ClinicalEvidence

Insomnia in the elderly

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ABSTRACT

INTRODUCTION: Up to 40% of adults have insomnia, with difficulty getting to sleep, early waking, or feeling unrefreshed on waking. The prevalence of insomnia increases with age. Other risk factors include psychological factors, stress, daytime napping, and hyperarousal. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug treatments for insomnia in elderly people? What are the effects of drug treatments for insomnia in elderly people? We searched: Medline, Embase, The Cochrane Library and other important databases up to October 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 28 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: benzodiazepines (brotizolam, flurazepam, loprazolam, midazolam, nitrazepam, quazepam, temazepam, and triazolam), cognitive behavioural therapy, diphenhydramine, exercise programmes, timed exposure to bright light, zaleplon, zolpidem, and zopiclone.

QUESTIONS

INTERVENTIONS

Key points

- Up to 40% of adults have insomnia, with difficulty getting to sleep, early waking, or feeling unrefreshed on waking.

  The prevalence of insomnia increases with age. Other risk factors include psychological factors, stress, daytime napping, and hyperarousal.

  Primary insomnia is a chronic and relapsing condition that may increase the risks of accidents, and is associated with dementia, depression and falls.

- We don't know whether CBT, exercise programmes or timed exposure to bright light can improve sleep quality compared with no treatment.

- Zaleplon,zolpidem, and zopiclone may improve sleep latency in elderly people, although long-term effects are unknown, and they are likely to cause adverse effects.

  Zolpidem and zopiclone may also increase sleep duration and improve sleep quality compared with placebo in the short term.

  Zaleplon has not been shown to improve sleep duration, number of awakenings, or sleep quality, and may cause rebound insomnia after discontinuation of treatment.

- Benzodiazepines may improve sleep outcomes compared with placebo or other treatments, but are likely to cause adverse effects.

  We don't know what the long-term effects of benzodiazepines are.

  Benzodiazepines can cause impairment of memory, cognitive and psychological function, and rebound insomnia. They may increase the risks of accidents, falls, and hip fractures in elderly people.

- We don't know whether diphenhydramine improves sleep quality in elderly people.

DEFINITION

Insomnia is defined by the *International Classification of Sleep Disorders-2* (ICSD-2) as repeated difficulty with sleep initiation, duration, consolidation, or quality, occurring despite adequate time and opportunity for sleep, and results in some form of daytime impairment. [1] **Chronic insomnia** is defined as insomnia occurring for at least three nights a week for 1 month or more. [2] **Primary insomnia** is defined as chronic insomnia without specific underlying medical, psychiatric, or other sleep disorders, such as sleep apnoea, depression, dementia, periodic limb movement disorder, or circadian rhythm sleep disorder. This review only covers primary insomnia in people aged 60 years and over.

INCIDENCE/ PREVALENCE

One population survey in Sweden found that across all adult age groups, up to 40% of people have insomnia. [3] A US survey in people aged 18–79 years found that insomnia affected 35% of all adults during the course of one year, and that prevalence increased with age, with estimates ranging from 31–38% in people aged 18–64 years, to 45% in people aged 65–79 years. [4] One US prospective cohort study in people aged over 65 years old found that between 23–34% had insomnia, and between 7–15% had chronic insomnia. [5] It also reported a higher incidence of insomnia in women than in men.

AETIOLOGY/ RISK FACTORS

The cause of insomnia is uncertain. The risk of primary insomnia increases with age and may be related to changes in circadian rhythms associated with age, or the onset of chronic conditions and poorer health as a result of aging. [6] Psychological factors and lifestyle changes may exacerbate perceived effects of changes in sleep patterns associated with age, leading to reduced satisfaction with sleep. [7] Other possible risk factors in all age groups include hyperarousal, chronic stress, and daytime napping. [2] [8]

PROGNOSIS

We found few reliable data on long-term morbidity and mortality in people with primary insomnia. Primary insomnia is a chronic and relapsing condition. [9] Likely consequences include reduced quality of life and increased risk of accidents owing to daytime sleepiness. People with primary insomnia may be at greater risk of dependence on hypnotic medication, depression, dementia, and falls, and may be more likely to require residential care. [10]

AIMS OF INTERVENTION

To improve satisfaction with sleep; to prevent daytime sleepiness and improve functional and cognitive ability during the daytime.

OUTCOMES

Sleep latency, fragmentation of sleep; early waking; quality of life; self-report of sleep satisfaction; sleep quality scales, such as the Pittsburgh Sleep Quality Index (PSQI); performance on attentional task tests; daytime functioning scales such as the Stanford Sleepiness Scale and the Epworth Sleepiness Scale; adverse effects of treatment.

METHODS

BMJ Clinical Evidence search and appraisal October 2006. The following databases were used to identify studies for this review: Medline 1966 to October 2006, Embase 1980 to October 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2006, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. Only systematic reviews and RCTs examining the effects of treatments in people with chronic primary insomnia were included. Where we have found two or more systematic reviews about a particular comparison, we have selected those that we judged to be the most robust and relevant. RCTs were included if 80% or more participants were reported to be aged 60 years or over and there were at least 10 people in each intervention group. We also did a search for cohort studies on specific harms of named interventions. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. **Non-English language studies:** We identified eight such studies, none of which were included in the systematic reviews reported. We are in the process of having these translated and, if appropriate, they will be included in the next update. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 16).

QUESTION What are the effects of non-drug treatments for insomnia in elderly people?

OPTION CBT

Symptom improvement
Compared with no treatment CBT (sleep hygiene, stimulus control, sleep restriction, muscle relaxation, and sleep education) may be no more effective at 3 months at improving sleep quality in people with primary insomnia compared with no treatment (low-quality evidence).

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits: We found one systematic review (search date 2002, 6 RCTs, 282 people with primary insomnia, at least 80% of whom were 60 years or over). [11] Only one of the RCTs (36 caregivers for people with dementia) identified by the review reported on outcomes relevant to the present review.

CBT versus no treatment:
The RCT found that group or individual CBT (consisting of sleep hygiene, stimulus control, sleep restriction, muscle relaxation, and sleep education) significantly improved Pittsburgh Sleep Quality Index scores compared with no treatment, immediately after treatment, and at 3 months (mean scores immediately after treatment: 7.8 with CBT *v* 10.6 with no treatment; WMD –2.80, 95% CI –5.44 to –0.16; mean scores at 3 months: 6.20 with CBT *v* 10.20 with no treatment; WMD –4.00, 95% CI –6.62 to –1.38). However, mean sleep quality scores were consistent with continuing insomnia, both with and without CBT.

