ClinicalEvidence

Insomnia (primary) in older people

December 2010

Cathy Alessi and Michael V Vitiello

ABSTRACT

INTRODUCTION: Up to 40% of older 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 older people? What are the effects of drug treatments for insomnia in older people? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2010 (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 34 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: antidepressants, benzodiazepines, cognitive behavioural therapy (CBT), diphenhydramine, exercise programmes, timed exposure to bright light, zaleplon, zolpidem, and zopiclone.

QUESTIONS

INTERVENTIONS

Key points

- Up to 40% of older 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 medical and psychiatric illnesses, psychological factors, stress, daytime napping, and hyperarousal.

  Primary insomnia is a chronic and relapsing condition that may increase the risks of accidents.

  Primary insomnia is chronic insomnia without specific underlying medical, psychiatric, or other sleep disorders. This review only covers primary insomnia in people aged 60 years and over.
- Cognitive behavioural therapy (CBT) improves sleep compared with no treatment.
- Exercise may improve symptoms compared with no treatment, but evidence is weak.
- We don't know whether timed exposure to bright light can improve sleep quality compared with no treatment.
- Zaleplon, zolpidem, and zopiclone may improve sleep latency in older people, although long-term effects are unknown, and they may 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 decrease the number of awakenings, and it may cause rebound insomnia after discontinuation of treatment.
- Benzodiazepines may improve sleep outcomes compared with placebo or other treatments, but they may cause adverse effects.

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

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

- We don't know whether diphenhydramine improves sleep quality in older people.
- We don't know whether antidepressants improve sleep outcomes in older people with primary insomnia, as we found no RCTs.

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 resulting 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 older people. For this review we define older people as 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 to 79 years found that insomnia affected 35% of all adults during the course of 1 year, and that prevalence increased with age, with estimates ranging from 31% to 38% in people aged 18 to 64 years, to 45% in people aged 65 to 79 years. [4] One US prospective cohort study in people aged >65 years found that between 23% and 34% had insomnia, and between 7% and 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 ageing. [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

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

METHODS

Clinical Evidence search and appraisal December 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to December 2010, Embase 1980 to December 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. Drug studies had to be at least single blinded; non-drug studies (e.g., exercise) could be open. Only systematic reviews and RCTs examining the effects of treatments in people with chronic primary insomnia were included. Where we found two or more systematic reviews about a particular comparison, we 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 included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA

and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 32). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of non-drug treatments for primary insomnia in older people (aged 60 years and older)?**

OPTION **CBT**

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- CBT improves sleep in older people with primary insomnia.

Benefits and harms

CBT versus no treatment:

We found 5 systematic reviews (search dates 2001 [although the review included some studies up to 2005], [11] 2002, [12] [13] and 2004 [14] [15]). The reviews identified 11 RCTs in total. There was much crossover of reporting across the various reviews, with 9 of the 11 RCTs reported in at least two of the reviews. All the reviews reported that the included studies demonstrated some improvements in symptoms with CBT compared with no treatment, although two reviews cautioned that the treatment effect was modest. [12] [13] Only two reviews performed meta-analyses, [12] [15] and we report only the results of the most recent review here. [15] We also found two subsequent RCTs. [16] [17]

Symptom improvement

Compared with no treatment CBT may be more effective at improving sleep outcomes in older people with primary insomnia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep latency					
[15] Systematic review	Number of people in analysis not reported. Participants aged at least 55 years 7 RCTs in this analysis	**Mean time to fall asleep** with CBT with no treatment Absolute numbers not reported The meta-analysis included RCTs with poor follow-up and 1 RCT of "comorbid geriatric insomnia" See further information on studies	Mean effect size –0.51 95% CI –0.77 to –0.25 P <0.001	○○○	CBT
[16] RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years Subgroup analysis See further information on studies for more details of study population	**Change from baseline in sleep onset latency , 8 weeks** From 44.61 minutes to 19.85 minutes with CBT From 41.42 minutes to 30.50 minutes with control (sham biofeedback) CBT consisted of 8 weekly 1-hour sessions	P <0.05	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] RCT	35 people aged >60 years with DSM-IV criteria for primary insomnia	**Change in self-reported mean time to fall asleep , 4 weeks** From 38.32 minutes to 16.80 minutes with brief behavioural treatment for insomnia (BBTI) From 29.67 minutes to 26.85 minutes with information-only control See further information on studies for details of interventions	P <0.05	○○○	BBTI
Sleep efficiency					
[15] Systematic review	Number of people in analysis not reported. Participants aged at least 55 years 6 RCTs in this analysis	**Ratio of time asleep to time in bed** with CBT with no treatment Absolute numbers not reported The meta-analysis included RCTs with poor follow-up and 1 RCT of "comorbid geriatric insomnia" See further information on studies	Mean effect size 0.38 95% CI 0.12 to 0.65 P <0.005	○○○	CBT
[16] RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years Subgroup analysis See further information on studies for more details of study population	**Change from baseline in sleep efficiency , 8 weeks** From 72.87% to 86.80% with CBT From 72.36% to 79.32% with control (sham biofeedback) CBT consisted of 8 weekly 1-hour sessions	P <0.05	○○○	CBT
Wake after sleep onset (WASO)					
[15] Systematic review	Number of people in analysis not reported. Participants aged at least 55 years 7 RCTs in this analysis	**WASO** with CBT with no treatment Absolute numbers not reported The meta-analysis included RCTs with poor follow-up and 1 RCT of "comorbid geriatric insomnia"	Mean effect size –0.73 95% CI –0.99 to –0.48 P <0.001	○○○	CBT
[16] RCT	47 hypnotic-dependent people with chronic insomnia aged 50 to 85 years, mean age 64 years Subgroup analysis See further information on studies for more details of study population	**Change from baseline in WASO , 8 weeks** From 71.55 minutes to 26.92 minutes with CBT From 58.07 minutes to 37.56 minutes with control (sham biofeedback) CBT consisted of 8 weekly 1-hour sessions	P <0.05	○○○	CBT
[17] RCT	35 people aged >60 years with DSM-IV criteria for primary insomnia	**Change in self-reported WASO , 4 weeks** From 61.21 minutes to 27.72 minutes with brief behavioural treatment for insomnia (BBTI) From 47.91 minutes to 35.5 minutes with information-only control	P <0.05	○○○	BBTI

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for details of interventions			

Adverse effects

No data from the following reference on this outcome. [15] [16] [17]

Further information on studies

[15] The meta-analyses included RCTs of participants whose mean age was at least 55 years. The review included only RCTs in which at least one intervention was CBT "or some recognised variant, including omnibus CBT, progression relaxation, sleep restriction, stimulus control, imagery training, paradoxical intention, and biofeedback".

[16] The authors stated that the study population was a subset of participants recruited for a larger study of withdrawal from chronic hypnotic use. Prescription medication used specifically to improve sleep was allowed as long as use was sustained and frequent. Although the authors did not specifically use the term primary insomnia to describe the population, the inclusion criteria of chronic insomnia without medical conditions or symptoms that may have affected sleep satisfy the definition of primary insomnia.

[17] BBTI was delivered in a single individual 45-minute session with a 30-minute booster session 2 weeks later. Post-intervention assessments were completed after 4 weeks. The initial session included information about mechanisms that regulate sleep, factors that influence sleep, and behaviours that promote or interfere with sleep quality. The information-only control was "designed to emulate the type of behavioural instructions most primary care patients might receive". People in the information-only control arm received brochures and a follow-up telephone call 2 weeks later.

Comment: The specific components of CBT varied across studies, but generally included stimulus control, sleep restriction, and cognitive therapy, with or without other components. However, some studies involved individual components of behavioural therapy, or other combinations of behavioural therapies for insomnia.

