

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

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Abstract

Objectives To quantify and compare potential benefits (subjective reports of sleep variables) and risks (adverse events and morning-after psychomotor impairment) of short term treatment with sedative hypnotics in older people with insomnia.

Data sources Medline, Embase, the Cochrane clinical trials database, PubMed, and PsychLit, 1966 to 2003; bibliographies of published reviews and meta-analyses; manufacturers of newer sedative hypnotics (zaleplon, zolpidem, zopiclone) regarding unpublished studies.

Selection criteria Randomised controlled trials of any pharmacological treatment for insomnia for at least five consecutive nights in people aged 60 or over with insomnia and otherwise free of psychiatric or psychological disorders.

Results 24 studies (involving 2417 participants) with extractable data met inclusion and exclusion criteria. Sleep quality improved (effect size 0.14, $P < 0.05$), total sleep time increased (mean 25.2 minutes, $P < 0.001$), and the number of night time awakenings decreased (0.63, $P < 0.001$) with sedative use compared with placebo. Adverse events were more common with sedatives than with placebo: adverse cognitive events were 4.78 times more common (95% confidence interval 1.47 to 15.47, $P < 0.01$); adverse psychomotor events were 2.61 times more common (1.12 to 6.09, $P > 0.05$), and reports of daytime fatigue were 3.82 times more common (1.88 to 7.80, $P < 0.001$) in people using any sedative compared with placebo.

Conclusions Improvements in sleep with sedative use are statistically significant, but the magnitude of effect is small. The increased risk of adverse events is statistically significant and potentially clinically relevant in older people at risk of falls and cognitive impairment. In people over 60, the benefits of these drugs may not justify the increased risk, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events.

Introduction

Insomnia often affects the quality of life for older people.¹⁻³ Acute episodes are usually treated with drugs.⁴ Between 5% and 33% of elderly people in North America and the United Kingdom are

prescribed a benzodiazepine or a benzodiazepine receptor agonist for sleep problems.^{5,6}

Adverse events that are associated with sedative use, such as ataxia, falls, or memory impairment, are thought to be particularly detrimental for older people.^{7,8} Despite the widespread use of sedative hypnotics in older people, the risk-benefit relation is not known. This meta-analysis aims to study the benefits of sedative use, as determined by subjective reported changes in sleep variables, and the risks, as determined by adverse events.

Methods

We searched Medline, Embase, the Cochrane clinical trials database, PubMed, and PsychLit from 1966 to 2003, and bibliographies of published reviews and meta-analyses for relevant titles. We asked the manufacturers of benzodiazepine receptor agonists about unpublished studies.

We considered double blind randomised controlled trials of sedative hypnotics in English that compared active treatment against placebo or another active comparator. In the included studies, participants had a mean age of at least 60 years and met predetermined diagnostic criteria for insomnia. Interventions were pharmacological treatments for insomnia for at least five consecutive nights. Any sedative hypnotic currently used in clinical practice was included in the search. We excluded studies of barbiturates and chloral hydrate or chloral hydrate derivatives as these are not recommended for elderly people.^{4,9}

Benefits were measured by the participants' perceived change in sleep. The variables that we considered were sleep quality, total sleep time, sleep onset latency or ease of getting to sleep, and number of awakenings during the night.

We categorised adverse events as cognitive adverse events (memory loss, confusion, disorientation); psychomotor-type adverse events (dizziness, loss of balance, or falls); and morning hangover effects. Morning impairment (as measured by performance tasks

