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Eszopiclone for insomnia (Review)

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Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M.
Eszopiclone for insomnia.
Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD010703.
DOI: 10.1002/14651858.CD010703.pub2.

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[Intervention Review]

Eszopiclone for insomnia

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: New, published in Issue 10, 2018.

Citation: Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M. Eszopiclone for insomnia. *Cochrane Database of Systematic Reviews* 2018, Issue 10. Art. No.: CD010703. DOI: 10.1002/14651858.CD010703.pub2.

ABSTRACT

Background

Insomnia is a major public health issue affecting between 6% to 10% of the adult population in Western countries. Eszopiclone is a hypnotic drug belonging to a newer group of hypnotic agents, known as new generation hypnotics, which was marketed as being just as effective as benzodiazepines for this condition, while being safer and having a lower risk for abuse and dependence. It is the aim of the review to integrate evidence from randomised controlled trials and to draw conclusions on eszopiclone's efficacy and safety profile, while taking methodological features and bias risks into consideration.

Objectives

To assess the efficacy and safety of eszopiclone for the treatment of insomnia compared to placebo or active control.

Search methods

We searched the Cochrane Central Register of Controlled trials (CENTRAL), MEDLINE, Embase, PsycINFO, PSYNDEX and registry databases (WHO trials portal, ClinicalTrials.gov) with results incorporated from searches to 10 February 2016. To identify trials not registered in electronic databases, we contacted key informants and searched reference lists of identified studies. We ran an update search (21 February 2018) and have placed studies of interest in awaiting classification/ongoing studies. These will be incorporated into the next version of the review, as appropriate.

Selection criteria

Parallel group randomised controlled trials (RCTs) comparing eszopiclone with either placebo or active control were included in the review. Participants were adults with insomnia, as diagnosed with a standardised diagnostic system, including primary insomnia and comorbid insomnia.

Data collection and analysis

Two authors independently extracted outcome data; one reviewer assessed trial quality and the second author cross-checked it.

Main results

A total of 14 RCTs, with 4732 participants, were included in this review covering short-term (≤ 4 weeks; 6 studies), medium-term (> 4 weeks ≤ 6 months; 6 studies) and long-term treatment (> 6 months; 2 studies) with eszopiclone. Most RCTs included in the review included participants aged between 18 and 64 years, three RCTs only included elderly participants (64 to 85 years) and one RCT included participants with a broader age range (35 to 85 years). Seven studies considered primary insomnia; the remaining studies considered secondary insomnia comorbid with depression (2), generalised anxiety (1), back pain (1), Parkinson's disease (1), rheumatoid arthritis (1) and menopausal transition (1).

Meta-analytic integrations of participant-reported data on sleep efficacy outcomes demonstrated better results for eszopiclone compared to placebo: a 12-minute decrease of sleep onset latency (mean difference (MD) -11.94 min, 95% confidence interval (CI) -16.03 to -7.86; 9 studies, 2890 participants, moderate quality evidence), a 17-minute decrease of wake time after sleep onset (MD -17.02 min, 95% CI -24.89 to -9.15; 8 studies, 2295 participants, moderate quality evidence) and a 28-minute increase of total sleep time (MD 27.70 min, 95% CI 20.30 to 35.09; 10 studies, 2965 participants, moderate quality evidence). There were no significant changes from baseline to the first three nights after drug discontinuation for sleep onset latency (MD 17.00 min, 95% CI -4.29 to 38.29; 1 study, 291 participants, low quality evidence) and wake time after sleep onset (MD -6.71 min, 95% CI -21.25 to 7.83; 1 study, 291 participants, low quality evidence). Adverse events during treatment that were documented more frequently under eszopiclone compared to placebo included unpleasant taste (risk difference (RD) 0.18, 95% CI 0.14 to 0.21; 9 studies, 3787 participants), dry mouth (RD 0.04, 95% CI 0.02 to 0.06; 6 studies, 2802 participants), somnolence (RD 0.04, 95% CI 0.02 to 0.06; 8 studies, 3532 participants) and dizziness (RD 0.03, 95% CI 0.01 to 0.05; 7 studies, 2933 participants). According to the GRADE criteria, evidence was rated as being of moderate quality for sleep efficacy outcomes and adverse events and of low quality for rebound effects and next-day functioning.

Authors' conclusions

Eszopiclone appears to be an efficient drug with moderate effects on sleep onset and maintenance. There was no or little evidence of harm if taken as recommended. However, as certain patient subgroups were underrepresented in RCTs included in the review, findings might not have displayed the entire spectrum of possible adverse events. Further, increased caution is required in elderly individuals with cognitive and motor impairments and individuals who are at increased risk of using eszopiclone in a non-recommended way.

PLAIN LANGUAGE SUMMARY

Eszopiclone (Lunesta) for sleep difficulty

Why is this review important?