Harms: The systematic review did not report on harms. [11]

Comment: In the RCT, Pittsburgh Sleep Quality Index was assessed by investigators who were blind to treatment allocation. [11] We found one subsequent RCT (75 adults), in which 45% of participants were older than 55 years. [12] It compared three treatments: CBT (sleep education, stimulus control, and restrictions on time spent in bed), relaxation therapy, and placebo (listening to descriptions of neutral activities before going to bed). The trial did not report separate results for different age groups. Overall, it found no significant differences among treatments for symptoms (measured on a 100-point insomnia symptom questionnaire). [12] We found one additional RCT comparing CBT against standard care. [13] It appeared to randomise clinics and analyse results by individual patients, making it difficult to interpret the results. The reported results found that CBT significantly improved Pittsburgh Sleep Quality at 3 and 6 months.

OPTION EXERCISE PROGRAMMES

Symptom improvement
Compared with no treatment Moderate-intensity exercise (30–40 minutes of walking or low-impact aerobics 4 times a week) is more effective than no treatment at improving sleep quality at 16 weeks in people with primary insomnia (moderate-quality evidence).

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits: We found one systematic review (search date 2002, 1 RCT, 43 people with primary insomnia, at least 80% aged 60 years and over) [14]

Exercise versus no treatment:
The review identified one RCT that compared 16 weeks of regular moderate intensity exercise (30–40 minutes of walking or low impact aerobics 4 times a week) with no treatment. It found that the exercise programme significantly improved Pittsburgh Sleep Quality Index more than no treatment at 16 weeks (mean Pittsburgh Sleep Quality Index score at 16 weeks: 5.4 with exercise therapy *v* 8.8 with no treatment; mean score improvement with exercise programme *v* no treatment: 3.4, 95% CI 1.9 to 5.4; P less than 0.001). [14]

Harms: The systematic review [14] gave no information about harms.

Comment: None.

OPTION TIMED EXPOSURE TO BRIGHT LIGHT

We found no clinically important results about the effects of timed bright light exposure compared with other treatments or no treatment in the treatment of elderly people with insomnia.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits: We found one systematic review (search date 2001) that compared the effects of timed bright light exposure with other treatments or no treatment in people aged 60 years and over. [15] It identified no RCTs. We found no subsequent RCTs.

Harms: The review gave no information about harms. [15]

Comment: Bright light has been found to assist with sleep-timing problems in other populations. [16] However, we found no good evidence about its effects in elderly populations.

QUESTION What are the effects of drug treatments for insomnia in elderly people?

OPTION DIPHENHYDRAMINE

We found no direct information about the effects of diphenhydramine in the treatment of elderly people with insomnia.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits: We found no RCTs looking at the effects of diphenhydramine on insomnia in elderly people.

Harms: We found no RCTs.

Comment: None.

OPTION BENZODIAZEPINES

Symptom improvement
Compared with placebo Benzodiazepines are more effective at 5 days at improving sleep quality and total time asleep, and at reducing the number of awakenings, compared with placebo (high-quality evidence).

Compared with benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone) Benzodiazepines are no more effective at improving sleep quality compared with benzodiazepine receptor agonists (moderate-quality evidence).

Adverse effects
Compared with benzodiazepine receptor agonists (zaleplon, zolpidem, zopiclone) Benzodiazepines seem to have similar cognitive, psychomotor-type, and overall adverse effects, compared with benzodiazepine receptor agonists (low-quality evidence).

Note
People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep. Benzodiazepines may be associated with an increased risk of falls, hip fractures, cognitive impairment, and car accidents.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits:

Benzodiazepines versus placebo:
We found one systematic review (search date 2003, 14 RCTs, 830 people aged 60 or over with insomnia) comparing any benzodiazepine versus placebo for at least 5 nights. [17] The review found that benzodiazepines significantly improved subjective sleep quality (7 RCTs, 277 people; mean subjective sleep quality score measured on a five-point scale: 3.1 with benzodiazepines *v* 2.7 with placebo; mean effect size: 0.37, 95% CI 0.01 to 0.73; P = 0.04), increased total sleep time (8 RCTs, 524 people; mean difference in increased total sleep time: 34.2 minutes, 95% CI 16.2 to 52.8 minutes; P less than 0.01), and reduced the number of awakenings (6 RCTs, 296 people, mean difference in reduced number of awakenings: 0.60 95% CI –0.41 to –0.78; P less than 0.0001) compared with placebo. [17] The review found insufficient data to analyse sleep onset latency or subjective ease of getting to sleep.

Benzodiazepines versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone):
We found one systematic review (search date 2003, 3 RCTs, 339 people), [17] which compared benzodiazepines (triazolam or nitrazepam) versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone). Meta-analysis found no significant difference in subjective sleep quality between the benzodiazepines and benzodiazepine receptor agonists (mean effect size: 0.04 95% CI –1.11 to 1.19; P value and absolute data not reported). The review did not analyse data for each drug separately. [17]

Harms:

Benzodiazepines and non-benzodiazepines (zopiclone, zaleplon, and zolpidem) versus placebo:
The systematic review [17] reported data for adverse effects associated with all sedative hypnotics, including zopiclone, zaleplon, and zolpidem, and did not report adverse effects associated with benzodiazepine use separately. It found that drowsiness or fatigue, headache, nightmares, and nausea or gastrointestinal disturbances were the most common adverse effects associated with sedative use, but did not meta-analyse data as severity was reported in only one RCT. Cognitive adverse effects were significantly more common with sedative use than with placebo (10 RCTs, 712 people, absolute data not reported; OR 4.78, 95% CI 1.47 to 15.47; P less than 0.01) and psychomotor-type adverse effects, such as dizziness and loss of balance, were also more common, though not significantly so (13 RCTs, 1016 people, OR 2.25, 95% CI 0.93 to 5.41; P = 0.07) and included 59 psychomotor effects, of which seven were serious events (6 falls, 3 resulting in broken bones, and 1 motor crash). [17] The review also found a significantly higher proportion of people taking sedative hypnotics with subjective morning or daytime fatigue (7 RCTs, 829 people: absolute data not reported; OR 3.82, 95% CI 1.88 to 7,80; P less than 0.001), and impairment on performance tasks the morning after treatment (4 RCT, 251 people: absolute data not reported; mean difference: 0.14, 95% CI 0.11 to 0.16; P value not reported; reported as significant) after sedative use compared with placebo. [17] The meta-analysis found that the risk of adverse events after sedative use was more than twice as likely as achieving enhanced quality of sleep. [17]

Benzodiazepines versus benzodiazepine receptor agonists:
See Zolpidem versus benzodiazepines under harms of Zolpidem, p 7 .