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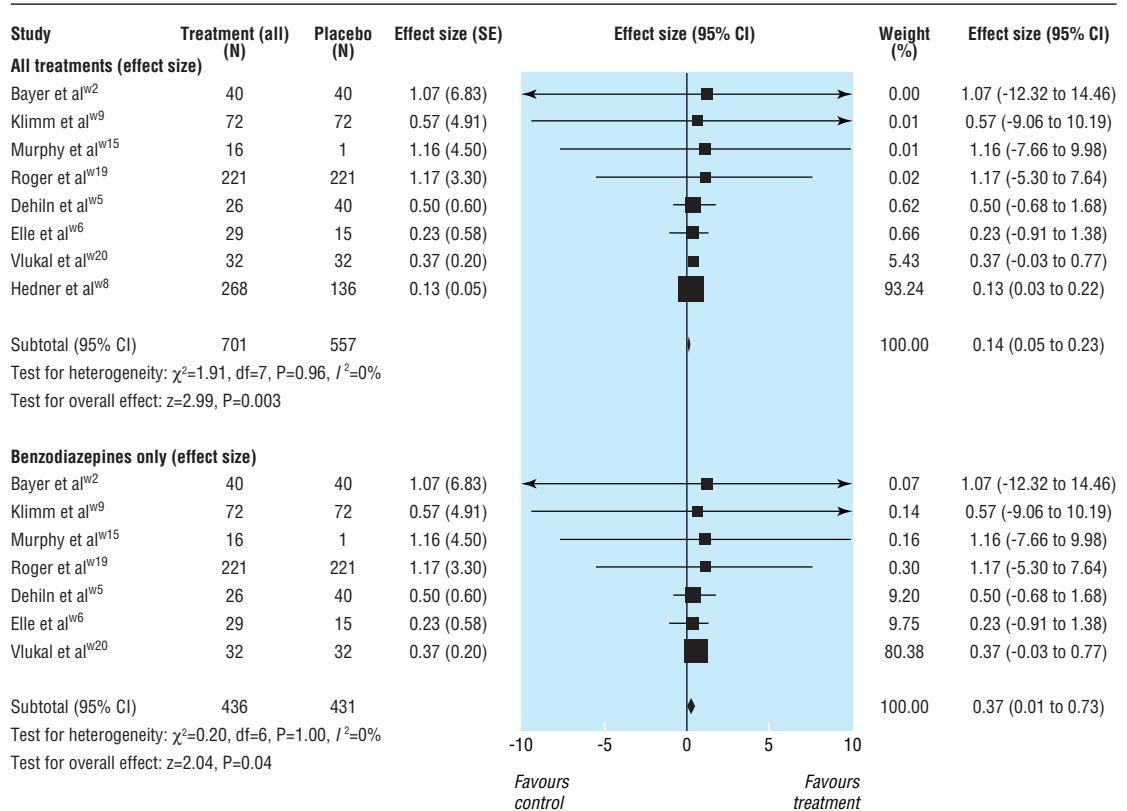


Fig 1 Mean effect size (95% confidence intervals) for subjective improvements in sleep quality with any sedative treatment and benzodiazepines only compared with placebo for at least five nights in people aged 60 or older with insomnia

such as reaction time or hand-eye coordination tasks) were analysed separately from adverse events.

As no standard accepted instrument measures sleep quality, we used effect sizes of the change in scores (Cohen's d). Similarly, as more than one instrument had been used to measure psychomotor impairment, we also calculated effect sizes for morning-after performance.

Common odds ratios were obtained for all adverse events. All results used random effects models and 95% confidence intervals. We used χ^2 analysis to test heterogeneity for all combined results.

Results

Of 120 studies identified, 20 satisfied inclusion and exclusion criteria and had extractable subjective data.^{w1-w20} Four further studies reported on adverse events only and have been included in the assessment of risk.^{w21-w24} A total of 830 participants were treated with a benzodiazepine, 106 with zopiclone, 384 with zolpidem, 609 with zaleplon, 14 with diphenhydramine, and 468 with placebo.

Sleep variables

On the basis of four studies (1072 participants), the number of patients who would need to be treated with a sedative for one to have an improvement in sleep quality is 13 (95% confidence interval 6.7 to 62.9).^{w1 w3 w8 w20}

Eight studies (719 participants) had extractable data on sleep quality for any sedative versus placebo.^{w2 w4 w6 w8 w9 w15 w19 w20} Reported sleep quality was significantly better with sedative use (mean effect size

0.14, 0.05 to 0.23; $P < 0.005$, fig 1). This effect size indicates a difference in mean scores on sleep quality for sedative versus placebo groups of 0.11 (SD 0.75). In the most heavily weighted study in the analysis,^{w8} this would correspond to mean scores of 3.8 in the placebo group and 3.7 in the sedative group on a seven point scale.

In eight studies (601 participants) with extractable data, the increase in total sleep time with any sedatives compared with placebo was 25.2 minutes (12.8 to 37.8 minutes; $P = 0.001$; test for heterogeneity $P = 0.10$).^{w3 w4 w10-w12 w14 w17 w20}

In six studies (441 participants), the mean number of awakenings decreased by 0.63 (-0.48 to -0.77, $P < 0.0001$; test for heterogeneity $P = 0.71$).^{w3 w5 w10 w12 w17 w19}

Adverse events

On the basis of all adverse events reported in 17 studies (2220 participants), the number needed to harm for sedative hypnotics compared with placebo is 6 (4.7 to 7.1).^{w1-w11 w13 w17 w20 w22-w24} The most common adverse events were drowsiness or fatigue, headache, nightmares, and nausea or gastrointestinal disturbances.

