Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits

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CRD summary
This review assessed the effects of short-term treatment with sedative hypnotics for insomnia in older people. The authors concluded that any treatment benefits were small and may not justify the increased risks in this population, particularly in those at risk of cognitive impairment or falls. This was a reasonably well-conducted review and the results appear reliable.

Authors' objectives
To determine the efficacy and safety of short-term treatment with sedative hypnotics for insomnia in older people.

Searching
MEDLINE, EMBASE, the Cochrane Controlled Trials Register and PsycLIT were searched from 1966 to 2003 for articles published in the English language; the search terms were reported. Reference lists from relevant articles and reviews were also checked. In addition, the pharmaceutical manufacturers of zaleplon, zopiclone and zolpidem were contacted for unpublished studies.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion in the review. Single- or multicentre parallel trials and crossover trials were included.

Specific interventions included in the review
Studies of any sedative hypnotics administered for at least 5 consecutive nights, compared with placebo or another active treatment, were eligible for inclusion. Studies of barbiturates and chloral hydrate or chloral hydrate derivatives were excluded. The pharmacological agents assessed in the review included benzodiazepines, zopiclone, zolpidem, zaleplon and diphenhydramine.

Participants included in the review
Individuals with insomnia aged 60 years or older were eligible for inclusion. Individuals with psychiatric disorders, concurrent use of drugs affecting the central nervous system, severe or acute physical illness that might disrupt sleep, or cognitive incapacity to report outcomes, were excluded. The study participants included out-patients, hospital in-patients, nursing home residents and attendees at a 'geriatric clinic'.

Outcomes assessed in the review
The outcome measures were self-reported changes in a number of sleep variables: sleep quality, total sleep time, sleep onset latency and the number of awakenings during the night. Adverse events were also recorded: cognitive adverse events (memory loss, confusion and disorientation), psychomotor difficulties (dizziness, loss of balance and falls) and residual morning sedation.

How were decisions on the relevance of primary studies made?
One reviewer assessed citations for relevance; decisions were checked by a second reviewer.

Assessment of study quality
The authors evaluated the primary studies according to the Jadad scale. This scale assesses randomisation, blinding and the reporting of withdrawals and drop-outs. Three investigators independently assessed the validity of the primary studies; two of these investigators were blinded to author, author affiliation and publication source. Any disagreements were resolved by consensus.
**Data extraction**
Two investigators independently extracted the data from the included studies; any disagreements were resolved by consensus.

**Methods of synthesis**
How were the studies combined?
Cohen's d was used to estimate the effect size for measures of sleep quality. Pooled odds ratios (ORs) and their associated 95% confidence intervals (CIs) were obtained using random-effects meta-analyses for both measures of sleep quality and adverse events. The number-needed-to-treat (NNT) and number-needed-to-harm (NNH) were calculated for sleep quality and adverse events, respectively.

Funnel plots and Begg and Mazumair's rank correlation test were used to assess publication bias for all primary outcomes.

How were differences between studies investigated?
A chi-squared analysis was used to assess between-study differences for all combined results. A 'trim and fill' method was used to adjust for any heterogeneity found, and the results recalculated.

**Results of the review**
Twenty-four RCTs (n=2,511) were included in the review.

Quality of sleep.
The NNT for sedative hypnotics compared with placebo was calculated as 13 (95% CI: 6.7, 62.9), based on 4 studies.

Reported sleep quality was significantly better in participants who had received sedative hypnotics than in those who had received placebo; the mean effect size was 0.14 (95% CI: 0.05, 0.23), based on 8 studies. Compared with placebo, benzodiazepines were associated with a significant improvement in sleep quality; the mean effect size was 0.37 (95% CI: 0.01, 0.73), based on 7 studies. Heterogeneity was not reported. No statistically significant difference was found when zopiclone was compared with placebo; the mean effect size was 0.41 (95% CI: -0.76, 1.58), based on 2 studies. No statistically significant difference was found when benzodiazepine receptor agonists were compared with zaleplon, zopiclone and zolpidem (combined); the mean effect size was 0.04 (95% CI: -1.11, 1.19), based on 3 studies. The test for heterogeneity was not significant.