Observational studies:
We found one systematic review that included observational data on the adverse effects of benzodiazepines. [18] One observational study included (169 people) found an association between falls and benzodiazepines (adverse event risk estimate: 1.8, 95% CI 0.9 to 3.6). [19] Data from four included observational studies suggested that long-acting benzodiazepines were associated with a greater risk (nearly a twofold increase) of hip fracture than shorter-acting benzodiazepines (adverse risk estimate for hip fractures, study 1 [nested case control, 1021 cases, 5605 controls]: [20] 1.8, 95% CI 1.3 to 2.8; study 2: [nested case control, 4501 cases, 24,041 controls]: [21] 1.7, 95% CI 1.5 to 2.0 with long-acting benzodiazepines *v* 1.1, 95% CI 0.9 to 1.3 with short-acting benzodiazepines; study 3 [case control, 209 cases, 207 controls]: [22] 1.6, 95% CI 0.95 to 2.5; study 4 [prospective cohort, 9516 women taking long-acting benzodiazepines]: [23] 1.6 95% CI 1.1 to 2.4). One included retrospective cohort study (16,262 people) reported an adverse risk estimate for injurious car crashes in people taking benzodiazepines of 1.5 (95% CI 1.2 to 1.9). [24]

Comment:

Clinical guide:
We found no good evidence about the long-term effects of benzodiazepines for insomnia in elderly people. There is little evidence about beneficial or adverse effects of benzodiazepines used for over 1 month. Few RCTs include enough people to detect relatively infrequent but important side effects, such as falls, or hip fractures. Observational studies suggest that benzodiazepines are associated with an increased risk of falls, hip fractures, cognitive impairment, and car accidents. [18] One study examining the toxicity of flurazepam in elderly people found this target group to be at high risk of adverse effects, as 43% of people were receiving concurrent treatment with an anti-anxiety drug. Adverse effects included drowsiness, confusion, and ataxia, and suggested a dose–response relationship. [25] We found few studies that measured the effect of treatments on daytime sleepiness, which is an important outcome to older people.

OPTION ZALEPLON

Symptom improvement
Compared with placebo Zaleplon may be more effective at improving sleep latency, but seems no more effective at reducing the number of awakenings, and total sleep time, in people with primary insomnia, compared with placebo (low-quality evidence).

Compared with benzodiazepines Benzodiazepine receptor agonists are no more effective at improving sleep quality compared with benzodiazepines (moderate-quality evidence).

Adverse effects
Compared with placebo Zaleplon has similar rates of treatment-emergent adverse effects, but increases rebound insomnia after discontinuation of treatment at 2 weeks, compared with placebo (moderate-quality evidence).

Compared with benzodiazepines Zaleplon seems to have similar cognitive, psychomotor-type, and overall adverse effects, compared with benzodiazepines (low-quality evidence).

Note

People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits:

Zalepon versus placebo:
We found one systematic review (search date 2000, 2 RCTs, 971 people with primary insomnia, with at least 80% aged 60 years or older) [26] and one subsequent RCT. [27] The first large RCT identified by the review (549 people with primary insomnia aged 65 years or older) was a four-arm trial, which compared zaleplon 5 mg and 10 mg, and zolpidem 5 mg versus placebo over 2 weeks. It also compared zaleplon 10 mg versus zolpidem 5 mg. [28] The second RCT (422 people aged 65 years or older with primary insomnia for at least 3 months) was a three-arm trial comparing zaleplon 5 mg and 10 mg versus placebo. [29] The subsequent RCT (double blind, 48 people aged 60–80 years with insomnia) used polysomnographic (PSG) screening records and post-sleep questionnaires to compare zaleplon 2, 5, and 10 mg versus placebo and each other at 2 days. [27]

Sleep latency:
The two large RCTs identified by the review found that zaleplon 5 mg significantly reduced median subjective sleep latency at 14 days compared with placebo, [28] [29] by 25 minutes in the first RCT (see table 1, p 14). [28] Only one of the two large RCTs found that 5 mg significantly reduced median subjective sleep compared with placebo at 7 days, [29] and the subsequent RCT found it more effective at 2 days (see table 1, p 14). [27] All three RCTs found that a 10 mg dose significantly reduced median subjective sleep latency compared with placebo, at 7 and 14 days [28] [29] and 2 days. [27] Results of the small subsequent RCT suggested a dose-effect relationship (see table 1, p 14). [27]

Total sleep time:
Both large RCTs found no significant difference in the improvement from baseline for median subjective total sleep time between zaleplon 5 mg and placebo at 14 days (see table 1, p 14). [28] [29] The second RCT found that 5 mg was significantly more effective than placebo at 7 days, but only by 8 minutes, [29] and the first RCT found no significant difference. [28] The small subsequent RCT found no significant difference in subjective sleep times between 5 mg dose and placebo at 2 days, but objective sleep duration was significantly increased (by 31 minutes) with zaleplon 5 mg compared with placebo (see table 1, p 14). [27] Both of the large RCTs found that zaleplon 10 mg significantly increased (by 5 minutes) median subjective total sleep time from baseline compared with placebo at 7 days, but found no significant difference at 14 days. [28] [29] The small subsequent RCT found a significant increase (by 22.5 minutes) with 10 mg compared with placebo at 2 days (see table 1, p 14). [27] It also found median objective total sleep time was significantly increased (by 20 minutes) with zaleplon 10 mg compared with placebo at 2 days (see table 1, p 14). [27] The small subsequent RCT found no significant difference in subjective or objective sleep times between 2 mg dose compared with placebo at 2 days. [27]

Sleep quality:
Both large RCTs found that zaleplon 10 mg significantly improved sleep quality compared with placebo at 7 days, but only by very small amounts. [27] Similar results were found for 10 mg at 14 days and for 5 mg at both 7 and 14 days (see table 1, p 14). [28] [29] The subsequent RCT did not report on sleep quality. [27]

Number of awakenings:
The small subsequent RCT found a slightly lower subjective number of awakenings with zaleplon 10 mg compared with placebo at 2 days. No other significant differences between treatment and placebo groups were found in the two RCTs identified by the review [28] [29] and the subsequent RCT [27] (see table 1, p 14).