On the basis of 10 studies (712 participants), cognitive effects were significantly more common with sedative use than with placebo (odds ratio 4.78, 1.47 to 15.47, $P < 0.01$; test for heterogeneity $P = 0.35$, fig 2).^{w4 w6 w7 w9 w10 w13 w19 w22-w24}

Psychomotor-type side effects were reported in 13 studies (1016 participants) and were more common after treatment with a sedative, but this result did not reach significance.^{w3-w7 w9-w11 w13 w19 w22-w24} Of the 59 psychomotor effects that were reported, seven were

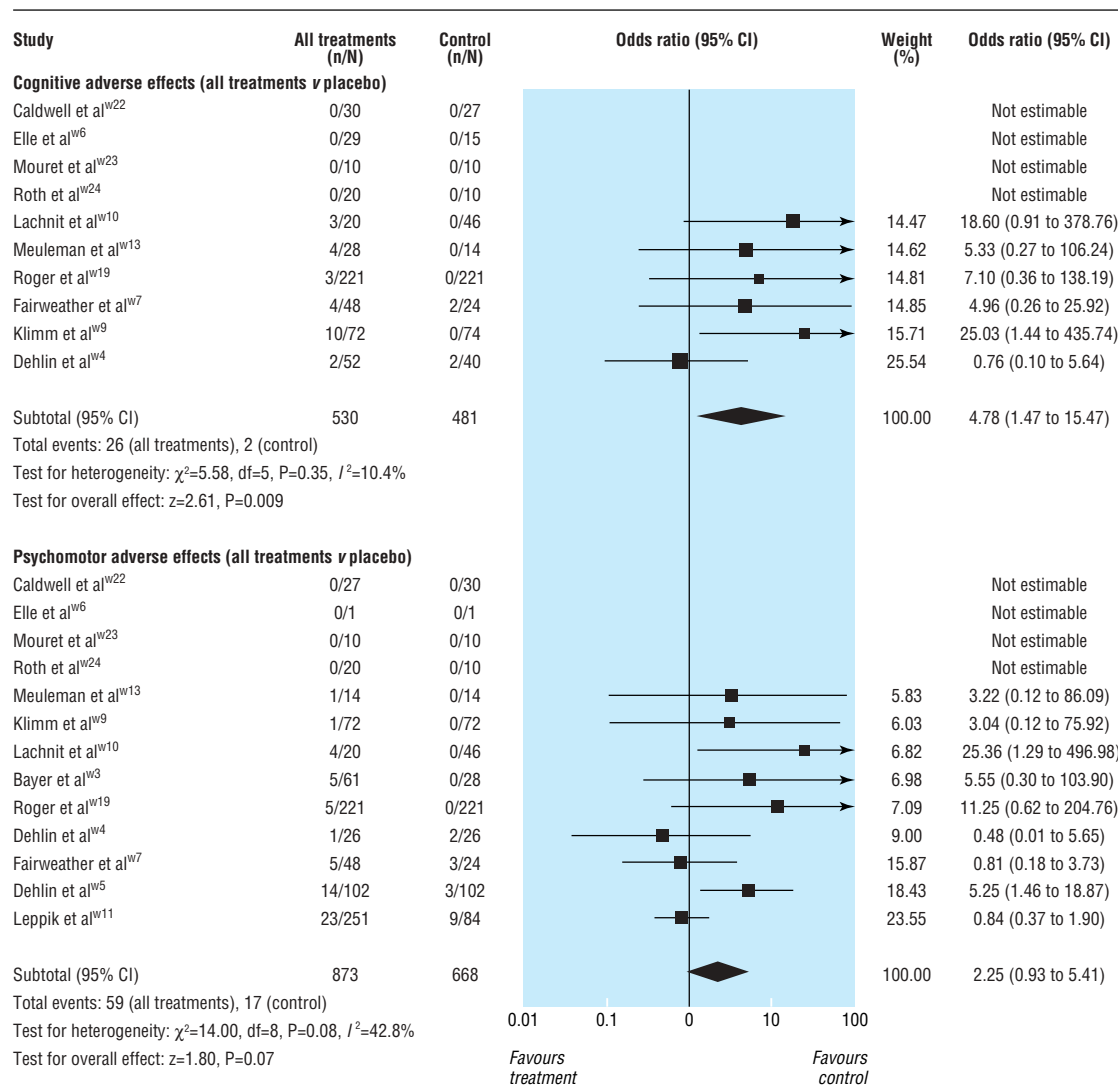


Fig 2 Cognitive and psychomotor adverse events, odds ratios, z scores, and test for heterogeneity for any sedative hypnotics taken for at least five nights in people aged 60 or older with insomnia

serious events (six falls and one motor vehicle crash). Three resulted in broken bones.