Sleep time.
Total sleep time was found to significantly improve in participants receiving any sedative compared with placebo; the mean increase in total sleep time was 25.2 minutes (95% CI: 12.8, 37.8), based on 8 studies. The test for heterogeneity was not significant. Compared with placebo, benzodiazepines significantly increased mean total sleep time by 34.2 minutes (95% CI: 16.2, 52.8), based on 8 studies. The test for heterogeneity was not significant. There were insufficient data available to analyse sleep onset latency or ease of going to sleep.

Number of awakenings.
Compared with placebo, the mean number of awakenings decreased significantly by 0.60 (6 studies; 95% CI: -0.41, -0.78) in participants receiving benzodiazepines. The test for heterogeneity was not significant.

Adverse events.
The NNH for sedative hypnotics compared with placebo was 6 (95% CI: 4.7, 7.1), based on all adverse events reported in 16 studies. The most common adverse events were drowsiness or fatigue, headache, nightmares, and nausea or gastrointestinal disturbances.
Cognitive effects: compared with placebo, sedative hypnotics were associated with significantly more cognitive side-effects; the OR was 4.78 (95% CI: 1.47, 15.47), based on 10 studies. The test for heterogeneity was not significant. No statistically significant difference was found when benzodiazepine receptor agonists were compared with zaleplon, zopiclone and zolpidem (combined); the OR was 1.12 (95% CI: 0.16, 7.76), based on 4 studies. The test for heterogeneity was not significant.

Psychomotor difficulties: no statistically significant difference between groups was demonstrated; the OR was 2.25 (95% CI: 0.93, 5.41), based on 13 studies. The test for heterogeneity was not significant. No statistically significant difference was found when benzodiazepine receptor agonists were compared with zaleplon, zopiclone and zolpidem (combined); the OR was 1.48 (95% CI: 0.75, 2.93), based on 4 studies. The test for heterogeneity was not significant.

Fatigue: compared with placebo, participants receiving sedative hypnotics reported significantly more morning or daytime fatigue; the OR was 3.82 (95% CI: 1.88, 7.80), based on 7 studies. Heterogeneity was not reported.

Morning impairment: participants receiving sedative hypnotics demonstrated significantly greater impairment in performance tasks than participants receiving placebo (d=0.14, 95% CI: 0.11, 0.16), based on 4 studies. The test for heterogeneity was not significant.

The funnel plot analysis demonstrated possible publication bias for the outcomes of sleep quality and total sleep time, which favoured positive results (P ≤0.5). The mean effect size did not change after 'fill and trim' methods were used to adjust the results.

Authors' conclusions
The effect of sedative hypnotics on sleep improvement in older people was small but statistically significant. The increased risk of adverse events was also statistically significant. The benefits of these treatments may not justify the increased risks in this population, particularly those at risk of cognitive impairment or falls.

CRD commentary
The review question was supported by clear inclusion and exclusion criteria in terms of the participants, interventions, outcomes and study designs. The search strategy was restricted by language and, as such, potentially relevant studies might have been missed. However, the authors assessed and attempted to correct for any publication bias found. The methods used to select studies and extract the data were likely to have reduced reviewer error or bias. The authors assessed the quality of the primary studies, and the results were reported. In addition, the authors acknowledged a number of limitations that should be taken into consideration: all sedatives and/or all benzodiazepines were grouped together for analyses, irrespective of dosages, half-life or potency; many of the outcomes were assessed through self-report measures; there was variation in the health status of the study participants; placebo run-in scores were used as control scores where studies had no control arm; and the exclusion of placebo responders in two studies. Between-study differences were assessed.

This was a reasonably well-conducted study and the results appear reliable.

Implications of the review for practice and research
Practice: The authors suggested that the added risk of an adverse event should be considered when prescribing sedative hypnotics to older patients. The authors added that non-pharmacological therapies might be a viable alternative treatment in this population.

Research: The authors did not state any implications for further research.

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Other publications of related interest
These additional published commentaries may also be of interest. Peri K. Review: sedative hypnotics may improve sleep quality but increase adverse effects in elderly people with insomnia. Evid Based Nurs 2006;9:87. Clarfield AM. Review: sedative hypnotics increase adverse effects more than they improve sleep quality in older persons with insomnia. Evid Based Med 2006;11:110. Clarfield AM. Review: Sedative-hypnotics increase adverse effects more than they improve sleep quality in older persons with insomnia. ACP J Club 2006;145:14.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.