Zaleplon versus benzodiazepines:
We found one systematic review, [17] which included three RCTs (339 people) comparing benzodiazepines (triazolam or nitrazepam) versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone). The review found no significant difference in subjective sleep quality between the benzodiazepines and benzodiazepine receptor agonists (mean effect size: 0.04 95% CI –1.11 to 1.19; P value and absolute data not reported). The review did not analyse data for zaleplon separately. [17]

Harms:

Zaleplon versus placebo:
The first RCT identified by the review found similar proportions of people with treatment emergent adverse events between groups: 56% with placebo, 56% with zaleplon 5 mg, and 59% with zaleplon 10 mg. The most common of these were headache, pain, somnolence, and rhinitis. [28] The second RCT identified by the review also found similar proportions of people with treatment-emergent ad-

verse events between groups: 74 (51%) with placebo, 68 (48%) with zaleplon 5 mg, and 59 (40%) with zaleplon 10 mg. The most common of these were headache, pain, and dizziness. [29] The subsequent RCT did not give any information on adverse effects. [27]

Zaleplon versus benzodiazepines:
The systematic review reported no significant difference between benzodiazepine receptor agonists (zolpidem, zoplicone and zaleplon) and benzodiazepines in the number of overall adverse effects (6 RCTs, 648 people: absolute data not reported; OR 1.11, 95% CI 0.59 to 2.07, P = 0.75), cognitive adverse effects (4 RCTs, 268 people: absolute data not reported; OR 1.12, 95% CI 0.16 to 7.76; P = 0.91) or psychomotor-type adverse effects (6 RCTs, 625 people: absolute data not reported; OR 1.48, 95% CI 0.75 to 2.93; P value not reported, reported as non-significant) . The review did not report results for zaleplon separately. [17]

Rebound insomnia:
The first large RCT found that, on the first night after discontinuing 2 weeks of treatment, median subjective total sleep time was significantly shorter with zaleplon 10 mg compared with placebo (median subjective total sleep time in minutes [change from baseline]: 300.00 [–8.57] with zaleplon 10 mg *v* 317.50 [+22.98] with placebo; P less than 0.05). [28] The second large RCT found that discontinuing zaleplon 10 mg caused significant rebound insomnia, shown by changes in subjective total sleep time (proportion of people with rebound insomnia: 17/136 [13%] with zaleplon 10 mg *v* 6/130 [5%] with placebo; P = 0.028). [29]

Comment: **Clinical guide:** There is a lack of pragmatic studies where the effects of zaleplon on elderly people taking other medication are assessed. Many elderly people take a range of drugs for various conditions, and there is an urgent need for studies demonstrating the effectiveness and adverse effects of hypnotics when taken in combination with other drugs by this target population. Long-term studies are also needed to establish the safety and effectiveness of the prolonged use of zaleplon. Although not recommended, it is quite common for people to be prescribed hypnotics for a long period of time. In the two RCTs included in the systematic review, the treatment study period was only 2 weeks.

OPTION ZOLPIDEM

Symptom improvement
Compared with placebo Zolpidem may be more effective at 1–28 days at improving sleep latency, reducing night awakenings, and increasing sleep duration and quality, compared with placebo (low-quality evidence).

Compared with benzodiazepines Zolpidem may be no more effective at improving sleep quality, total sleep times, sleep latency, and ease of falling asleep, compared with benzodiazepines (low-quality evidence).

Different doses compared with each other Different doses of zolpidem seem to have similar sleep outcomes (sleep latency, total sleep time, number of awakenings, and overall sleep quality) at 7–28 days in people with insomnia (low-quality evidence).

Adverse effects
Compared with benzodiazepines Zolpidem seems to have similar cognitive, psychomotor-type, and overall adverse effects, compared with benzodiazepines (low-quality evidence).

Note
People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits: **Zolpidem versus placebo:**
We found one systematic review (search date 2003), [17] four additional RCTs, [28] [30] [31] [32] and one subsequent RCT. [33] The systematic review included three RCTs comparing zolpidem versus placebo, but reported that data were insufficient for inclusion in a meta-analysis of benefits. [17] The first additional RCT (549 people with primary insomnia aged 65 years or older), was a four-arm trial comparing zolpidem 5 mg versus zaleplon 5 mg and 10 mg versus placebo. [28] It found that, compared with placebo, zolpidem 5 mg significantly improved sleep outcomes at 7 and 14 days for sleep latency (median subjective sleep latency at 7 days: absolute numbers presented graphically; P less than 0.05; at 14 days: absolute numbers presented graphically; P less than 0.01), duration of sleep (median subjective total sleep time in minutes, at 7 days: 360 with zolpidem 5 mg *v* 318 with placebo; P less than 0.001; at 14 days: 360 with zolpidem 5 mg *v* 326 with placebo; P less than 0.01), sleep quality (median subjective sleep quality [reduction from baseline] at 7 and 14 days: 3.50 [−0.67] with zolpidem 5 mg *v* 4.00 [−0.29] with placebo; P less than 0.001), and

number of awakenings (median subjective number of awakenings at 7 days: 1.7 with zolpidem 5 mg *v* 2.0 with placebo; P less than 0.01; at 14 days: 1.6 with zolpidem 5 mg *v* 1.9 with placebo; P less than 0.05). [28] The second additional RCTs (double blind parallel group design, 221 inpatients aged 61–94 years with chronic insomnia) compared single doses of zolpidem 5 mg, 10 mg, 20 mg, and 30 mg versus placebo versus triazolam for 21 nights. [30] It found that, compared with placebo, higher doses of zolpidem significantly improved most sleep outcomes at 1 day, including sleep latency (111 inpatients: subjective sleep latency score [1 = 15 minutes, 2 = 15–30 minutes, 3 = 30–60 minutes, and 4 = over 60 minutes]: 3.0 with placebo *v* 2.1 with 10 mg [P less than 0.05] *v* 1.8 with 20 mg [P less than 0.01]; 1.9 with 30 mg [P less than 0.05]; 2.1 with 10 mg [P less than 0.05]; 1.8 with 20 mg [P less than 0.01]; 1.9 with 30 mg [P less than 0.05], all P values for dose *v* placebo), sleep duration (subjective total sleep time in hours: 7.6 with zolpidem 10 mg; 7.6 with zolpidem 20 mg; 7.7 with zolpidem 30 mg *v* 6.7 with placebo; P less than 0.05 for all comparisons *v* placebo), and number of awakenings (1.0 with zolpidem 20 mg; 1.1 with zolpidem 30 mg *v* 2.1 with placebo; P less than 0.05 for comparisons *v* placebo), but found no significant difference in sleep quality between groups (data presented graphically; reported as not significant). [30] The third additional RCT (357 inpatients aged 19–71 years with transient insomnia on the night before elective surgery) compared zolpidem 10 mg versus triazolam 0.25 g versus placebo. [31] It provided limited evidence that zolpidem was more effective than placebo for improving subjective measures of sleep latency, ease of falling asleep, total sleep time, number of awakenings, and quality of sleep at 7 days (absolute data not reported, reported as significant). [31] The fourth additional RCT (published only as an abstract, 335 people aged 59–95 years old with chronic insomnia lasting 3 months or more) was a four arm trial comparing zolpidem 5 mg versus temazepam 15 mg versus 0.125 mg triazolam versus placebo in an intervention lasting 4 weeks. [32] It found that zolpidem 5 mg significantly reduced sleep latency compared with placebo at up to 4 weeks (sleep latency at 4 weeks in minutes [baseline range: 50–60]; 26.9 with zolpidem 5 mg *v* 36.2 with placebo; reported as significant). [32] It found that improvements in sleep duration with zolpidem 5 mg over 4 weeks compared with placebo did not typically reach significance. [32] We found a report [33] of a subsequent RCT (published only as an abstract, 205 people aged 65 and older with primary insomnia) comparing 6.25 mg zolpidem CR (extended-release formula) versus placebo for 3 weeks. [33] It found that zolpidem CR significantly improved mean objective wake time after sleep onset, measured by polysomnography in the sleep laboratory, compared with placebo on nights 1 and 2 (mean decrease from baseline in minutes : seconds for nights 1/2: –32:41 with zolpidem CR 6.25 mg *v* –6:59 with placebo; P = 0.0001; on nights 15/16: –18:22 with zolpidem CR 6.25 mg *v* –6:56 with placebo; P = 0.004). [33] It also found that zolpidem CR significantly improved mean latency to persistent sleep from baseline compared with placebo (mean decrease from baseline in minutes: seconds for nights 1/2:–17:10 with zolpidem CR 6.25 mg *v* –6:55 with placebo; P = 0.0001; for nights 15/16: –14:18 with zolpidem CR 6.25 mg *v* –8:30 with placebo; P = 0.026). [33] Zolpidem CR recipients showed significant improvements in mean sleep efficiency scores on nights 1 and 2 compared with placebo, but the difference did not quite reach significance on night 15 and 16 (nights 1/2: +10.2% with zolpidem CR 6.25 mg *v* +3.0% with placebo; P less than 0.0001; nights 15/16: +5.9% with zolpidem CR 6.25 mg *v* +3.5% with placebo; P = 0.051). [33]