OPTION EXERCISE PROGRAMMES

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- Exercise may improve sleep symptoms in older people with primary insomnia, but evidence is weak.

Benefits and harms

Exercise versus no treatment:

We found one systematic review of exercise therapy (search date 2002, 1 RCT; 43 people with primary insomnia, at least 80% of whom were aged 60 years or over), [18] and one subsequent RCT of Tai Chi Chih in people with "moderate sleep complaints". [19]

Symptom improvement

Moderate-intensity exercise compared with no treatment Moderate-intensity exercise (30–40 minutes of walking or low-impact aerobics 4 times a week, or Thai Chi Chih 3 times a week) may be more effective at improving sleep quality at 16 to 25 weeks in people with primary insomnia, but evidence is weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[18] Systematic review	43 people with primary insomnia, at least 80% aged 60 years and over Data from 1 RCT	**Pittsburgh Sleep Quality Index (PSQI) , 16 weeks** 5.4 with exercise therapy 8.8 with no treatment	Mean score improvement with exercise programme *v* no treatment: 3.4 95% CI 1.9 to 5.4 P <0.001	○○○	exercise therapy
[19] RCT	52 people aged 59 to 86 years Subgroup analysis The trial included people with moderate sleep complaints as well as people with no sleep complaints. We report the only subgroup analysis for the 52 people with PSQI global score at least 5 at baseline	**Proportion of people with PSQI of at least 5 at baseline who achieved PSQI <5 , 25 weeks** 19/30 (63%) with Tai Chi Chih 7/22 (32%) with health education control Prespecified subgroup analysis See further information on studies for details of treatments and secondary outcomes	P <0.05	○○○	Tai Chi Chih
[19] RCT	52 people aged 59 to 86 years Subgroup analysis The trial included people with moderate sleep complaints as well as people with no sleep complaints. We report the only subgroup analysis for the 52 people with PSQI global score at least 5 at baseline	**Change from baseline in PSQI global sleep quality score , 25 weeks** From 6.67 to 2.30 with Tai Chi Chih From 8.18 to 6.97 with health education control Prespecified subgroup analysis See further information on studies for details of treatments and secondary outcomes	P <0.001	○○○	Tai Chi Chih

Adverse effects

No data from the following reference on this outcome. [18] [19]

Further information on studies

[18] Moderate-intensity exercise consisted of 30 to 40 minutes of walking or low-impact aerobics 4 times a week.

[19] Active treatment consisted of a 3 times-weekly 16-week teaching phase. Follow-up was after a further 9 weeks. The health education control consisted of 16 didactic sessions, with two sessions specifically on sleep hygiene. The Tai Chi Chih group also reported improvements from baseline in sleep quality (P <0.05), sleep efficiency (P <0.05), sleep duration (P <0.01), and sleep disturbance (P <0.01), also measured by PSQI.

Comment: None.

OPTION TIMED EXPOSURE TO BRIGHT LIGHT

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- We found insufficient evidence on the effects of timed exposure to bright light from one small RCT.

Benefits and harms

Timed exposure to bright light versus no treatment:

We found one systematic review (search date 2001) [20] comparing the effects of timed bright light exposure versus other treatments or no treatment in people aged 60 years and over, which identified no RCTs. We found one small subsequent RCT. [21]

Symptom improvement

Compared with no treatment We don't know whether timed exposure to bright light is more effective at improving sleep symptoms in people aged 60 years and over with primary insomnia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total sleep time					
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in total sleep time, measured by actigraphy , 12 weeks** From 412.2 minutes to 384.0 minutes with evening bright light (4000 lux) From 408.0 minutes to 392.6 minutes with morning bright light (4000 lux) From 402.4 minutes to 383.3 minutes with placebo (evening dim light [65 lux]) From 369.8 minutes to 365.2 minutes with placebo (morning dim light [65 lux]) This analysis based on 50 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in total sleep time, measured by polysomnography , 12 weeks** From 361.3 minutes to 353.3 minutes with evening bright light (4000 lux) From 336.3 minutes to 345.5 minutes with morning bright light (4000 lux) From 364.3 minutes to 358.9 minutes with placebo (evening dim light [65 lux]) From 320.7 minutes to 320.0 minutes with placebo (morning dim light [65 lux]) This analysis based on 49 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in total sleep time, subjective measure , 12 weeks** From 340.9 minutes to 380.3 minutes with evening bright light (4000 lux)	Between-group P values not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		From 339.2 minutes to 367.5 minutes with morning bright light (4000 lux) From 345.8 minutes to 378.9 minutes with placebo (evening dim light [65 lux]) From 320.6 minutes to 291.1 minutes with placebo (morning dim light [65 lux]) This analysis based on 51 people. See further information on studies			
Wake after sleep onset (WASO)					
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in WASO, measured by actigraphy , 12 weeks** From 57.2 minutes to 52.1 minutes with evening bright light (4000 lux) From 66.2 minutes to 55.7 minutes with morning bright light (4000 lux) From 54.7 minutes to 65.6 minutes with placebo (evening dim light [65 lux]) From 61.3 minutes to 63.0 minutes with placebo (morning dim light [65 lux]) This analysis based on 50 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in WASO, measured by polysomnography , 12 weeks** From 77.8 minutes to 64.5 minutes with evening bright light (4000 lux) From 88.8 minutes to 86.4 minutes with morning bright light (4000 lux) From 73.4 minutes to 64.7 minutes with placebo (evening dim light [65 lux]) From 82.9 minutes to 68.2 minutes with placebo (morning dim light [65 lux]) This analysis based on 49 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in WASO, subjective measure , 12 weeks** From 63.8 minutes to 30.8 minutes with evening bright light (4000 lux) From 74.0 minutes to 48.9 minutes with morning bright light (4000 lux) From 65.2 minutes to 55.6 minutes with placebo (evening dim light [65 lux])	Between-group P values not reported Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		From 69.5 minutes to 63.3 minutes with placebo (morning dim light [65 lux]) This analysis based on 51 people. See further information on studies			
Sleep efficiency					
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in sleep efficiency %, measured by actigraphy , 12 weeks** From 80.1% to 79.8% with evening bright light (4000 lux) From 80.6% to 82.4% with morning bright light (4000 lux) From 82.3% to 77.8% with placebo (evening dim light [65 lux]) From 78.9% to 76.7% with placebo (morning dim light [65 lux]) This analysis based on 50 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in sleep efficiency %, measured by polysomnography , 12 weeks** From 76.8% to 78.2% with evening bright light (4000 lux) From 72.5% to 74.3% with morning bright light (4000 lux) From 75.9% to 76.5% with placebo (evening dim light [65 lux]) From 72.2% to 74.1% with placebo (morning dim light [65 lux]) This analysis based on 49 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant
[21] RCT **4-armed trial**	61 adults meeting primary insomnia criteria, mean age 63.6 years, range 54 to 78 years	**Change from baseline in sleep efficiency %, subjective measure , 12 weeks** From 67.4% to 79.5% with evening bright light (4000 lux) From 66.8% to 77.0% with morning bright light (4000 lux) From 71.6% to 76.9% with placebo (evening dim light [65 lux]) From 69.4% to 73.1% with placebo (morning dim light [65 lux]) This analysis based on 51 people. See further information on studies	Between-group P values not reported Reported as not significant	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [21]

Further information on studies

[21] The RCT randomised on a 2:1 basis (with more people in the bright-light group). The two dim-light (placebo) groups contained fewer than 10 people in each group. All participants received sleep hygiene instructions. Light exposure was for 45 minutes daily for 12 weeks. The RCT reported that adherence to treatment at 12 weeks in the various groups was 83% (bright morning light), 77% (bright evening light), 69% (dim morning light), and 61% (dim evening light).