Insomnia is the medical term for sleep difficulty covering trouble falling asleep, difficulties staying asleep, waking up too early or experiencing sleep as non-restorative. Insomnia can be treated with different methods including behaviour modification, relaxation techniques, or sleeping medication. Eszopiclone (Lunesta) is a sleeping medication that belongs to a class of sleeping tablets known as non-benzodiazepine hypnotics.

Who will be interested in this review?

People who are affected by insomnia, general practitioners, professionals working in health services, and addiction treatment and health policy makers.

What questions does this review aim to answer?

The review aimed to find out more about the wanted effects and unwanted effects of eszopiclone. Wanted effects included the immediate effects eszopiclone has on sleep; unwanted effects included side effects, effects on next-day functioning, but also addictive properties of the drug.

Which studies were included in the review?

The review summarised findings from 14 clinical studies with 4732 people, either receiving eszopiclone or an identically-appearing, but inert substance (placebo).

What does the evidence from the review tell us?

On average, people taking eszopiclone fell asleep 12 minutes faster than those taking placebo, were 17 minutes less awake during the night and had, in total, about half an hour more sleep than people in the placebo group. As side effects, eszopiclone can cause unpleasant taste, dizziness, dry mouth, and tiredness during the day. Clinical studies did not find evidence that eszopiclone was causing serious harm or withdrawal symptoms or whether it was addictive if it was stopped and not taken after several weeks or months of treatment. Nevertheless, as clinical studies included in the review did not cover certain groups (e.g. elderly people with cognitive or motor problems or certain conditions of medication intake), it is important for patients to consult their doctor who knows their medical history and condition.

What should happen next?

Future research needs to compare eszopiclone with other sleep medications to help physicians and patients decide which of the available treatment options to prefer. In addition, sleep medications that are also well tolerated by elderly individuals and individuals with alcohol or drug problems need to be identified.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Eszopiclone for insomnia

Eszopiclone versus placebo for insomnia

Patient or population: Patients with insomnia
Settings: Outpatient
Intervention: Eszopiclone

Comparator: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Eszopiclone			
Sleep onset latency Participant reports. Scale from 30 to 540 minutes; fewer minutes equalled better outcome; CFB and double-blind average values included	The mean sleep onset latency in the control groups was **20 to 65.7 minutes**	The mean sleep onset latency in the intervention groups was **11.94 minutes lower** (16.03 to 7.86 lower)	2890 (9 studies)	⊕⊕⊕⊖ **moderate**[1]	
Wake time after sleep onset Participant reports. Scale from: 30 to 540 minutes; fewer minutes equalled better outcome; CFB and double-blind average values included	The mean wake time after sleep onset ranged across control groups from **46 to 78.1 minutes**	The mean wake time after sleep onset in the intervention groups was **17.02 minutes lower** (24.89 to 9.15 lower)	2295 (8 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Rebound insomnia - sleep onset latency Scale from: 0 to 540 minutes. Follow-up: 3 days (14 days); fewer minutes equalled better outcome; CFB were calculated by subtracting the mean average of the first three nights of the placebo run-out period from initial scores	The mean rebound insomnia - sleep onset latency in the control group was **-24.02 minutes**	The mean rebound insomnia - sleep onset latency in the intervention groups was **17 minutes higher** (4.29 lower to 38.29 higher)	291 (1 study)	⊕⊕⊖⊖ **low**[3]	
Rebound insomnia - wake time after sleep onset Scale from: 0 to 540 minutes. Follow-up: 3 days (14 days); fewer minutes equalled better outcome; CFB were calcu-	The mean rebound insomnia - sleep onset latency in the control group was **-22.15 minutes**	The mean rebound insomnia - wake time after sleep onset in the intervention groups was **6.71 minutes lower**	291 (1 study)	⊕⊕⊖⊖ **low**[3]	

lated by subtracting the mean average of the first three nights of the placebo run-out period from initial scores		(21.25 lower to 7.83 higher)			
Total sleep time Participant reports. Scale from: 300 to 840; more minutes equalled better outcome; CFB and double-blind average values included	The mean total sleep time ranged across control groups from **324.8 to 382.2 minutes**	The mean total sleep time in the intervention groups was **27.70 minutes higher** (20.30 to 35.09 higher)	2935 (9 studies)	⊕⊕⊕⊖ **moderate**[1]	
Next-day alertness Participant reports. Scale from: 0 to 10 points; higher scores equalled better outcome; CFB and double-blind average values included	The mean next-day alertness ranged across control groups from **5.7 to 7.3 on a 11-point Likert Scale**	The mean next-day alertness in the intervention groups was **0.46 points higher** (0.28 to 0.63 higher)	2061 (8 studies)	⊕⊕⊖⊖ **low**[4]	
Serious adverse events (as defined in the primary study) Participant reports. Serious adverse events observed during double-blind treatment period	**Study population**		4289 (12 studies)	⊕⊕⊕⊖ **moderate**[1]	Risks were calculated from pooled risk differences
	9 per 1000	**9 per 1000** (-1 to 19)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] We downgraded evidence for sleep efficacy outcomes and adverse events by one grade due to methodological limitations (omission of specific design features from trial reports; taste properties of eszopiclone potentially revealing the identity of medication).
[2] Even though some inconsistency of results was shown for WASO, heterogeneity was mainly attributable to one trial (Scharf 2005), whose exclusion resulted into a I^2 reduction from 55% to 6%.
[3] We downgraded evidence for rebound insomnia outcomes by two grades as five RCTs (with a duration > two weeks) applied open-label extensions, naturalistic follow-ups or no follow-up, which we did not consider appropriate to control bias effects
[4] We downgraded evidence for next-day alertness assessed through subjective measures by two grades as it was expected to be rather the objective than the subjective measures of next-day functioning that might determine the risk of harm, including injuries and accidents
CFB: Change from baseline