Zolpidem versus benzodiazepines:
The systematic review, [17] meta-analysed three RCTs (339 people) comparing benzodiazepines (triazolam or nitrazepam) versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone). It found no significant difference in subjective sleep quality between the benzodiazepines and benzodiazepine receptor agonists (mean effect size: 0.04 95% CI –1.11 to 1.19; P value and absolute data not reported). The review did not analyse data for zolpidem separately. [17]

The first additional RCT (published only as an abstract, 357 inpatients aged 19−71 years with transient insomnia on the night before elective surgery compared zolpidem 10 mg versus triazolam 0.25 g versus placebo. [31] It found no significant difference between zolpidem and triazolam in subjective results for total sleep time, sleep latency, quality of sleep, and ease of falling asleep. It found a slight significance that triazolam reduced the number of awakenings by 0.7 time per night compared with zolpidem. [31] The second additional RCT (published only as an abstract, 335 people aged 59–95 years old with chronic insomnia for 3 months or more) was a four-arm trial comparing zolpidem 5 mg versus temazepam 15 mg versus triazolam 0.125 mg versus placebo over 4 weeks. [32] It suggested a greater improvement in sleep latency with zolpidem 5 mg compared with temazepam, and similar results for zolpidem and triazolam (absolute data and significance not reported). [32]

Different doses of zolpidem versus each other:
We found two RCTs comparing different doses of zolpidem. [30] [34] The first RCT (84 inpatients aged under 60 years with insomnia, recruited from geriatric centres) compared zolpidem 10 and 20 mg versus flunitrazepam 1 mg for 28 days. [35] It found no significant differences in subjective improvements between 10 and 20 mg doses for sleep latency, total sleep time, and number of nocturnal at 28 days (sleep latency score [scale: 1 = less than 15 minutes, 2 = 15–30 minutes,

3 = 30–60 minutes, and 4 = over 60 minutes]: 2.0 with 10 mg *v* 2.1 with 20 mg; total sleep time score [scale: 1 = less than 6 hours, 2 = 6–8 hours, 3 = over 8 hours]: 2.0 with zolpidem 10 mg *v* 2.0 with zolpidem 20 mg; number of awakenings score [scale: 0 = no awakenings, 1 = once, 2 = 2–3 times, 3 = 4 or more]: 1.6 with 10 mg *v* 1.7 with zolpidem 20 mg; all comparisons reported as not significant). [30] The second RCT (60 inpatients in a neurology department, with moderate to severe insomnia) compared zolpidem 10 mg versus 20 mg over 7 days. [34] It found no difference between treatments for significant improvements in sleep latency, total sleep time, number of awakenings, and overall sleep quality compared with baseline. [34]

Harms:

Zolpidem versus placebo:
We found one systematic review, [17] one subsequent RCT, [33] and four additional RCTs, [28] [30] [36] [32] The systematic review [17] reported data for adverse effects associated with all sedative hypnotics, including benzodiazepines, versus placebo, and did not report adverse effects associated with zopiclone, zaleplon, and zolpidem use separately. For further information, see harms of Benzodiazepines, p 4 .

The first additional RCT [28] found that the most common treatment-emergent adverse events were headache, pain, somnolence, and rhinitis (63% with zolpidem 5 mg *v* 56% with placebo). [28] It found a significant increase in central nervous system adverse effects with zolpidem 5 mg compared with placebo (25% with zolpidem 5 mg *v* 14% with placebo; P less than 0.05). It also found a significant increase in rebound insomnia on the first night of discontinuing treatment in the zolpidem group (median sleep latency in minutes [change from baseline] : 60 [+1.75] with zolpidem *v* 44 [–23.79] with placebo; P less than 0.01; median subjective total sleep time in minutes [change from baseline]: 300.00 [–8.57] with zolpidem *v* 317.50 [+22.98] with placebo; P less than 0.001). [28] The second additional RCT found that the severity and frequency of adverse effects increased with dose: 2/23 [9%] with placebo (nightmares and coated mouth), 1/22 [5%] with 5 mg (perspiration), 1/18 [6%] with 10 mg (epigastralgia), and 2/22 [9%] with 20 mg (fall; morning somnolence), and 7/22 [32%] with 30 mg (nocturnal agitation, nocturnal fall, transient moderate disorientation on waking, and nocturnal incontinence). [30] In the third additional RCT, adverse effects included sleepiness/drowsiness, headache, tiredness, and nausea, and the frequency of mild and moderate events increased with dose (severe adverse events: 0/24 [0%] with placebo, 4/24 [17%] with 5 mg, 2/24 [8%] with zolpidem 10 mg; withdrawals from adverse events: 0/24 [0%] with placebo, 1/24 [4%] with 5 mg, and 2/24 [8%] with 10 mg). [36] In the fourth additional RCT, the most frequently reported treatment-emergent adverse effects were headache, myalgia, drowsiness, and nausea (52/82 [63%] zolpidem 5 mg *v* 47/84 [56%] with placebo). [32] The report of the subsequent RCT found that the most frequently reported treatment-emergent adverse effects of zolpidem were headache (14.1% with zolpidem CR *v* 10.4% with placebo), dizziness (8.1% with zolpidem CR *v* 2.8% with placebo), somnolence (6.1% with zolpidem CR *v* 4.7% with placebo), and nasopharyngitis (6.1% with zolpidem CR *v* 3.8% with placebo), but did not assess the significance of these differences. [33]