There were significantly more subjective reports of morning or daytime fatigue (seven studies, 829 participants) after treatment than after placebo (odds ratio 3.82, 1.88 to 7.80, $P < 0.001$).^{w3 w4 w9 w11 w13 w19 w21}

Impairment on performance tasks the morning after sedative use (four studies, 251 participants) was significantly greater than after placebo ($d=0.14$, 0.11 to 0.16; test for heterogeneity $P=0.57$).^{w3 w4 w7 w12}

Publication bias

Funnel plot analyses indicated a possible publication bias on outcomes of sleep quality and total sleep time favouring positive results ($r_s=0.78$, $P \leq 0.05$). The mean effect size did not change after “trim and fill” to correct estimates of effect size, and the result was still significant in favour of sedatives ($d=0.14$, $P \leq 0.05$ for sleep quality; mean increase in total sleep time = 15 minutes, $P \leq 0.05$).

Discussion

Treatment with sedative hypnotics improves the quality of sleep but the effect size (0.14) is small according to the classification by Cohen (in which a small effect size is about 0.2).¹⁰ Findings for both total sleep time and number of night time awakenings showed significant although small improvements in patients who took a sedative rather than placebo.

The risk of adverse events was higher with sedative treatment. Most adverse events were reported to be reversible and not severe.^{w1 w3-w11 w19 w20 w22 w24} Patients who took sedatives had a higher incidence of falls and motor vehicle crashes.

The number needed to treat for improved sleep quality was 13 and the number needed to harm for any adverse event was 6. This ratio indicates that an adverse event is more than twice as likely as enhanced quality of sleep. This ratio can be used as a rough indicator only, as more than double the number of participants contributed to the “harm” data than to the “effectiveness” data (2220 v 1072).

Although meta-analyses have examined the effects of benzodiazepines and benzodiazepine-receptor agonists, they have not examined their effects in older people. Nowell et al combined five studies that included people under 65 with insomnia and found a positive effect size of 0.62 (0.45 to 0.79) for benzodiazepines and zolpidem versus placebo for sleep quality scores.¹¹ Smith et al found an effect size of 1.2 when pharmacotherapy was compared with placebo in their meta-analysis of studies including both younger and older adults.¹² These studies describe greater overall effects of sedative on sleep quality than we found. Although our results for sleep quality were heavily weighted by one study that had a large sample size ($n=404$),¹⁸ removing this study from the analysis resulted in a mean effect size that was still lower than those reported by previous meta-analyses ($d=0.37$).

Similarly, in a meta-analysis of benzodiazepine use in adults with insomnia, Holbrook et al found a significant increase in total sleep time of 48.4 minutes with benzodiazepine use.¹³ Smith et al reported a significant increase in total sleep time of 40.5 minutes with pharmacotherapy compared with placebo and a decrease in the number of awakenings experienced during the night (-1.17).¹² These results are more positive than those in the present meta-analysis. This may indicate that sedative medications, particularly benzodiazepines may benefit older patients less than younger adults.

Holbrook et al found a significant increase in adverse events with benzodiazepine use (odds ratio 1.8, 1.4 to 2.4). The increase in psychomotor-type side effects found with sedative use in our study (odds ratio 2.61) is similar to the increase in reports of dizziness and lightheadedness found in the Holbrook meta-analysis after benzodiazepine use (odds ratio 2.6, 0.7 to 10.3). Holbrook et al also report a significant increase in reports of daytime fatigue with benzodiazepine use (odds ratio 2.4, 1.8 to 3.4).¹³ This is lower than our reported odds ratio for reports of daytime fatigue (odds ratio 3.82). This may indicate that older people have similar or greater potential for risks such as adverse events than younger adults.

Loss of memory and confusion have been reported with older sedative hypnotics such as triazolam and newer sedatives such as zolpidem in patients of all ages.¹⁴⁻¹⁵ The risk for these events may be even higher in elderly patients. Although investigators in the studies we included stated that patients were not cognitively impaired, they did not always use validated scales such as the mini-mental state examination to support these claims. Any pre-existing cognitive impairment may exacerbate confusion or memory problems.¹⁶

An increased risk for adverse events is consistent with reported risks for falls and motor vehicle crashes or household incidents.¹⁷ Older people may be at greater risk for adverse effects because of pharmacokinetic considerations, such as reduced clearance of certain sedative hypnotics.¹⁸⁻²⁰ There is also some evidence of pharmacodynamic differences such as increased sensitivity to peak drug effects.²⁰

We found that the impairment of performance tasks the morning after sedatives are used, though significant, is small. This may indicate that, even when fatigue is reported, reaction time or hand-eye coordination after sedative use does not deviate greatly from normal.