BACKGROUND

Description of the condition

Affecting between 6% to 10% of the adult population in Western countries, insomnia is not only a psychological burden to the individual affected by the condition, but also a major public health issue (Moloney 2011; Morin 2006; Morin 2012; Ohayon 2002; Ohayon 2009; Roth 2003). Complaints increase with age and are twice as prevalent in women than in men (Morin 2012).

The predominant symptom of insomnia is difficulty initiating sleep (sleep-onset insomnia), maintaining sleep (sleep-maintenance insomnia) or early morning awakening with inability to return to sleep (Riemann 2015). According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013), and the third edition of the International Classification of Sleep Disorders (ICSD-3) (American Academy of Sleep Medicine 2014), dissatisfaction with sleep quantity or quality has to occur at least three nights per week over at least three months to be diagnosed as chronic insomnia. In addition, diagnosis of insomnia disorder requires that sleep problems occur despite adequate opportunity for sleep and cause at least one related daytime impairment, affecting social, occupational, or other important areas of functioning.

Insomnia criteria in the DSM-5 (American Psychiatric Association 2013), and ICSD-3 (American Academy of Sleep Medicine 2014) differ from previous classifications by considering frequency criteria and by increasing duration of the condition from one to three months. However, the most fundamental change to former definitions is that primary insomnia and secondary insomnia are not considered as different conditions anymore, but rather as a common category for insomnia disorder. Since causal attribution labels are removed now, insomnia disorder can be recognised as a condition requiring clinical attention irrespective of the presumed underlying causes (Morin 2012; Riemann 2014).

Various models of insomnia refer to a common framework proposed by Spielman 1991, distinguishing between predisposing, precipitating, and perpetuating factors. While predisposing factors, such as maladaptive coping stress strategies, cognitive-emotional hyperarousal and older age, make individuals more vulnerable to sleeping problems (Fernández-Mendoza 2010), increased life-stress, irregular sleep habits, and poor sleep hygiene further precipitate their occurrence (Bastien 2004). If sleep is repeatedly disturbed, a further perpetuation of the problem results from the selective attention directed towards the inability to fall asleep, creating a vicious cycle that often leads to chronicity. The neurocognitive model of insomnia (Perlis 1997; Buysse 2011) emphasises the role of hyperarousal, including an increased level of somatic, cognitive and cortical activity, which is enforced through classical conditioning and which promotes abnormal levels of sensory and information processing, thought to render the insomniac individual especially vulnerable to perturbation by environmental or other stimuli (Riemann 2009). The inhibition model developed by Espie 2002, conceptualises insomnia as the failure to inhibit wakefulness rather than the inability to induce sleep and underscores the originally functional role of wakefulness in the presence of stressors. If a 'threat' is not eliminated, attention is increasingly focused on sleep and motivational processes, including the conscious intent to fall asleep. The attention-intention-effort pathway model (Espie 2006), explains how these processes interfere with the otherwise automatic response of inhibiting wakefulness. Current research outlines the interaction between genetics, personality, coping styles and sleep-interfering processes like increased stress-reactivity and hyperarousal (Harvey 2018; Palagini 2014). It is hypothesized that epigenetic mechanisms involved in both sleep regulation and brain-stress response persist into adulthood through effects on brain plasticity (Palagini 2014).

Insomnia has traditionally been considered as a symptom of another disease, rather than a discrete disorder (Morin 2012). Even though insomnia is often associated with psychiatric and medical conditions that contribute to sleep disturbance in diverse ways (Katz 1998; Krystal 2012b), it is now conceptualised as a discrete disorder and as an independent risk factor for further medical and psychiatric problems (Morin 2012). Insomnia is known to increase the risk for depression and substance use disorders (Falcón 2009; Johnson 2001; Riemann 2007; Roane 2008), and coronary heart disease (e.g. Cappuccio 2011; Ferrie 2007; Li 2014; Parthasaraty 2015; Sofi 2014; Winkelman 2015; Xiao 2014). Besides causing psychological distress, insomnia leads to next-day cognitive and psychomotor impairments (Fortier-Brochu 2012; Shekleton 2010), irritability, and decreased job performance (Metlaine 2005), and has been shown to reduce life quality (Rosekind 2010; Zammit 1999), and longevity (Roth 2009a). Untreated insomnia does usually not remit with time (Angst 1989; Leshner 2005), underscoring the need for effective and safe treatment interventions.