Comment: Bright light has been found to assist with circadian rhythm abnormalities in other populations. [22]

QUESTION What are the effects of drug treatments for primary insomnia in older people (aged 60 years and older)?

OPTION DIPHENHYDRAMINE

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- We found insufficient evidence on the effects of diphenhydramine from one small RCT.

Benefits and harms

Diphenhydramine versus placebo:

We found one small crossover RCT looking at the effects of diphenhydramine on insomnia in older people. [23]

Symptom improvement

Compared with placebo We don't know whether diphenhydramine is more effective at improving sleep outcomes, in older people with primary insomnia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality and time					
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed temazepam 15 mg	**Subjective sleep quality (scale 1–5) , 14 days** 3.0 with diphenhydramine 50 mg for 14 nights 2.9 with placebo	P value not reported Reported as not significant	⟷	Not significant
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed temazepam 15 mg	**Subjective sleep onset latency , 14 days** 34.2 minutes with diphenhydramine 50 mg for 14 nights 36.8 minutes with placebo	P value not reported Reported as not significant	⟷	Not significant
[23] RCT	25 people aged 70 to 89 years with primary insomnia; 20 people complet-	**Number of awakenings (subjective measure) , 14 days** 1.7 with diphenhydramine 50 mg for 14 nights	P <0.05	○○○	diphenhydramine 50 mg

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design **3-armed trial**	ed at least 1 treatment arm The remaining arm assessed temazepam 15 mg	2.0 with placebo			
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed temazepam 15 mg	**Subjective total sleep time , 14 days** 6.6 hours with diphenhydramine 50 mg for 14 nights 6.3 hours with placebo	P value not reported Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed temazepam 15 mg	**Total number of adverse events , 14 days** 90 with diphenhydramine 50 mg for 14 nights 90 with placebo The most commonly reported adverse effects in both groups were fatigue, drowsiness, dry mouth, and joint stiffness/pain 2 people withdrew from the diphenhydramine arm owing to oversedation and nausea	P value not reported Reported as not significant	⟷	Not significant

Further information on studies

Comment: Although the RCT [23] reported above suggests that diphenhydramine may decrease the number of night-time awakenings, this finding is probably of limited clinical importance.

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- Benzodiazepines may improve sleep outcomes compared with placebo or other treatments, but they may cause adverse effects.
- Benzodiazepines can cause impairment of memory, cognitive function, and psychological function, and rebound insomnia. They may increase the risks of accidents, falls, and hip fractures, cognitive impairment, and car accidents.
- People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

Benefits and harms

Benzodiazepines versus placebo:

We found one systematic review (search date 2003, 14 RCTs, 830 people aged at least 60 years with insomnia) comparing any benzodiazepine versus placebo for at least 5 nights, [24] as well as one additional RCT [23] and one subsequent RCT. [25]

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 in older people with primary insomnia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[24] Systematic review	277 people aged 60 years or over with insomnia 7 RCTs in this analysis	**Mean subjective sleep-quality score (measured on a 5-point scale) , at least 5 nights** 3.1 with benzodiazepines 2.7 with placebo	Mean effect size 0.37 95% CI 0.01 to 0.73 P = 0.04	○○○	benzodiazepines
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed diphenhydramine 50 mg	**Subjective sleep quality (scale 1–5) , 14 days** 3.3 with temazepam 15 mg for 14 nights 2.9 with placebo	P <0.05	○○○	temazepam
Total sleep time					
[24] Systematic review	524 people aged 60 years or over with insomnia 7 RCTs in this analysis	**Total sleep time , at least 5 nights** with benzodiazepines with placebo Absolute numbers not reported	Mean difference in increased total sleep time: 34.2 minutes 95% CI 16.2 minutes to 52.8 minutes P <0.01	○○○	benzodiazepines
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed diphenhydramine 50 mg	**Subjective total sleep time , 14 days** 6.9 hours with temazepam 15 mg for 14 nights 6.3 hours with placebo	P <0.05	○○○	temazepam
[25] RCT **4-armed trial**	78 people aged at least 55 years (mean age 65 years) with primary insomnia 40 people in this analysis The remaining arms assessed CBT and CBT plus temazepam	**Change from baseline in total sleep time , 8 weeks** From 340.21 minutes to 383.90 minutes with temazepam (variable dose) From 331.04 minutes to 350.70 minutes with placebo See further information on studies regarding dosage and follow-up	P <0.01	○○○	temazepam
Number of awakenings					
[24] Systematic review	296 people aged 60 years or over with insomnia 6 RCTs in this analysis	**Number of awakenings , at least 5 nights** with benzodiazepines with placebo	Mean difference in reduced number of awakenings: –0.60 95% CI –0.41 to –0.78 P <0.0001	○○○	benzodiazepines

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed diphenhydramine 50 mg	**Number of awakenings (subjective measure) , 14 days** 1.5 with temazepam 15 mg for 14 nights 2.0 with placebo	P <0.05	○○○	temazepam
Sleep onset latency					
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed diphenhydramine 50 mg	**Subjective sleep onset latency , 14 days** 25.4 minutes with temazepam 15 mg for 14 nights 36.8 minutes with placebo	P <0.05	○○○	temazepam
Sleep efficiency					
[25] RCT **4-armed trial**	78 people aged at least 55 years (mean age 65 years) with primary insomnia The remaining arms assessed CBT and CBT plus temazepam	**Change from baseline in sleep efficiency , 8 weeks** From 72.37% to 82.68% with temazepam (variable dose) From 69.11% to 73.39% with placebo 40 people in this analysis See further information on studies regarding dosage and follow-up	P <0.01	○○○	temazepam

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] Systematic review	830 people aged 60 years or over with insomnia	**Adverse effects** with any sedative Drowsiness or fatigue, headache, nightmares, and nausea or GI disturbances were the most common adverse effects associated with sedative use For full details see further information on studies below	Significance not assessed		
[24] Systematic review	712 people aged 60 years or over with insomnia 10 RCTs in this analysis	**Cognitive adverse effects** with benzodiazepines, zopiclone, zaleplon, or zolpidem with placebo Absolute results not reported	OR 4.78 95% CI 1.47 to 15.47 P <0.01	●●○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] Systematic review	1016 people aged 60 years or over with insomnia 13 RCTs in this analysis	**Psychomotor adverse effects** with benzodiazepines, zopiclone, zaleplon, or zolpidem with placebo Absolute results not reported Adverse effects included 59 psychomotor adverse effects, of which 7 were serious events (6 falls, 3 resulting in broken bones, and 1 motor crash)	OR 2.25 95% CI 0.93 to 5.41 P = 0.07	⟷	Not significant
[24] Systematic review	829 people aged 60 years or over with insomnia 7 RCTs in this analysis	**Subjective morning or daytime fatigue** with benzodiazepines, zopiclone, zaleplon, or zolpidem with placebo Absolute results not reported	OR 3.82 95% CI 1.88 to 7.80 P <0.001	●●○	placebo
[24] Systematic review	829 people aged 60 years or over with insomnia 7 RCTs in this analysis	**Impairment on performance tasks the morning after treatment** with benzodiazepines, zopiclone, zaleplon, or zolpidem with placebo Absolute results not reported	Mean difference: 0.14 95% CI 0.11 to 0.16 Reported as significant P value not reported	○○○	placebo
[23] RCT **Crossover design** **3-armed trial**	25 people aged 70 to 89 years with primary insomnia; 20 people completed at least 1 treatment arm The remaining arm assessed diphenhydramine 50 mg	**Total number of adverse events , 14 days** 90 with temazepam 15 mg for 14 nights 90 with placebo The most commonly reported adverse effects in both groups were fatigue, drowsiness, dry mouth, light-headedness, headaches, and joint stiffness 1 person withdrew from the temazepam group after dizziness that resulted in a fall; another withdrew owing to morning dizziness, and another owing to GI reflux Morning-after psychomotor impairment (using the digit symbol substitution test and the manual tracking task) was not different between groups	P value not reported Reported as not significant	⟷	Not significant

No data from the following reference on this outcome. [25]

Benzodiazepines versus zolpidem:

See option on zolpidem, p 20 .