Zolpidem versus benzodiazepines:
The systematic review reported no significant difference between benzodiazepine receptor agonists (zolpidem, zoplicone and zaleplon) and benzodiazepines in the number of overall adverse effects (6 RCTs, 648 people: absolute data not reported; OR 1.11, 95% CI 0.59 to 2.07, P = 0.75), cognitive adverse effects (4 RCTs, 268 people: absolute data not reported; OR 1.12, 95% CI 0.16 to 7.76; P = 0.91) or psychomotor-type adverse effects (6 RCTs, 625 people: absolute data not reported; OR 1.48, 95% CI 0.75 to 2.93; P value not reported, reported as non-significant). The review did not report results for zolpidem separately. [17]

One of the three RCTs included in the review (221 inpatients aged 58–98 years) compared zolpidem 5 mg versus temazepam 15 mg versus triazolam 0.125 mg versus placebo over 4 weeks. It found that adverse events were more common in the triazolam group (adverse events: 11/70 [16%] with zolpidem 5 mg *v* 8/74 [11%] with zolpidem 10 mg *v* 16/77 [21%] with triazolam 15 mg; significance not reported). The most common adverse effect was nightmares. [37] The second additional RCT compared zolpidem 5 mg versus triazolam 0.125 mg versus temazepam 15 mg versus placebo over 4 weeks, the most frequently reported treatment-emergent adverse effects were headache, myalgia, drowsiness, and nausea (52/82 [63%] zolpidem 5 mg *v* 54/85 [64%] with triazolam *v* 56/84 [67%] with temazepam; significance not reported). [32]

Comment:

Few studies have been conducted to assess the long-term effects of hypnotic use. There is a lack of pragmatic studies where the effects of zolpidem on elderly people taking medication are assessed. Many elderly people take a range of drugs for various different conditions, and there is an urgent need for studies demonstrating the effectiveness and adverse effects of hypnotics when taken in combination with other drugs by this target population. Long-term studies are also needed to establish the safety and effectiveness of the prolonged use of zolpidem. Although, not recommended,

it is quite common for people to be prescribed hypnotics for a long period of time. In the RCTs included in this *BMJ Clinical Evidence* review, the treatment study period was only up to 4 weeks.

OPTION ZOPICLONE

Symptom improvement
Compared with placebo Esozopiclone (the active isomer of zopiclone) is more effective at 2 weeks than placebo at improving sleep latency, maintenance, duration, and quality and depth of sleep, in people with chronic, primary insomnia, although it does not reduce the number of awakenings (high-quality evidence).

Compared with benzodiazepines Zopiclone may be no more effective than benzodiazepines at improving sleep quality, total sleep times, sleep latency, and ease of falling asleep (low-quality evidence).

Adverse effects
Compared with benzodiazepines Zopiclone seems to have similar cognitive, psychomotor-type, and overall adverse effects compared with benzodiazepines (low-quality evidence).

Note
People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

For GRADE evaluation of interventions for insomnia in the elderly see table, p 16 .

Benefits:

Zopiclone versus placebo:
We found one systematic review (search date 2005), which identified two large RCTs. [38] The first RCT (published only as an abstract; 264 people aged 65−85 years with primary, chronic insomnia) compared eszopiclone 2 mg versus placebo for 2 weeks. [39] The second RCT (231 people aged 65−85 with primary, chronic insomnia) was a three-arm trial comparing eszopiclone 1 and 2 mg versus placebo for 2 weeks. [40] The results of this second RCT should be interpreted with caution, as it was an industry supported study in which all the researchers, with the exception of the primary author, were employed by, sat on the Advisory Board for, or had received research support from the maker of the drug; the authors of the RCT also disclosed that they wrote the paper with the assistance of that drug manufacturer.

Sleep latency:
The first RCT found that eszopiclone 2 mg significantly improved sleep onset compared with placebo at 2 weeks, although the size of this difference was not reported, making the clinical importance of this result unclear (absolute data not reported; P less than 0.05). [39] The second RCT found significant improvements from baseline in medium sleep latency with 2 mg but not 1 mg doses of eszoplicone compared with placebo at 2 weeks (median improvement from baseline in minutes: 10.3 with eszopiclone 2 mg *v* 5.3 with placebo; P = 0.0059; 10.9 with eszopiclone 1 mg *v* 5.3 with placebo; P greater than or equal to 0.05). [40]

Sleep maintenance and duration:
The first RCT found eszopiclone 2 mg significantly improved sleep maintenance and duration compared with placebo at 2 weeks, although the size of this difference was not reported, making the clinical importance of this result unclear (absolute data not reported; P less than 0.05). [39] The second RCT found that 2 mg eszopiclone significantly improved wake after sleep onset (WASO) and total sleep time (TST) from baseline compared with placebo at 2 weeks (median improvements from baseline, WASO in minutes: +30.6 with eszopiclone 2 mg *v* −5.7 with placebo; P = 0.0009; TST in minutes: 75.1 with eszopiclone 2 mg *v* 14.3 with placebo, P = 0.0002). However, it found that the difference in WASO or TST improvements from baseline between 1 mg doses of eszopiclone and placebo at 2 weeks was not significant (WASO in minutes: 24.0 with eszopiclone 1 mg *v* -5.7 with placebo; P greater than or equal to 0.05; TST in minutes: 51.7 with eszopiclone 1 mg *v* 14.3 with placebo; P greater than or equal to 0.05). [40]

Sleep quality and depth:
The first RCT found that eszopiclone 2 mg significantly improved sleep quality and depth compared with placebo at 2 weeks, although the size of this difference was not reported, making the clinical importance of this result unclear (absolute data not reported; P less than 0.05). [39] The second RCT reported that eszopiclone 2 mg significantly, if only slightly, improved both sleep quality scores (sleep quality measured on the 11-point Likert scale, median improvement from baseline: 1.7 with eszopiclone 2 mg *v* 0.9 with placebo; P = 0.0018) and sleep depth scores (sleep depth measured on the 11-point Likert scale, median improvement from baseline: 2.1 with eszopiclone 2 mg *v* 1.1 with placebo; P = 0.0064) compared with placebo at 2 weeks. [40] However, it found no significant differences between eszopiclone 1 mg and placebo at 2 weeks (Likert sleep quality score, median improvement from baseline: 1.4 with eszopiclone 1 mg *v* 0.9 with placebo; P greater than or equal

to 0.05; Likert sleep depth score median improvement from baseline: 1.6 with eszopiclone 1 mg *v* 1.1 with placebo; P greater than or equal to 0.05). [40]

Number of awakenings:
The systematic review reported that the two RCTs found no significant difference in the number of awakenings per night between either eszopiclone 1 mg or 2 mg compared with placebo at 2 weeks. [38]

Different doses of zoplicone versus each other:
We found no RCTs comparing different doses of zoplicone versus each other.