Description of the intervention

Insomnia is still under-recognised and often goes untreated (Morin 2012). Even though often recommended as first-line treatments for chronic insomnia (Hajak 1997; Ramakrishnan 2007; van Straten 2018), non-pharmacological treatment strategies, including cognitive behavioural therapy (CBT), are rarely used in clinical practice (Cape 2015). Benzodiazepine hypnotics are effective for short-term treatment of insomnia (Buscemi 2007), but carry the risk of rebound insomnia, withdrawal symptoms, dependence (Ballenger 2000; Lader 1999; Royal College of Psychiatrists 1997), and next-day hangover effects, responsible for traffic and machine operation accidents (Barbone 1998), self injuries and hip fractures, the latter commonly seen in elderly patients (Bolton 2008; Woolcott 2009).

In the 1980s and early 1990s, a new group of hypnotic agents, known as new generation hypnotics, non-benzodiazepine hypnotics, benzodiazepine receptor agonists or 'z-drugs', were introduced to the markets. Meanwhile, zopiclone, zolpidem, zaleplon and eszopiclone, four different non-benzodiazepine hypnotic compounds, have been developed and introduced as insomnia therapies (Nutt 2010). Eszopiclone is a pyrrolo pyrazine derivative of the cyclopyrrolone class and the (S)-enantiomer of racemic zopiclone. While racemic zopiclone was approved in 1986 for the European market and used as a hypnotic in many countries for more than two decades without being licensed in the USA, eszopiclone (Lunesta) received the US Food and Drug Administration (FDA) approval in December 2004. In the USA, eszopiclone is approved for short- or long-term treatment of sleep onset and sleep maintenance insomnia in adults and is marketed in 1 mg, 2 mg and 3 mg film-coated tablets. To date, eszopiclone is not available in Europe as the originator of Lunesta, Sepracor Pharmaceuticals Ltd, withdrew the application for a centralised marketing authorisation for Lunivia to the European Medicines Agency (EMEA) in 2009 (European Medicines Agency 2009).

As shown by animal studies, the (S)-enantiomer of racemic zopiclone is the one of two stereoisomers that mainly mediates its hypnotic effects (Melton 2005; Hair 2008). Accordingly, recommended clinical dosages are about 50% lower for eszopiclone compared to racemic zopiclone (Greenblatt 2012). The recommended starting dose for eszopiclone was initially 2 mg in non-elderly adults and 1 mg for elderly patients (Sepracor 2004 [pers comm]; Hair 2008) and lowered to 1 mg for men and women of all age groups by a current FDA safety alert (Food and Drug Administration 2015) due to the risk of next-day impairments as shown in a randomised, double-blind cross-over study (Boyle 2012). The maximum recommended dose of eszopiclone is 3 mg in non-elderly and 2 mg in elderly subjects (Lunesta 2004 [pers comm]). Eszopiclone is rapidly absorbed (maximum plasma concentration (T_{max} ~ one hour), has a relatively long elimination half-life time ($t_{1/2}$ ~ six hours) compared to other non-benzodiazepine hypnotic compounds, and was shown not to accumulate after multiple once-daily administration (Hair 2008; Nutt 2010). Eszopiclone is known to cause a bitter or metallic taste, while there is no convincing explanation for this effect (Greenblatt 2012). The drug is classified as a Schedule IV controlled substance (Najib 2006).

How the intervention might work

Similar to benzodiazepines, non-benzodiazepine hypnotics develop their sedative properties through activity at the gamma-aminobutyric acid-A (GABA-A) receptor, whose endogenous ligand, GABA, is the major inhibitory neurotransmitter in the central nervous system, involved in anxiolysis, sedation, seizure suppression and muscle relaxation (Bateson 2004; Rudolph 2011). The GABA-A receptor is composed of five protein subunits and at least 19 distinct subunit isoforms, mediating different behavioural and pharmacological responses (Dolder 2007; Drover 2004; Dündar 2004b; Sieghart 2006). Alpha 1 subunits of the GABA-A receptor are thought to be mainly responsible for the mediation of sedative drug effects, alpha 2 and alpha 3 subunits for anxiolytic and antidepressant drug activities, and alpha 5 receptor subunits for cognitive effects including memory and learning (Lingford-Hughes 2002; Nutt 2010). While benzodiazepines modulate different subunits of the GABA-A receptor, the non-benzodiazepine hypnotics, zaleplon and zolpidem, bind more selectively to the alpha 1-containing receptor subtypes responsible for sedation (Monti 2007). Accordingly, non-benzodiazepine hypnotics are assumed to produce an advantageous clinical profile compared to benzodiazepines, particularly with respect to residual effects, tolerance and dependence (Drover 2004; Follesa 2002). The cyclopyrrolone derivates, zopiclone and eszopiclone, are not receptor subtype-specific, but zopiclone has shown to have high affinity binding sites in the cerebral cortex, hippocampus and cerebellum, and greater affinity for alpha 1 and alpha 2 subunits than benzodiazepines (Najib 2006). Like racemic (R,S) zopiclone, eszopiclone shows relatively high binding affinity for the alpha 1, but also for the 2 and 3 receptor subtype, which might indicate that eszopiclone has both hypnotic and anxiolytic effects (Greenblatt 2012; Nutt 2010).