Further information on studies

[24] The review found insufficient data to analyse sleep-onset latency or subjective ease of getting to sleep. **Adverse effects:** The review 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. The review found that drowsiness or fatigue, headache, nightmares, and nausea or GI disturbances were the most common adverse effects associated with sedative use in the included studies, but it did not perform a meta-analysis owing to heterogeneity (only 1 RCT reported on symptom severity). 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.

[25] Initial dose was 7.5 mg a night, gradually increased based on treatment response and adverse effects, up to 30 mg a night. Participants were instructed to use the medication at least 2 to 3 nights a week, and could take it nightly if they chose. Bearing in mind the potential variation in dosage among participants, results should be interpreted with caution. The RCT also noted that the improvements in symptoms with temazepam were not sustained at 24-month follow-up.

Comment:

Clinical guide:
We found no good evidence about the long-term effects of benzodiazepines for insomnia in older people. There is little evidence about beneficial or adverse effects of benzodiazepines used for >1 month. Few RCTs include enough people to detect relatively infrequent but important adverse 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. [26] One study examining the toxicity of flurazepam in older 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. [27] We found few studies measuring the effect of treatments on daytime sleepiness, which is an important outcome for older people.

OPTION ZALEPLON

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- Zaleplon may improve sleep latency in older people, although long-term effects are unknown, and it is likely to cause adverse effects.
- Zaleplon may also increase sleep duration and improve sleep quality compared with placebo in the short term.
- People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.
- Zaleplon has similar rates of treatment-emergent adverse effects, but increases rebound insomnia after discontinuation of treatment at 2 weeks, compared with placebo.

Benefits and harms

Zaleplon versus placebo:

We found one systematic review (search date 2000, 2 RCTs, 971 people with primary insomnia, at least 80% of whom were aged 60 years or older) [28] and one subsequent RCT. [29] The review did not perform a meta-analysis so we report each trial separately.

Symptom improvement

Compared with placebo Zaleplon may be more effective at improving sleep latency and total sleep time in people with primary insomnia, but we don't know about number of awakenings (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep latency					
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median subjective sleep latency , 2 days** 43.8 minutes with zaleplon 2 mg 30.0 minutes with zaleplon 5 mg 25.0 minutes with zaleplon 10 mg	Reported as significant for zaleplon 5 mg and 10 mg only P = 0.654 for zaleplon 2 mg *v* placebo P = 0.017 for zaleplon 5 mg *v* placebo	○○○	zaleplon (5 mg and 10 mg only)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		45.0 minutes with placebo	P <0.001 for zaleplon 10 mg *v* placebo		
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median objective sleep latency , 2 days** 27.0 minutes with zaleplon 2 mg 23.4 minutes with zaleplon 5 mg 14.6 minutes with zaleplon 10 mg 30.1 minutes with placebo	P = 0.015 for zaleplon 2 mg *v* placebo P <0.001 for zaleplon 5 mg *v* placebo P <0.001 for zaleplon 10 mg *v* placebo	○○○	zaleplon (2 mg, 5 mg, and 10 mg)
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective sleep latency in minutes , 7 days** with zaleplon 5 mg with zaleplon 10 mg with placebo Absolute results reported graphically	Reported that zaleplon 10 mg significantly reduced sleep latency compared with placebo; P <0.001 Reported no significant difference for zaleplon 5 mg *v* placebo	○○○	zaleplon (10 mg only)
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective sleep latency , 14 days** –36.75 minutes with zaleplon 5 mg Reported graphically with zaleplon 10 mg –11.79 minutes with placebo Absolute results reported graphically	P <0.001 for zaleplon 5 mg or 10 mg *v* placebo	○○○	zaleplon (5 mg and 10 mg)
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective sleep latency in minutes , 7 and 14 days** with zaleplon 5 mg with zaleplon 10 mg with placebo Absolute numbers not reported	P <0.001 for zaleplon 5 mg and 10 mg *v* placebo at either time frame	○○○	zaleplon (5 mg and 10 mg)
Total sleep time					
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median subjective total sleep time , 2 days** 330.0 minutes with zaleplon 2 mg 330.0 minutes with zaleplon 5 mg 367.5 minutes with zaleplon 10 mg 345.0 minutes with placebo	P = 0.776 for zaleplon 2 mg *v* placebo P = 0.140 for zaleplon 5 mg *v* placebo P = 0.140 for zaleplon 10 mg *v* placebo	⟷	Not significant
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median objective sleep duration , 2 days** 364.6 minutes with zaleplon 2 mg 375.3 minutes with zaleplon 5 mg 365.0 minutes with zaleplon 10 mg 344.6 minutes with placebo	P = 0.239 for zaleplon 2 mg *v* placebo P = 0.003 for zaleplon 5 mg *v* placebo P = 0.030 for zaleplon 10 mg *v* placebo	○○○	zaleplon (5 mg and 10 mg only)
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective total sleep time (improvement from baseline) , 7 days** Result reported graphically with zaleplon 5 mg	P <0.05 for zaleplon 10 mg *v* placebo No significant difference for zaleplon 5 mg *v* placebo	○○○	zaleplon (10 mg only)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		345 (+28.86) minutes with zaleplon 10 mg 318 (+23.48) minutes with placebo			
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective total sleep time (improvement from baseline) , 14 days** with zaleplon 5 mg with zaleplon 10 mg with placebo Absolute results reported graphically	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective total sleep time (improvement from baseline) , 7 days** 342.0 (+16.3) minutes with zaleplon 5 mg 342.9 (+38.6) minutes with zaleplon 10 mg 346.1 (+24.1) minutes with placebo	P <0.05 for both zaleplon 5 mg and 10 mg *v* placebo	○○○	zaleplon (5 mg or 10 mg)
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective total sleep time (improvement from baseline) , 7 days** 351.7 (+26.0) minutes with zaleplon 5 mg 351.4 (+47.1) minutes with zaleplon 10 mg 346.1 (+24.1) minutes with placebo	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant
Subjective sleep quality					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective sleep-quality score, from 1 = excellent to 7 = poor (improvement from baseline) , 7 days** 3.83 (+0.46) with zaleplon 5 mg 3.67 (+0.46) with zaleplon 10 mg 4.00 (+0.29) with placebo	P <0.05 for zaleplon 10 mg *v* placebo No significant difference for zaleplon 5 mg *v* placebo	○○○	zaleplon (10 mg only)
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective sleep-quality score, from 1 = excellent to 7 = poor (improvement from baseline) , 14 days** 3.75 (+0.54) with zaleplon 5 mg 3.63 (+0.51) with zaleplon 10 mg 4.00 (+0.29) with placebo	Reported no significant difference for zaleplon 5 mg *v* placebo	⟷	Not significant
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective sleep-quality score, from 1 = excellent to 7 = poor (improvement from baseline) , 7 days** 3.80 (+0.40) with zaleplon 5 mg 3.80 (+0.50) with zaleplon 10 mg 3.90 (+0.30) with placebo	P <0.01 for zaleplon 10 mg and 5 mg *v* placebo	○○○	zaleplon (5 mg and 10 mg)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective sleep-quality score, from 1 = excellent to 7 = poor (improvement from baseline) , 14 days** 3.70 (+0.50) with zaleplon 5 mg 3.80 (+0.50) with zaleplon 10 mg 3.80 (+0.40) with placebo	P <0.05 for zaleplon 10 mg and 5 mg *v* placebo	○○○	zaleplon (5 mg and 10 mg)
Number of awakenings					
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median subjective number of awakenings , 2 days** 3.0 with zaleplon 2 mg 3.0 with zaleplon 5 mg 2.5 with zaleplon 10 mg 2.8 with placebo	P = 0.671 for zaleplon 2 mg *v* placebo P = 0.906 for zaleplon 5 mg *v* placebo P = 0.045 for zaleplon 10 mg *v* placebo	○○○	zaleplon (10 mg only)
[29] RCT **4-armed trial**	48 people with insomnia aged 60 to 80 years	**Median objective number of awakenings , 2 days** 21.0 with zaleplon 2 mg 19.5 with zaleplon 5 mg 18.8 with zaleplon 10 mg 19.5 with placebo	Not significant for each dose of zaleplon *v* placebo P = 0.872 for zaleplon 2 mg *v* placebo P = 0.623 for zaleplon 5 mg *v* placebo P = 0.969 for zaleplon 10 mg *v* placebo	⟷	Not significant
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective number of awakenings , 7 days** 1.8 with zaleplon 5 mg 1.8 with zaleplon 10 mg 1.8 with placebo	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Median subjective number of awakenings , 7 days** 1.9 with zaleplon 5 mg 1.7 with zaleplon 10 mg 1.9 with placebo	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective number of awakenings , 7 days** 2.0 with zaleplon 5 mg 2.0 with zaleplon 10 mg 2.0 with placebo	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Median subjective number of awakenings , 14 days** 2.0 with zaleplon 5 mg 1.0 with zaleplon 10 mg 2.0 with placebo	No significant difference for either zaleplon 5 mg or 10 mg *v* placebo	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall adverse effects					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arm evaluated zolpidem	**Treatment-emergent adverse events** 56% with zaleplon 5 mg 59% with zaleplon 10 mg 56% with placebo The most common of these were headache, pain, somnolence, and rhinitis			
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more	**Treatment-emergent adverse effects** 68 (48%) with zaleplon 5 mg 59 (50%) with zaleplon 10 mg 74 (51%) with placebo			
Rebound insomnia					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years and over The remaining arms evaluated zaleplon 5 mg and zolpidem	**Median subjective total sleep time (change from baseline) , first night after discontinuing medication** 300.00 (–8.57) minutes with zaleplon 10 mg 317.50 (+22.98) minutes with placebo	P <0.05 for zaleplon 10 mg *v* placebo	○○○	placebo
[31] RCT **3-armed trial**	422 people aged 65 years or over with primary insomnia for 3 months or more The remaining arm evaluated zaleplon 5 mg	**Proportion of people with rebound insomnia** 17/136 (13%) with zaleplon 10 mg 6/130 (5%) with placebo	P = 0.03 for zaleplon 10 mg *v* placebo	○○○	placebo