Zoplicone versus benzodiazepines:
We found one systematic review (search date 2003, 3 RCTs, 339 people), [17] which compared benzodiazepines (triazolam or nitrazepam) versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone). The review found no significant difference in subjective sleep quality between benzodiazepines and benzodiazepine receptor agonists (mean effect size: 0.04 95% CI −1.11 to 1.19; P value and absolute data not reported). The review did not analyse data for zopiclone separately. [17]

Harms:

Zopiclone versus placebo:
The first RCT reported no rebound insomnia after treatment withdrawal, and that the most common adverse effect of eszopliclone was unpleasant taste (further data not reported). [39] The second RCT reported a similar proportion of overall adverse effects between groups (43% with eszopliclone 2 mg *v* 40% with eszopliclone 1 mg *v* 40% with placebo; significance not reported). The most common adverse events were headache (15.4% with 2 mg *v* 15.3% with 1 mg *v* 15% with placebo; significance not reported) unpleasant taste (11% with eszopliclone 2 mg *v* 8% with eszopliclone 1 mg *v* 1% with placebo; significance not reported), somnolence (4% with 2 mg *v* 8% with 1 mg *v* 9% with placebo; significance not reported), and dyspepsia (1% with 2 mg *v* 6% with 1 mg *v* 3% with placebo; significance not reported). It also reported that there were no severe adverse effects, accidental falls, amnesia, or hallucinations related to treatment. [40]

Zoplicone versus benzodiazepines:
The systematic review reported no significant difference between benzodiazepine receptor agonists (zolpidem, zoplicone and zaleplon) and benzodiazepines in the number of overall adverse effects (6 RCTs, 648 people: absolute data not reported; OR 1.11, 95% CI 0.59 to 2.07, P = 0.75), cognitive adverse effects (4 RCTs, 268 people: absolute data not reported; OR 1.12, 95% CI 0.16 to 7.76; P = 0.91) or psychomotor-type adverse effects (6 RCTs, 625 people: absolute data not reported; OR 1.48, 95% CI 0.75 to 2.93; P value not reported, reported as non-significant). The review did not report results for zopiclone separately. [17]

Comment:

While the RCTs suggest promising results for short-term use of hypnotics for treatment of primary insomnia in elderly people, there is still a lack of evidence assessing the long-term effects of hypnotic use.

There is a lack of good-quality pragmatic studies where the effects of zopiclone on elderly people taking other medication are assessed. Many elderly people take a range of drugs for various different conditions, and there is an urgent need for studies demonstrating the effectiveness and adverse effects of hypnotics when taken in combination with other drugs by this target population. Long-term studies are also needed to establish the safety and effectiveness of the prolonged use of zolpidem. Although it is quite common for people to be prescribed hypnotics for a long period of time, it is not recommended. In the RCTs included in this *BMJ Clinical Evidence* review, the treatment study period was only up to 2 weeks.

GLOSSARY

Cognitive behavioural therapy The following cognitive behavioural therapies were considered in this review: stimulus control, sleep hygiene education, muscle relaxation, sleep restriction, and cognitive therapy. Stimulus control consists of measures to control the stimuli that affect sleep, such as establishing a standard wake up time, getting out of bed during long periods of wakefulness, and eliminating non-nocturnal sleep. Sleep hygiene education informs people about lifestyle modifications that may impair or enhance sleep, such as avoiding alcohol, heavy meals, and exercise before going to bed, and aims to alter expectations about normal sleep durations. Muscle relaxation involves sequential muscle tensing and relaxing. Sleep restriction reduces the time spent in bed to increase the proportion of time spent asleep while in bed. Cognitive therapy aims to identify and alter beliefs and expectations about sleep and sleep onset (e.g. beliefs about “necessary” sleep duration). Cognitive behavioural therapy may be undertaken on a one-to-one basis (individual therapy) or with a group of people (group therapy).
Likert scale A method of measuring attitudes that asks respondents to indicate their degree of agreement or disagreement with statements, according to a scoring system (usually 5 points). For example, subjects may be asked to rate their pain on a scale where none = 0, mild = 1, moderate = 2, severe = 3, and extreme = 4.

Pittsburgh Sleep Quality Index (PSQI) A validated 21 point scale (0 = best, 21 = worst) to measure subjective sleep quality. A score above 5 indicates insomnia.
Sleep onset latency The interval of time between "settling down" to go to sleep and the actual onset of sleep.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SUBSTANTIVE CHANGES

Benzodiazepines One systematic review on sedative hypnotics added. [17] Categorisation unchanged (Trade-off between benefits and harms).
Zopiclone Two systematic reviews added; [38] [17] categorisation changed from Unknown effectiveness to Trade-off between benefits and harms.
Zaleplon One systematic review on sedative hypnotics added. [17] Categorisation changed from Likely to be beneficial to Trade off between benefits and harms.
Zolpidem One systematic review on sedative hypnotics [17] and one subsequent RCT [33] added; categorisation changed from Likely to be beneficial to Trade off between benefits and harms.

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Insomnia in the elderly

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Disclaimer

TABLE 1 **RCTs comparing different doses of zaleplon versus placebo for the treatment of insomnia in elderly people.**