Further differences in the clinical effects of non-benzodiazepine hypnotics are assumed to be associated with their unique pharmacokinetic profiles, including the bioavailability of the drug, the volume of distribution and the elimination half-life time (Drover 2000). Like zopiclone, eszopiclone has a longer half-life time than the non-benzodiazepine hypnotic compounds, zaleplon or zolpidem, and is thus expected to be particularly useful for the treatment of sleep-maintenance insomnia (Drover 2000). The prolonged elimination time of eszopiclone may, on the other hand, increase the risk of next-day impairments (Nutt 2010). Considering the rapid onset of action, eszopiclone appears to have an improved pharmacokinetic profile compared to racemic zopiclone, presumably due to the absence of the confounding effects of (R)-zopiclone, resulting in a slightly faster onset of action and a reduced individual variability in response (Greenblatt 2012; Nutt 2010). Levels of (S)-desmethylzopiclone, one of the active metabolites of eszopiclone and zopiclone, are lower than those seen after an equivalent effective dose of racemic zopiclone, suggesting a reduced risk of residual effects for the pure active enantiomer (Brunello 2008).

Why it is important to do this review

Use of hypnotic drugs increased over the past decades, with a striking rise in prescriptions for non-benzodiazepine hypnotics (Bertisch 2014). Being marketed as just as effective as benzodiazepines, while being safer and having a lower risk for abuse and dependence, non-benzodiazepine hypnotics have meanwhile replaced benzodiazepines as the most commonly prescribed hypnotic drugs and emerged as the first-line drugs for insomnia treatment (Erman 2005; Hausken 2009; Hoffmann 2009; NHS Prescribing Service 2010; Siriwardena 2008).

At the same time, there is an increasing controversy about the safety profile of non-benzodiazepine hypnotics (Cimolai 2007). Various reviews of preclinical and clinical evidence (Drover 2004; Dündar 2004a; Dündar 2004b; Montplaisir 2003; Zammit 2009), post-marketing surveillance studies (Delahaye 1990; Jaffe 2004), and reviews of case study reports (Hajak 2003; Lader 1999; Soyka 2000) confirm the advantages of non-benzodiazepine hypnotics in terms of next-day impairments and their potential for abuse and dependence. Double-blind studies examining the subjective effects of zolpidem in drug-naive individuals (Licata 2008) and assessing polysomnographic withdrawal effects of zopiclone and zolpidem in healthy subjects (Vorderholzer 2001) have found a low risk of tolerance and dependency for these drugs, if taken in recommended doses. Further studies and reviews, likewise referring to patient surveys and pharmacovigilance data, rate the abuse liability of non-benzodiazepine hypnotics as comparable to that of benzodiazepine hypnotics (e.g. Hoffmann 2009; Hoffmann 2014; Siriwardena 2008; Victorri-Vigneau 2014). Parasomnia, amnesia, and hallucinations have been documented as adverse events of zolpidem (Ben-Hamou 2011) and there is evidence that eszopiclone can cause euphoria and hallucination if taken in elevated doses (Scharf 2006; Monti 2007).

In addition, current evidence indicates that the risk of the non-benzodiazepine hypnotic drugs in causing next-day impairments might be higher than initially assumed (Gunja 2013). While a first randomised, double-blind, placebo-controlled, cross-over trial did not indicate next-day residual effects for 3 mg nighttime eszopiclone in young to middle-aged individuals (Boyle 2008), a subsequent study applying a mild sleep restriction protocol (Boyle 2012) demonstrated next-day impairments, giving reason for a FDA safety alert (see also Description of the intervention; Food and Drug Administration 2015). Retrospective analyses of medical care and health insurance data demonstrate an alerting risk for falls, injuries, and hip fractures for zolpidem (Finkle 2011; Wang 2001) and for

non-benzodiazepine hypnotic substances in general (Berry 2013; Diem 2014). Eszopiclone might also decrease immune function, as indicated by a meta-analysis of data submitted to the FDA, which showed an increased risk of infections for eszopiclone (Joya 2009). Carcinogenicity and mutagenesis associated with eszopiclone have been discussed and require further monitoring (Strebbing 2005).

It is the aim of the review to integrate efficacy and safety data from randomised controlled trials (RCTs) on eszopiclone, to allow the drawing of conclusions on the drug`s efficacy and safety profile, while taking study quality and bias risks into consideration. This review forms part of a suite of four reviews on non-benzodiazepine hypnotics for insomnia; the other three reviews will assess the effectiveness and safety of zolpidem (Rösner 2013a), zopiclone (Rösner 2013b) and zaleplon (Rösner 2013c).