No data from the following reference on this outcome. [29]

Zaleplon versus benzodiazepines:

See option on zolpidem, p 20 .

Further information on studies

[29] The RCT used polysomnographic (PSG) screening records and post-sleep questionnaires to assess outcomes.

Comment: **Clinical guide:**

There is a lack of pragmatic studies where the effects of zaleplon on older people taking other medication are assessed. Many older 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

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- Zolpidem may improve sleep latency in older people, although long-term effects are unknown, and it is likely to cause adverse effects.
- Zolpidem may also increase sleep duration and improve sleep quality compared with placebo in the short term.
- People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

Benefits and harms

Zolpidem versus placebo :

We found one systematic review (search date 2003), [24] and three additional RCTs. [30] [32] [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. [24] We also found one additional RCT that gave information on adverse effects of zolpidem in healthy older volunteers. [34]

Symptom improvement

Compared with placebo We don't know whether zolpidem 10 mg and 20 mg differ in effectiveness at improving sleep outcomes in older people with primary insomnia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective sleep-quality score, from 1 = excellent to 7 = poor (reduction from baseline) , 7 days** 3.50 (−0.67) with zolpidem 5 mg 4.00 (−0.29) with placebo Absolute results reported graphically	P <0.001	○○○	zolpidem
[32] RCT **6-armed trial**	221 inpatients aged 61 to 94 years with chronic insomnia The remaining arms evaluated triazolam and zolpidem 5 mg	**Sleep quality , 1 day** with zolpidem 10 mg with zolpidem 20 mg with zolpidem 30 mg with placebo Absolute results reported graphically Results for zolpidem 5 mg *v* placebo not clear	Reported as not significant	⟷	Not significant
Total sleep time					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective total sleep time , 7 days** 360 minutes with zolpidem 5 mg 318 minutes with placebo Absolute results reported graphically	P <0.001	○○○	zolpidem
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older	**Median subjective total sleep time , 14 days** 360 minutes with zolpidem 5 mg 326 minutes with placebo	P <0.01	○○○	zolpidem

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arms evaluated zaleplon 5 mg and 10 mg	Absolute results reported graphically			
[32] RCT **6-armed trial**	221 inpatients aged 61 to 94 years with chronic insomnia The remaining arms evaluated triazolam and zolpidem 5 mg	**Subjective total sleep time in hours , 1 day** 7.6 hours with zolpidem 10 mg 7.6 hours with zolpidem 20 mg 7.7 hours with zolpidem 30 mg 6.7 hours with placebo Results for zolpidem 5 mg *v* placebo not clear	P <0.05 for all comparisons	○○○	zolpidem
Number of awakenings					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective number of awakenings , 7 days** 1.7 with zolpidem 5 mg 2.0 with placebo Absolute results reported graphically	P <0.01	○○○	zolpidem
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective number of awakenings , 14 days** 1.6 with zolpidem 5 mg 1.9 with placebo Absolute results reported graphically	P <0.05	○○○	zolpidem
[32] RCT **6-armed trial**	221 inpatients aged 61 to 94 years with chronic insomnia The remaining arms evaluated triazolam, zolpidem 5 mg, and zolpidem 10 mg	**Number of awakenings , 1 day** 1.0 with zolpidem 20 mg 1.1 with zolpidem 30 mg 2.1 with placebo Results for zolpidem 5 mg *v* placebo not clear	P <0.05 for all comparisons	○○○	zolpidem
Sleep latency					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective sleep latency , 7 and 14 days** with zolpidem 5 mg with placebo Absolute results reported graphically	P <0.05 at 7 days P <0.01 at 14 days	○○○	zolpidem
[32] RCT **6-armed trial**	111 inpatients aged 61 to 94 years with chronic insomnia The remaining arms evaluated triazolam and zolpidem 5 mg	**Subjective sleep-latency score (1 = 15 minutes, 2 = 15–30 minutes, 3 = 30–60 minutes, and 4 = over 60 minutes) , 1 day** 2.1 with zolpidem 10 mg 1.8 with zolpidem 20 mg 1.9 with zolpidem 30 mg 3.0 with placebo Results for zolpidem 5 mg *v* placebo unclear	P <0.05 for zolpidem 10 mg P <0.01 for zolpidem 20 mg P <0.05 for zolpidem 30 mg	○○○	zolpidem