Ref	Participants	Intervention and comparison	Results
Median subjective sleep latency in minutes			
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 43.8 with zaleplon 2 mg *v* 45.0 with placebo; P = 0.654 30.0 with zaleplon 5 mg *v* 45.0 with placebo; P = 0.017 25.0 with zaleplon 10 mg *v* 45.0 with placebo; P less than 0.001
[28]	549 people with primary insomnia aged 65 years and over	Zaleplon 5 and 10 mg *v* placebo	At 7 days: Improvement from baseline in both zaleplon 5 mg and placebo group; data presented graphically; reported as NS At 14 days: –36.75 with zaleplon 5 mg *v* –11.79 with placebo; P less than 0.001 At 7 and 14 days: zaleplon 10 mg > placebo; data presented graphically; P less than 0.001
[29]	422 people aged 65 years or over with primary insomnia for 3 months or more	Zaleplon 5 and 10 mg *v* placebo	At 7 and 14 days: zaleplon 5 and 10 mg > placebo; data presented graphically; P less than 0.001
Median objective sleep latency in minutes			
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 27.0 with zaleplon 2 mg *v* 30.1 with placebo; P = 0.015 23.4 with zaleplon 5 mg *v* 30.1 with placebo; P less than 0.001 14.6 with zaleplon 10 mg *v* 30.1 with placebo; P less than 0.001
Median subjective total sleep time in minutes (improvement from baseline)			
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 330.0 with zaleplon 2 mg *v* 345.0 with placebo; P = 0.776 350.0 with zaleplon 5 mg *v* 345.0 with placebo; P = 0.140 367.5 with zaleplon 10 mg *v* 345.0 with placebo; P = 0.011
[28]	549 people with primary insomnia aged 65 years and over	Zaleplon 5 and 10 mg *v* placebo	At 7 and 14 days: Subjective improvement in both zaleplon 5 mg and placebo groups from baseline presented graphically; NS At 7 days: 345 (+28.86) with zaleplon 10 mg *v* 318 (+23.48) with placebo; P less than 0.05 At 14 days: Subjective improvement in both zaleplon 10 mg and placebo groups from baseline presented graphically; NS
[29]	422 people aged 65 years and over with primary insomnia for 3 months or more	Zaleplon 5 and 10 mg *v* placebo	At 7 days: 342.0 (+16.3) with zaleplon 5 mg *v* 346.1 (+24.1) with placebo; P less than 0.05 At 14 days: 351.7 (+26.0) with zaleplon 5 mg *v* 342.9 (+20.9) with placebo; NS At 7 days: 342.9 (+38.6) with zaleplon 10 mg *v* 346.1 (+24.1) with placebo; P less than 0.05 At 14 days: 351.4 (+47.1) with zaleplon 10 mg *v* 342.9 (+20.9) with placebo; NS
Median objective sleep duration in minutes			

Ref	Participants	Intervention and comparison	Results
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 364.6 with zaleplon 2 mg *v* 344.6 with placebo; P = 0.239 375.3 with zaleplon 5 mg *v* 344.6 with placebo; P = 0.003 365.0 with zaleplon 10 mg *v* 344.6 with placebo; P = 0.030
Median subjective sleep quality score (improvement from baseline)*			
[28]	549 people with primary insomnia aged 65 years or over	Zaleplon 5 and 10 mg *v* placebo	At 7 days: 3.83 (+0.46) with zaleplon 5 mg *v* 4.00 (+0.29) with placebo; NS At 14 days: 3.75 (+0.54) with zaleplon 5 mg *v* 4.00 (+0.29) with placebo; NS At 7 days: 3.67 (+0.46) with zaleplon 10 mg *v* 4.00 (+0.29) with placebo; P less than 0.05 At 14 days: 3.63 (+0.51) with zaleplon 10 mg *v* 4.00 (+0.29) with placebo; NS
[29]	422 people aged 65 or over with primary insomnia for 3 months or more	Zaleplon 5 and 10 mg *v* placebo	At 7 days: 3.80 (+0.40) with zaleplon 5 mg *v* 3.90 (+0.30) with placebo; P less than 0.01 At 14 days: 3.70 (+0.50) with zaleplon 5 mg *v* 3.80 (+0.40) with placebo; P less than 0.05 At 7 days: 3.80 (+0.50) with zaleplon 10 mg *v* 3.90 (+0.30) with placebo; P less than 0.01 At 14 days: 3.70 (+0.60) with zaleplon 10 mg *v* 3.80 (+0.40) with placebo; P less than 0.05
Median subjective number of awakenings			
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 3.0 with zaleplon 2 mg *v* 2.8 with placebo; P = 0.671 3.0 with zaleplon 5 mg *v* 2.8 with placebo; P = 0.906 2.5 with zaleplon 10 mg *v* 2.8 with placebo; P = 0.045
[28]	549 people with primary insomnia aged 65 years or over	Zaleplon 5 and 10 mg *v* placebo	At 7 days: 1.8 with zaleplon 5 mg *v* 2.0 with placebo; NS At 14 days: 1.9 with zaleplon 5 mg *v* 1.9 with placebo; NS At 7 days: 1.8 with zaleplon 10 mg *v* 2.0 with placebo; NS At 14 days: 1.7 with zaleplon 10 mg *v* 1.9 with placebo; NS
[29]	422 people aged 65 years or over with primary insomnia for 3 months or more	Zaleplon 5 and 10 mg *v* placebo	At 7 days: 2.0 with zaleplon 5 mg *v* 2.0 with placebo; NS At 14 days: 2.0 with zaleplon 5 mg *v* 2.0 with placebo; P less than 0.05 At 7 days: 2.0 with zaleplon 10 mg *v* 2.0 with placebo; NS At 14 days: 2.0 with zaleplon 10 mg *v* 1.0 with placebo; NS
Median objective number of awakenings			
[27]	48 people with insomnia, aged 60–80 years	Zaleplon 2, 5, and 10 mg *v* placebo	At 2 days: 21.0 with zaleplon 2 mg *v* 19.5 with placebo; P = 0.872 19.5 with zaleplon 5 mg *v* 19.5 with placebo; P = 0.623 18.8 with zaleplon 10 mg *v* 19.5 with placebo; P = 0.969

Ref	Participants	Intervention and comparison	Results

NS, not significant; SL, median sleep latency; TST, median total sleep time; >, favours treatment; <, favours placebo. * Scale: 1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor; 6 = very poor; 7 = extremely poor.

TABLE **GRADE evaluation of interventions for insomnia**

Important outcomes	**Sleep improvement, quality of life, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of non-drug treatments for insomnia in elderly people?									
1 (36) [11]	Symptom improvement	CBT *v* no treatment	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (43) [14]	Symptom improvement	Exercise *v* no treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of drug treatments for insomnia in elderly people?									
14 (830) [17]	Symptom improvement	Benzodiazepine *v* placebo	4	0	0	0	0	High	
3 (339) [17]	Symptom improvement	Benzodiazepine *v* benzodiazepine receptor agonists	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (1019) [27] [28] [29]	Symptom improvement	Zaleplon *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (815) [28] [29]	Adverse effects	Zaleplon *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (1667) [28] [30] [31] [32] [33]	Symptom improvement	Zolpidem *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
3 (1031) [17] [31] [32]	Symptom improvement	Zolpidem *v* benzodiazepines	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (144) [30] [34]	Symptom improvement	Different doses of zolpidem compared with each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
16 (1541) [17]	Adverse effects	Benzodiazepine receptor agonists *v* benzodiazepines	4	–2	0	0	0	Low	Quality point deducted for incomplete reporting of results, and for not reporting results separately for comparator
2 (495) [39] [40]	Symptom improvement	Zopiclone *v* placebo	4	–1	+1	0	0	High	Quality point deducted for incomplete reporting of results. Consistency point added for dose response

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.