OBJECTIVES

The objectives of the review are:

1. to determine the effectiveness of eszopiclone for insomnia treatment in comparison with placebo and active comparators;
2. to determine the safety profile of eszopiclone in comparison with placebo and active comparators; and
3. to compare eszopiclone with other non-benzodiazepine hypnotics in terms of effectiveness and safety.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel group randomised controlled trials (RCTs), comparing eszopiclone with either placebo or active control in its efficacy to improve sleep and its risk of causing adverse events, withdrawal symptoms, or rebound insomnia. Run-out phases were included if controlled with placebo. Cross-over trials were not included in the review due to sleep stabilising effects that have been reported for eszopiclone after discontinuation of dosing (Zammit 2004), making it difficult to control carry-over effects by wash-out.

Types of participants

Adults aged 18 years and over with insomnia, as diagnosed using a standardised diagnostic system such as the DSM (American Psychiatric Association 2013), the ICD (World Health Organization 1992), or the ICSD (American Academy of Sleep Medicine 2014), were included irrespective of insomnia type (primary insomnia; insomnia associated with comorbid conditions; see Differences between protocol and review). We did not include healthy subjects from laboratory models of transient sleep as it is unclear whether these conditions are generalisable to clinical insomnia.

Types of interventions

Experimental intervention: eszopiclone as monotherapy.

Comparator interventions: placebo, other non-benzodiazepine hypnotics, short-/ intermediate-/long-acting benzodiazepines; other active controls that allowed double-blind treatment. Any treatment setting (inpatient and outpatient) and any formulation were included.

Types of outcome measures

Outcomes of the review are a selection of outcomes considered in primary studies (see Characteristics of included studies). We selected the primary and secondary outcomes of the review with regard to the clinical relevance of outcome criteria and the avoidance of conceptual overlaps. All types of measurement including objective measures (e.g. polysomnography) and participant-reported sleep measures, as well as different types of scores (change from baseline scores, double-blind average scores), were considered. If both objective and subjective measures were provided in a study publication, subjective measures were included in the meta-analysis and we examined the impact of measurement type with sensitivity analyses (see Sensitivity analysis). Change from baseline scores and double-blind average scores were integrated in the same meta-analyses, as outlined by Deeks 2011. For the assessment of adverse events (withdrawal symptoms and next-day alertness), any types of outcome measures were included.

Timing of outcome assessment

Double-blind average scores were based on the average of the results over the double-blind treatment period. While change from baseline scores for efficacy outcomes were obtained by subtracting the measurement at the end of treatment from initial scores, change from baseline values for discontinuation outcomes (rebound insomnia) were calculated by subtracting the mean average of the first three nights of the placebo run-out period from initial scores. Safety was assessed over the entire double-blind treatment period, and discontinuation effects over the first three nights of the placebo run-out period. Interventions up to four weeks were considered as short-term treatments, interventions between four weeks and six months as medium-term treatments, and interventions with a duration over six months as long-term treatments.

Primary outcomes

Primary efficacy outcomes

1. Sleep onset latency (SOL)
2. Wake time after sleep onset (WASO)

Treatment effectiveness was assessed through two outcomes: 1. 'sleep onset latency' (SOL), defined as the length of time (in minutes) after lights-out until sleep onset, and 2. 'wake time after sleep onset' (WASO), defined as the length of time (in minutes) of wakefulness after the onset of persistent sleep. The consideration of two effectiveness outcomes was reasoned by their conceptual distinctiveness, with SOL measuring a drug's impact on sleep onset, and WASO measuring the potential to improve sleep maintenance; the former reflecting its suitability for the treatment of sleep-onset insomnia and the latter for sleep-maintenance insomnia (see Description of the condition).

Primary discontinuation outcomes

1. Withdrawal symptoms
2. Rebound insomnia

Discontinuation effects were assessed through 1. withdrawal symptoms, defined as adverse symptoms that either a) appeared for the first time during the placebo run-out period, or b) already appeared during treatment, but deteriorated during the

placebo run-out interval; and 2.rebound insomnia, defined as the temporary worsening of sleep during the placebo run-out interval. Worsening of sleep was evaluated as mean change from baseline for the primary efficacy outcomes (SOL, WASO) during the first three days of the placebo run-out period (Gillin 1989). The consideration of two variables for assessing effects of drug discontinuation was based on the fact that most studies provided data on either one or the other outcome.

Secondary outcomes

1. Total sleep time (TST)
2. Next-day alertness
3. Adverse events (AEs)

Total sleep time (TST) was the total time (in minutes) a person spent sleeping during the in-bed interval. Calculated as time in bed minus SOL and minus WASO (Schutte-Rodin 2008),TST is a common outcome measure in insomnia treatment, reflecting both sleep onset and maintenance effects within a single variable (Goforth 2014). To avoid conceptual overlaps with the primary efficacy outcomes, TST was considered as a secondary outcome of the review. Next-day alertness reflected the state of vigilance the day after hypnotics had been taken and was mainly assessed with an 11-point-Likert scale (0 to 10), with higher scores indicating improved function. Adverse events (AEs) were all types of unfavourable symptoms that occurred during the course of the study.