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wake after sleep onset (WASO)					
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Mean reduction in WASO in minutes:seconds by polysomnography , nights 1/2** 67:16 to 35:23 with zolpidem extended release (XR) 6.25 mg daily for 3 weeks 70:15 to 62:31 with placebo	P <0.0001	○○○	zolpidem
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Mean reduction in WASO in minutes:seconds by polysomnography , nights 15/16** 67:16 to 49:43 with zolpidem XR 6.25 mg daily for 3 weeks 70:15 to 62:45 with placebo	P <0.0042	○○○	zolpidem
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Mean reduction in patient-reported WASO in minutes:seconds , 1 week** 27:03 with zolpidem XR 6.25 mg daily for 3 weeks 9:46 with placebo	P = 0.005	○○○	zolpidem
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Mean reduction in patient-reported WASO in minutes:seconds , 2 weeks** 26:46 with zolpidem XR 6.25 mg daily for 3 weeks 10:08 with placebo	P = 0.02	○○○	zolpidem
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Mean reduction in patient-reported WASO in minutes:seconds , 3 weeks** 29:04 with zolpidem XR 6.25 mg daily for 3 weeks 14:15 with placebo	P = 0.02	○○○	zolpidem

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall adverse effects					
[24] Systematic review	830 people aged 60 years or over with insomnia	**Adverse effects** with any sedative hypnotic The review 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 option on benzodiazepines, p 11			
[30] RCT	549 people with primary insomnia	**Adverse effects** 63% with zolpidem			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	56% with placebo Absolute results reported graphically The most common treatment-emergent adverse events were headache, pain, somnolence, and rhinitis			
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Central nervous system adverse effects** 25% with zolpidem 14% with placebo Absolute results reported graphically	P <0.05	○○○	placebo
[32] RCT **6-armed trial**	221 inpatients aged 61 to 94 years with chronic insomnia The remaining arm evaluated triazolam	**Adverse effects** 1/22 (5%) with zolpidem 5 mg 1/18 (6%) with zolpidem 10 mg 2/22 (9%) with zolpidem 20 mg 7/22 (32%) with zolpidem 30 mg 2/23 (9%) with placebo Adverse effects included: nightmares and coated mouth with placebo; perspiration with zolpidem 5 mg; epigastralgia with zolpidem 10 mg; fall and morning somnolence with zolpidem 20 mg; nocturnal agitation, nocturnal fall, transient moderate disorientation on waking, and nocturnal incontinence with zolpidem 30 mg			
[34] RCT **Crossover design**	24 older volunteers	**Severe adverse events** 0/24 (0%) with placebo 4/24 (17%) with zolpidem 5 mg 2/24 (8%) with zolpidem 10 mg	Significance not assessed		
[34] RCT **Crossover design**	24 older volunteers	**Withdrawals from adverse events** 0/24 (0%) with placebo 1/24 (4%) with zolpidem 5 mg 2/24 (8%) with zolpidem 10 mg	Significance not assessed		
[33] RCT	205 people aged 65 to 87 years, mean age 70.2 years, with primary insomnia	**Proportion of people with adverse effects , 3 weeks** 38% with zolpidem XR 6.25 mg daily for 3 weeks 40% with placebo Absolute numbers not reported The most frequently reported adverse effects were headache (14% with zolpidem *v* 11% with placebo), dizziness (8% with zolpidem *v* 3% with placebo), somnolence (6% with zolpidem *v* 5% with placebo), and nasopharyngitis (6% with zolpidem *v* 4% with placebo)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rebound insomnia					
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median sleep latency (change from baseline)** 60 (+1.75) minutes with zolpidem 44 (–23.79) minutes with placebo Absolute results reported graphically	P <0.01	○○○	placebo
[30] RCT **4-armed trial**	549 people with primary insomnia aged 65 years or older The remaining arms evaluated zaleplon 5 mg and 10 mg	**Median subjective total sleep time (change from baseline)** 300.00 (–8.57) minutes with zolpidem 317.50 (+22.98) minutes with placebo Absolute results reported graphically	P <0.001	○○○	placebo

Zolpidem versus benzodiazepines:

We found one systematic review (search date 2003), [24] which performed a meta-analysis of three RCTs (339 people) comparing benzodiazepines (triazolam or nitrazepam) versus benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone).

Symptom improvement

Benzodiazepine receptor agonists compared with benzodiazepines We don't know whether benzodiazepine receptor agonists (zolpidem, zaleplon, zopiclone; results combined in analysis) are more effective than benzodiazepines (triazolam, nitrazepam, results combined in analysis) at improving subjective sleep quality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality					
[24] Systematic review	339 people 3 RCTs in this analysis	**Subjective sleep quality** with benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone) with benzodiazepines (triazolam or nitrazepam)	Mean effect size +0.04 95% CI –1.11 to +1.19 P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] Systematic review	648 people 6 RCTs in this analysis	**Number of overall adverse effects** with benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone) with benzodiazepines (triazolam or nitrazepam) Absolute results not reported	OR 1.11 95% CI 0.59 to 2.07 P = 0.75	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] Systematic review	268 people 4 RCTs in this analysis	**Cognitive adverse effects** with benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone) with benzodiazepines (triazolam or nitrazepam) Absolute results not reported	OR 1.12 95% CI 0.16 to 7.76 P = 0.91	⟷	Not significant
[24] Systematic review	625 people 6 RCTs in this analysis	**Psychomotor-type adverse effects** with benzodiazepine receptor agonists (zaleplon, zolpidem, and zopiclone) with benzodiazepines (triazolam or nitrazepam) Absolute results not reported	OR 1.48 95% CI 0.75 to 2.93 P value not reported Reported as not significant	⟷	Not significant
[35] RCT **4-armed trial**	221 inpatients aged 58 to 98 years In review [24] The remaining arm evaluated temazepam 15 mg	**Adverse events** 11/70 (16%) with zolpidem 5 mg 8/74 (11%) with zolpidem 10 mg 16/77 (21%) with triazolam 15 mg The most common adverse effect was nightmares	Significance not assessed		

Different doses of zolpidem versus each other:

We found two RCTs comparing different doses of zolpidem. [36] [37]

Symptom improvement

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep quality and duration					
[36] RCT	84 inpatients with insomnia, recruited from geriatric centres	**Sleep-latency score (scale: 1 = <15 minutes, 2 = 15–30 minutes, 3 = 30–60 minutes, and 4 = >60 minutes) , 28 days** 2.0 with zolpidem 10 mg 2.1 with zolpidem 20 mg	Reported as not significant	⟷	Not significant
[36] RCT	84 inpatients with insomnia recruited from geriatric centres	**Number of awakenings score (scale: 0 = no awakenings, 1 = once, 2 = 2–3 times, 3 = 4 or more) , 28 days** 1.6 with zolpidem 10 mg 1.7 with zolpidem 20 mg	Reported as not significant	⟷	Not significant
[37] RCT	60 inpatients in a neurology department with moderate to severe insomnia	**Sleep quality and duration , 60 days** with zolpidem 10 mg with zolpidem 20 mg Absolute results not reported	No significant difference reported between treatments for significant improvements in sleep latency, total sleep time, number of awakenings, and overall sleep quality compared with baseline	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [36] [37]

Further information on studies

Comment: **Clinical guide:**
Few studies have been conducted assessing the long-term effects of hypnotic use. There is a lack of pragmatic studies where the effects of zolpidem on older people taking medication are assessed. Many older 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 *Clinical Evidence* review, the treatment study period was only up to 4 weeks.

OPTION ZOPICLONE

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- Zopiclone may improve sleep latency in older people.
- Zopiclone may also increase sleep duration and improve sleep quality compared with placebo in the short term.
- People using sedative hypnotics are twice as likely to experience adverse events as they are enhanced quality of sleep.