What is already known on this topic

Benzodiazepines and newer benzodiazepine receptor agonists are thought to be efficacious for sleep disturbances in elderly people

They are associated with risks that are particularly detrimental in elderly people, such as ataxia, cognitive effects, and falls

Little is known about how the risks and benefits compare for non-prescription sedative hypnotics

What this study adds

In people over 60 the benefits associated with sedative use are marginal and are outweighed by the risks, particularly if patients are at high risk for falls or cognitive impairment

Limitations of this study

Interpretation of this meta-analysis must take into account that all sedatives or all benzodiazepines were grouped together for analyses, irrespective of differences in half life, potency, or dosage. The studies used various measures of collecting subjective sleep variables: ordinal scales (three, five, or seven point), visual analogue scales, and combined scales. Furthermore, although subjective reports create more variable results than objective measures, we focused on subjective outcome measures because consumption of healthcare resources is driven by subjective report rather than objective measures of sleep.

Another potential source of variability was the health status of the participants in the studies. Some were community dwelling ambulatory patients attending a health clinic and others were inpatients on a geriatric ward. Differences in environment or health status may affect how people respond to subjective assessments. Furthermore, although studies were double blind, the psychotropic effects of sedative hypnotics may be cues that compromise blinding, which may in turn affect subjective reports.

Dependence and habituation are some of the major concerns with sedative use, but were not addressed directly in any of the studies. These factors also weigh on the risk-benefit relation, but their role could not be determined in this study.

Conclusions

Although the improvements in sleep variables obtained from prescription sedative hypnotics are statistically significant, the effect size is small, and the clinical benefits may be modest at best. The added risk of an adverse event may not justify these benefits, particularly in a high risk elderly population. These factors should be considered when sedative hypnotics are prescribed for older patients. Non-pharmacological therapies such as cognitive behaviour therapy have been shown to be as efficacious as pharmacotherapy for insomnia in older people.¹²⁻²¹ Because fewer risks are associated with behavioural therapies,¹²⁻²² they may be a viable treatment alternative in a healthy elderly population with no cognitive impairment.

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Preterm birth in twins after subfertility treatment: population based cohort study

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Abstract

Objectives To assess gestational length and prevalence of preterm birth among medically and naturally conceived twins; to establish the role of zygosity and chorionicity in assessing gestational length in twins born after subfertility treatment.

Design Population based cohort study.

Setting Collaborative network of 19 maternity facilities in East Flanders, Belgium (East Flanders prospective twin survey).

Participants 4368 twin pairs born between 1976 and 2002, including 2915 spontaneous twin pairs, 710 twin pairs born after ovarian stimulation, and 743 twin pairs born after in vitro fertilisation or intracytoplasmic sperm injection.

Main outcome measures Gestational length and prevalence of preterm birth.

Results Compared with naturally conceived twins, twins resulting from subfertility treatment had on average a slightly decreased gestational age at birth (mean difference 4.0 days, 95% confidence interval 2.7 to 5.2), corresponding to an odds ratio of 1.6 (1.4 to 1.8) for preterm birth, albeit confined to mild preterm birth (34-36 weeks). The adjusted odds ratios of preterm birth after subfertility treatment were 1.3 (1.1 to 1.5) when controlled for birth year, maternal age, and parity and 1.6 (1.3 to 1.8) with additional control for fetal sex, caesarean section, zygosity, and chorionicity. Although an increased risk of preterm birth was therefore seen among twins resulting from

subfertility treatment, the risk was largely caused by a first birth effect among subfertile couples; conversely, the risk of prematurity was substantially levelled off by the protective effect of dizygotic twinning.

Conclusions Twins resulting from subfertility treatment have an increased risk of preterm birth, but the risk is limited to mild preterm birth, primarily by virtue of dizygotic twinning.

Introduction

Efforts to increase the success rates of subfertility treatment have been accompanied by a rise in the rate of multifetal pregnancies.¹ About half of medically conceived babies in the United States and Europe are born as twins,²⁻³ and almost half of all twins result from subfertility treatment.¹ Despite widespread concern about the effects of medically aided conception on perinatal outcome, few studies have investigated outcomes in twins,⁴ and largely conflicting results have been reported.⁵ Adverse pregnancy outcome in twins relates to the high prevalence of preterm birth and is exacerbated by monozygotic and monochorionic twinning.⁶⁻⁸ Whether subfertility treatment also impinges on gestational length in twins as among singletons is unclear,⁵⁻⁹ as is the extent to which type of

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