Hierarchy of outcome assessment

The study endpoints of the primary outcomes were considered as essential to determine efficacy and safety of eszopiclone, while secondary outcomes had only complementary value in the interpretation of results. Thereby, the primary efficacy outcomes, SOL and WASO, were considered as distinctive compounds and weighted equally in the determination of sleep efficacy. Discontinuation effects were considered as being present if either adverse events or indicators of sleep efficacy changed during the placebo run-out period.

Search methods for identification of studies

Electronic searches

The Cochrane Common Mental Disorders Group's Trials Search Co-ordinator (TSC) searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 onwards), Embase (1980 onwards), PsycINFO (1987 onwards) and PSYNDEX (in English and German) with a last update of the search on February 10, 2016 (Appendix 2). The WHO trials portal and ClinicalTrials.gov were searched to identify any ongoing or completed trials with unpublished results. Search strategies were developed by the TSC comprehensively to simultaneously address different non-benzodiazepine hypnotic compounds (eszopiclone, zopiclone, zolpidem, zaleplon). The results of the search and reviews for zopiclone, zolpidem and zaleplon will be presented in Rösner 2013a, Rösner 2013b and Rösner 2013c, respectively.

In keeping with the MECIR conduct standard (C37 re-running searches within 12 months of publication), we ran an update search on CENTRAL, CCMDCTR, MEDLINE, Embase, PsycINFO and the international trial registries (21 February 2018). We identified three new studies which we have placed in 'awaiting classification'/'ongoing studies', these will be incorporated in the next version of the review, as appropriate.

Searching other resources

We contacted key informants, experts, public sponsors, and drug manufacturers with the request to indicate further studies of potential relevance. For this purpose, we provided reference lists with identified studies and the criteria for inclusion and exclusion in the review. Finally, we handsearched the reference lists of included studies and current reviews to complete and to verify the preceding searches. All eligible studies identified with the search were included irrespective of language, publication type, or status.

Data collection and analysis

Selection of studies

We assessed the eligibility and relevance of trials on the basis of their abstracts retrieved from the electronic searches. For studies that appeared to meet the inclusion criteria according to the abstract information, we obtained full-text versions for closer inspection. Two review authors assessed the relevance and eligibility of studies independently. The process of study identification and its results were outlined as a flow diagram according to the PRISMA statement (Moher 2009).

Data extraction and management

Two review authors extracted relevant outcome data independently into prespecified data extraction forms and compared data value by value. In case of disagreements, we have undertaken the following sequential procedures in descending order:

1. comparison of published and extracted information to identify transcription and comprehension errors;
2. explanation of the coding decisions by each review author, followed by consensus discussion and arbitration.

Finally, after comparisons and corrections were concluded, we entered data into the Review Manager software (Review Manager 2014). For meta-analyses, we planned to compare eszopiclone individually with either placebo or active control (though we only found placebo-controlled trials). It had been planned to group benzodiazapine-active control drugs according to their duration of action into short-acting (less than five hours), intermediate-acting (five to 24 hours) and long-acting (more than 24 hours) agents (Greenblatt 1981), potentially generating the following comparisons:

1. eszopiclone versus placebo:
2. eszopiclone versus other new generation hypnotics;
3. eszopiclone versus short-acting benzodiazepines;
4. eszopiclone versus intermediate-acting benzodiazepines;
5. eszopiclone versus long-acting benzodiazepines;
6. eszopiclone versus other active controls (compounds to be specified at a later date).

Assessment of risk of bias in included studies

We assessed the risk of bias in accordance with The Cochrane Collaboration's 'Risk of bias' assessment tool (Higgins 2011). We considered the equivalence of baseline characteristics and the

equivalence of treatment utilisation as further bias risks in the rating of the item 'free of other bias'. We judged the general susceptibility to bias effects in consideration of the objectivity of outcome information and rated this separately for measures of sleep and next-day functioning. Two review authors independently assessed the risk of bias and divergent ratings were resolved by consensus discussion. The criteria considered as constitutive for the rating of bias risks are outlined in Appendix 1.