Benefits and harms

Zopiclone versus placebo:

We found one systematic review (search date 2005), which identified two large RCTs. [38] [39] One included RCT was published only as an abstract. Hence, we have not reported the results further. [38] The results of the second RCT are reported below, but should be interpreted with caution, because 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. [39] The authors of the RCT also disclosed that they wrote the paper with the assistance of that drug manufacturer. We found one additional RCT. [40]

Symptom improvement

Compared with placebo Eszopiclone (the active isomer of zopiclone) may be more effective than placebo at improving sleep latency, duration, and sleep quality in older people with chronic primary insomnia, but not at reducing the number of awakenings a night (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Sleep latency					
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Sleep latency (median improvement from baseline) , 2 weeks** 10.9 minutes with eszopiclone 1 mg 10.3 minutes with eszopiclone 2 mg 5.3 minutes with placebo	Significant difference for eszopiclone 2 mg *v* placebo only P greater than or equal to 0.05 for eszopiclone 1 mg P = 0.0059 for eszopiclone 2 mg *v* placebo	○○○	eszopiclone 2 mg

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] RCT	388 people with primary insomnia aged 65 to 85 years	**Mean decrease from baseline in subjective sleep latency , 12 weeks** 24.6 minutes with eszopiclone 2 mg daily 19.9 minutes with placebo See further information on studies for details of low follow-up	P = 0.0014	○○○	eszopiclone
Sleep maintenance and duration					
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Wake after sleep onset (WASO; median improvement from baseline) , 2 weeks** +24.0 minutes with eszopiclone 1 mg +30.6 minutes with eszopiclone 2 mg –5.7 minutes with placebo	P greater than or equal to 0.05 for eszopiclone 1 mg P = 0.0009 for eszopiclone 2 mg *v* placebo	○○○	eszopiclone (2 mg only)
[40] RCT	388 people with primary insomnia aged 65 to 85 years	**Mean decrease from baseline in WASO , 12 weeks** 36.4 minutes with eszopiclone 2 mg daily 14.8 minutes with placebo See further information on studies for details of low follow-up	P <0.0001	○○○	eszopiclone
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Total sleep time (TST; median improvement from baseline) , 2 weeks** 51.7 minutes with eszopiclone 1 mg 75.1 minutes with eszopiclone 2 mg 14.3 minutes with placebo	P greater than or equal to 0.05 for eszopiclone 1 mg *v* placebo P = 0.0002 for eszopiclone 2 mg *v* placebo	○○○	eszopiclone (2 mg only)
[40] RCT	388 people with primary insomnia aged 65 to 85 years	**Change in mean self-reported TST , 12 weeks** From 297.9 to 360.1 minutes with eszopiclone 2 mg daily Placebo result reported graphically See further information on studies for details of low follow-up	P <0.0001	○○○	eszopiclone
Sleep quality and depth					
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Sleep quality measured on the 11-point Likert scale (median improvement from baseline) , 2 weeks** 1.4 with eszopiclone 1 mg 1.7 with eszopiclone 2 mg 0.9 with placebo	P greater than or equal to 0.05 for eszopiclone 1 mg *v* placebo P = 0.0018 for eszopiclone 2 mg *v* placebo	○○○	eszopiclone (2 mg only)
[39] RCT **3-armed trial**	231 people aged 65 to 85 with primary, chronic insomnia	**Sleep depth measured on the 11-point Likert scale (median improvement from baseline) , 2 weeks** 1.6 with eszopiclone 1 mg 2.1 with eszopiclone 2 mg	P greater than or equal to 0.05 for eszopiclone 1 mg *v* placebo P = 0.006 for eszopiclone 2 mg *v* placebo	○○○	eszopiclone (2 mg only)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		1.1 with placebo			
Number of awakenings					
[39] RCT **3-armed trial**	231 people aged 65 to 85 with primary, chronic insomnia	**Number of awakenings a night , 2 weeks** with eszopiclone 1 mg with eszopiclone 2 mg with placebo Absolute results not reported	No significant difference reported between either eszopiclone 1 mg or 2 mg and placebo	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Overall adverse effects , 2 weeks** 40% with eszopiclone 1 mg 43% with eszopiclone 2 mg 40% with placebo The RCT reported that there were no severe adverse effects, accidental falls, amnesia, or hallucinations related to treatment	Significance not assessed		
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Headache , 2 weeks** 15.3% with eszopiclone 1 mg 15.4% with eszopiclone 2 mg 15% with placebo	Significance not assessed		
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Unpleasant taste , 2 weeks** 8% with eszopiclone 1 mg 11% with eszopiclone 2 mg 1% with placebo	Significance not assessed		
[40] RCT	388 people with primary insomnia aged 65 to 85 years	**Unpleasant taste , 12 weeks** 12% with eszopiclone 2 mg daily 2% with placebo Absolute numbers not reported See further information on studies for details of low follow-up	P <0.001	○○○	placebo
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Somnolence , 2 weeks** 8% with eszopiclone 1 mg 4% with eszopiclone 2 mg 9% with placebo	Significance not assessed		
[39] RCT **3-armed trial**	231 people aged 65 to 85 years with primary, chronic insomnia	**Dyspepsia , 2 weeks** 6% with eszopiclone 1 mg 1% with eszopiclone 2 mg 3% with placebo	Significance not assessed		

Zopiclone versus benzodiazepines:
See option on zolpidem, p 20 .

Further information on studies

[40] Treatments were given for a 12-week double-blind study period, followed by a 4-week follow-up period to assess potential discontinuation effects. While adherence was high in the initial 12-week period (>97%), only 74% of people completed follow-up.

Comment: None.

Clinical guide:
While the RCTs suggest promising results for short-term use of hypnotics for treatment of primary insomnia in older 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 older people taking other medication are assessed. Many older 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 *Clinical Evidence* review, the treatment study period was only up to 2 weeks.

OPTION ANTIDEPRESSANTS New

- For GRADE evaluation of interventions for Insomnia (primary) in older people, see table, p 32 .
- We don't know whether antidepressants improve sleep outcomes in older people with primary insomnia, as we found no studies.

Benefits and harms

Antidepressants:
We found no systematic review or RCTs.

Further information on studies

Comment: In this option we have included trials of antidepressants in older people with primary insomnia only, and have excluded trials in people with depression.

GLOSSARY

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.

Polysomnography Polysomnography is the electrographic monitoring of sleep using, for example, electroencephalogram (EEG), electromyography (EMG), and respiratory measurements.

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).

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.

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.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antidepressants New option added. Categorised as Unknown Effectiveness as we found no RCT evidence to assess the effects of this intervention.

Benzodiazepines New evidence added. [23] [25] Categorisation unchanged (Trade-off between benefits and harms).

Diphenhydramine New evidence added. [23] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge the effects of this intervention.

Exercise programmes New evidence added. [19] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge the effects of this intervention.

Timed exposure to bright light New evidence added. [21] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge the effects of this intervention.

Zolpidem New evidence added. [33] Categorisation unchanged (Trade-off between benefits and harms).

Zopiclone New evidence added. [40] Categorisation unchanged (Trade-off between benefits and harms).

CBT New evidence added, [11] [14] [15] [16] [17] categorisation changed (Unknown effectiveness to Beneficial).

REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic and coding manual. 2005.
2. National Heart, Lung and Blood Institute Working Group on Insomnia. Insomnia: assessment and management in primary care. *Am Fam Physician* 1999;59:3029–3038.[PubMed]
3. Liljenberg B, Almqvist M, Hetta J, et al. Age and the prevalence of insomnia in adulthood. *Eur J Psychiatry* 1989;3:5–12.
4. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. *Arch Gen Psychiatry* 1985;42:225–232.[PubMed]
5. Foley DJ, Monjan AA, Brown SL, et al. Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep* 2005;18:425–432.[PubMed]
6. Tjepkema M. Insomnia. *Health Rep* 2005;17:82–103.
7. Bliwise DL. Sleep in normal aging and dementia. *Sleep* 1993;16:40–81.[PubMed]
8. National Center on Sleep Disorders Research Working Group. Recognizing problem sleepiness in your patients. *Am Fam Physician* 1999;59:937–944.[PubMed]
9. Reynolds CF, Buysse DJ, Kupfer DJ. Treating insomnia in older adults: taking a long term view. *JAMA* 1999;281:1034–1035.[PubMed]
10. Cricco M, Simonsick EM, Foley DJ. The impact of insomnia on cognitive functioning in older adults. *J Am Geriatr Soc* 2001;49:1185–1189.[PubMed]
11. McCurry SM, Logsdon RG, Teri L, et al. Evidence-based psychological treatments for insomnia in older adults. *Psychol Aging* 2007;22:18–27.[PubMed]
12. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
13. Montgomery P, Dennis J. A systematic review of non-pharmacological therapies for sleep problems in later life. *Sleep Med Rev* 2004;8:47–62.[PubMed]
14. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep* 2006;29:1398–1414.[PubMed]
15. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 2006;25:3–14.[PubMed]
16. Soeffing JP, Lichstein KL, Nau SD, et al. Psychological treatment of insomnia in hypnotic-dependant older adults. *Sleep Med* 2008;9:165–171.[PubMed]
17. Germain A, Moul DE, Franzen PL, et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med* 2006;2:403−406.[PubMed]
18. Montgomery P, Dennis J. Physical exercise for sleep problems in adults aged 60+. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2002.
19. Irwin MR, Olmstead R, Motivala SJ, et al. Improving sleep quality in older adults with moderate sleep complaints: a randomized controlled trial of Tai Chi Chih. *Sleep* 2008;31:1001−1008.[PubMed]
20. Montgomery P, Dennis J. Bright light therapy for sleep problems in adults aged 60+. In: The Cochrane Library, Issue 3, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2001.
21. Friedman L, Zeitzer JM, Kushida C, et al. Scheduled bright light for treatment of insomnia in older adults. *J Am Geriatr Soc* 2009;57:441–452.[PubMed]
22. Skjerve A, Bjorvatn B, Holsten F. Light therapy for behavioural and psychological symptoms. *Int J Geriatr Psychiatry* 2004;19:516−522.[PubMed]
23. Glass JR, Sproule BA, Herrmann N, et al. Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial. *J Clin Psychopharmacol* 2008;28:182−188.[PubMed]
24. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;331:1169–1173.[PubMed]
25. Morin CM, Colecchi C, Stone J, et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA* 1999;281:991–999.[PubMed]
26. Grad RM. Benzodiazepines for insomnia in community-dwelling elderly: a review of benefit and risk. *J Fam Pract* 1995;41:473−481.[PubMed]
27. Greenblatt DJ, Allen MD, Shader RI. Toxicity of high-dose flurazepam in the elderly. *Clin Pharmacol Ther* 1977;21:355−361.[PubMed]
28. Maidment ID. Zaleplon for insomnia. *J Pharmacol Technol* 2001;17:39−43.

29. Walsh JK, Fry J, Richardson GS, et al. Short-term efficacy of Zaleplon in older patients with chronic insomnia. *Clin Drug Invest* 2000;20:143−149.
30. Ancoli-Israel S, Walsh JK, Mangano RM, et al. Zaleplon, a novel nonbenzodiazepine hypnotic effectively treats insomnia in elderly patients without causing rebound effects. *Prim Care Companion J Clin Psychiatry* 1999;1:114−120.[PubMed]
31. Hedner J, Yaeche R, Emilien G, et al. Zaleplon shortens subjective sleep latency and improves subjective sleep quality in elderly patients with insomnia. The Zaleplon Clinical Investigator Study Group. *Int J Geriatr Psychiatry* 2000;15:704−712.[PubMed]
32. Roger M, Dallot JY, Salmon O, et al. Hypnotic effects of Zolpidem in geriatric patients: a dose-finding study. In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach. New York: Raven Press, 1998:279−287.
33. Walsh JK, Soubrane C, Roth T, et al. Efficacy and safety of zolpidem extended release in elderly primary insomnia patients. *Am J Geriatr Psychiatry* 2008;16:44−57.[PubMed]
34. Fairweather D, Kerr J, Hindmarch I. The effects of acute and repeated doses of zolpidem on subjective sleep, psychomotor performance and cognitive function in elderly volunteers. *Eur J Clin Pharmacol* 1992;43:597−601.[PubMed]
35. Roger M, Attali P, Coquelin J. Multicenter, double-blind, controlled comparison of zolpidem and triazolam in elderly patients with insomnia. *Clin Ther* 1993;15:127−135.[PubMed]
36. Emeriau JP, Descamps A, Dechelotte P, et al. Zolpidem and flunitrazepam: a multicenter trial in elderly hospitalized patients. In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach. New York: Raven Press, 1998:317−326.
37. Lorizio A, Terzano M, Parrino L. Controlled study of the efficacy and safety of two oral doses of zolpidem (10 and 20 mg). In: Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach. New York: Raven Press, 1998:385.
38. Najib J. Eszopiclone, a nonbenzodiazepine sedative-hypnotic agent for the treatment of transient and chronic insomnia. *Clin Ther* 2006;28:491–516.[PubMed]
39. Scharf M, Erman M, Rosenberg R, et al. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. *Sleep* 2005;28:720–727.[PubMed]
40. Ancoli-Israel S, Krystal AD, McCall WV, et al. A 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of eszopiclone 2 mg on sleep/wake function in older adults with primary and comorbid insomnia. *Sleep* 2010;33:225−234.[PubMed]

Cathy Alessi
Professor
David Geffen School of Medicine at UCLA
Veterans Administration Greater Los Angeles Healthcare System
Los Angeles
USA

Michael V Vitiello
Professor, Psychiatry and Behavioural Sciences
University of Washington
Seattle
USA

Competing interests: CA has received research funding from Sepracor Inc, the Veterans Administration, and the National Institutes of Health within the past 5 years. CA has also been a consultant for Prescription Solutions Inc within this time. MVV has served as a speaker and consultant for Tareda Pharmaceuticals and as a consultant for Sanofi-Aventis.

We would like to acknowledge the previous contributors of this review: Paul Montgomery and Jane Lilly.

Disclaimer

GRADE **Evaluation of interventions for Insomnia (primary) in older people.**

Important outcomes					Symptom improvement				
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of non-drug treatments for primary insomnia in older people (aged 60 years and older)?									
at least 9 (at least 82) [15] [16] [17]	Symptom improvement	CBT versus no treatment	4	0	0	–1	0	Moderate	Directness point deducted for mixed population (unclear in 1 study; comorbid insomnia in another) and range of variants of CBT assessed (unclear if all variants equally effective)
2 (95) [18] [19]	Symptom improvement	Exercise versus no treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and for subgroup analysis
1 (61) [21]	Symptom improvement	Timed exposure to bright light versus no treatment	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results
What are the effects of drug treatments for primary insomnia in older people (aged 60 years and older)?									
1 (25) [23]	Symptom improvement	Diphenhydramine versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and weak methods
at least 9 (at least 627) [24] [23] [25]	Symptom improvement	Benzodiazepines versus placebo	4	0	0	0	0	High	
3 (1019) [29] [30] [31]	Symptom improvement	Zaleplon versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inconsistent results depending on outcome measured and dose used
3 (970) [30] [32] [33]	Symptom improvement	Zolpidem versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for short follow-up in 1 RCT (1 day)
3 (339) [24]	Symptom improvement	Zolpidem versus benzodiazepines	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for subjective outcome
2 (144) [36] [37]	Symptom improvement	Different doses of zolpidem versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (619) [39] [40]	Symptom improvement	Zopiclone versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for low follow-up (74% in 1 RCT)

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.