. Many studies had a crossover design but this aspect of study quality was not assessed and further details were not provided. There was substantial heterogeneity in the results of the trials; the authors acknowledged that these were due to variations in doses, durations of treatment, follow-up durations, concomitant medications, clinical baseline features and sample sizes. The authors also acknowledged the absence of adequate information for subgroup analyses. The clinical value of the numerous pooled results in which significant statistical heterogeneity was present was questionable.

Limited assessment of study quality, substantial heterogeneity and an absence of trial population details make the reliability of the authors' conclusions uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that gamma hydroxybutyrate was effective for cataplexy attacks, subjective daytime sleepiness, subjective nocturnal awakenings and daytime sleep attacks.

**Research:** The authors stated that further well-designed placebo-controlled studies with adequate power were required. New research should use standardised outcomes with adequate follow-up and no other medication to investigate the effects of gamma hydroxybutyrate on night-time sleep disturbances in narcolepsy. The role of gamma hydroxybutyrate in sleep paralysis and hypnagogic hallucinations should be verified.

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