Measures of treatment effect

We measured treatment effects for continuous outcomes with the mean differences (MD), as these were measured on the same scale. As more commonly reported, we gave priority to final measurement scores compared to change-from-baseline scores, if both types of outcomes were provided in the trial publication. Nevertheless, we pooled change and final scores in meta-analysis as outlined by Deeks 2011, using the (unstandardized) mean difference method in RevMan (Review Manager 2014). For subjective measures of next-day functioning, higher scores indicate a more positive state; if provided differently in the primary study, scales were reversed in their polarity. Adverse events were assessed using risk difference (RD) as this measure can also be calculated in cases where there are no events in either group (Deeks 2011). We calculated all treatment effects together with 95% confidence intervals (CIs). A P value of 0.05 and below has been chosen to indicate statistical significance of effects. We planned to measure treatment effects for dichotomous effectiveness outcomes using risk ratio (RR) and 'number needed to treat for an additional beneficial outcome' (NNTB) or 'number needed to treat for an additional harmful outcome' (NNTH) for outcomes that reached statistical significance, but, beside adverse events, no additional dichotomous data were available. We did not provide NNTH for adverse events as these related to the number of events, not participants (see Unit of analysis issues). In the future, if we find any dichotomous data, we plan to calculate NNTB for effects on binary outcomes which reach statistical significance.

Unit of analysis issues

Only individually randomised trials with the individual participant constituting the unit of analysis were included in the review. In multi-arm studies with different dose schedules, only the initially recommended dose group (2 mg in non-elderly, 1 mg in elderly participants; see Types of interventions) was considered. Meta-analyses of adverse events were based on number of events, which did not necessarily correspond with the number of participants (as one participant can theoretically report multiple adverse events). The latter did not apply to dropouts due to adverse events, where the number of participants matched exactly the number of dropout events.

Dealing with missing data

Outcome statistics were included in the review, as provided by the study publications, irrespective of how missing individuals were handled in the primary analysis. We imputed sample sizes for continuous outcomes which were not explicitly provided in the trial publication by the size of treatment-received samples or, if not available, by the size of the randomised sample. Missing standard deviations were obtained from standard errors (SEs) or CIs for group means, missing SEs from standard deviations (SDs), CIs, or t values and P values. If only the medians were provided in the trial publications, outcome statistics were not included in the meta-analyses, but information on the significance of effects (yes, no) was inserted into an overview table and described qualitatively in the discussion of results.

Assessment of heterogeneity

We quantified inconsistency across studies with the I^2 statistic (Higgins 2003), using threshold values for substantial heterogeneity as outlined by Deeks 2011. Heterogeneity was assumed if the I^2 value was above 75%. The Tau^2 statistic was additionally considered to provide an estimate of between-study variance (Rücker 2008), independent of the sample size. In cases of heterogeneity, we attempted to identify and explain the heterogeneity using subgroup analysis.

Assessment of reporting biases

If there are more than 10 included studies in future versions of this review, we will graphically illustrate the risk of publication bias with the funnel plot method (Egger 1997; Light 1984).

Data synthesis

For synthesising aggregate outcome measures, we used a random-effects model (DerSimonian 1986), with study effects being weighted using the Mantel-Haenszel approach (Mantel 1959).

Subgroup analysis and investigation of heterogeneity

Due to age-related changes in the architecture of sleep and pharmacokinetic changes, elderly participants are repeatedly shown to respond differently to hypnotic drugs than younger people (Dolder 2007). In addition, there is evidence that treatment effects might depend on insomnia as a primary or secondary condition (Krystal 2012b; Wilson 2010). Thus, we conducted subgroup analyses limited to samples, a) of age groups over 65 years and b) of participants with insomnia associated with psychiatric and medical comorbidity to determine differential effectiveness of eszopiclone in participants with older age or with comorbid insomnia. To additionally investigate whether effects demonstrated in investigator-initiated studies significantly differed from sponsor-initiated studies as a result of funding bias (Lexchin 2003), we compared both groups of trials by subgroup analyses.

Sensitivity analysis

We conducted sensitivity analyses to determine the influence of the following variables on the primary effectiveness outcomes (SOL, WASO):

1. the method of sleep efficacy measurement by integrating effects measured with polysomnography;
2. the method of withdrawal assessment by integrating scores of the Benzodiazepine Withdrawal Symptom Questionnaire.

Summary of findings tables

Summary of findings tables were completed to summarise the best evidence for all relevant outcomes including SOL, WASO, withdrawal symptoms, rebound insomnia, TST, next-day alertness and adverse events. The rating of single GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision, publication bias) and upgrading quality of evidence (magnitude, dose-response gradient, change of results by confounding) was reasoned and outlined in detail under Quality of the evidence.

The GRADE assessment was performed by one author (SRO) and discussed with a second author (CE) in case of ambiguity.

RESULTS

Description of studies

Results of the search

Search for studies

Results of the electronic biomedical database searches (to February 2016), simultaneously addressing different non-benzodiazepine hypnotic compounds (eszopiclone, zopiclone, zolpidem, zaleplon) were screened in parallel (by SR, CE) and allocated to different reviews, as appropriate. Results of the search and reviews for zopiclone, zolpidem and zaleplon will be presented in Rösner 2013a, Rösner 2013b and Rösner 2013c, respectively. The steps of trial identification for eszopiclone and their results are illustrated in Figure 1 as a flow diagram, according to the PRISMA statement (Moher 2009).

Figure 1. Study flow diagram (search results to Feb 2016)

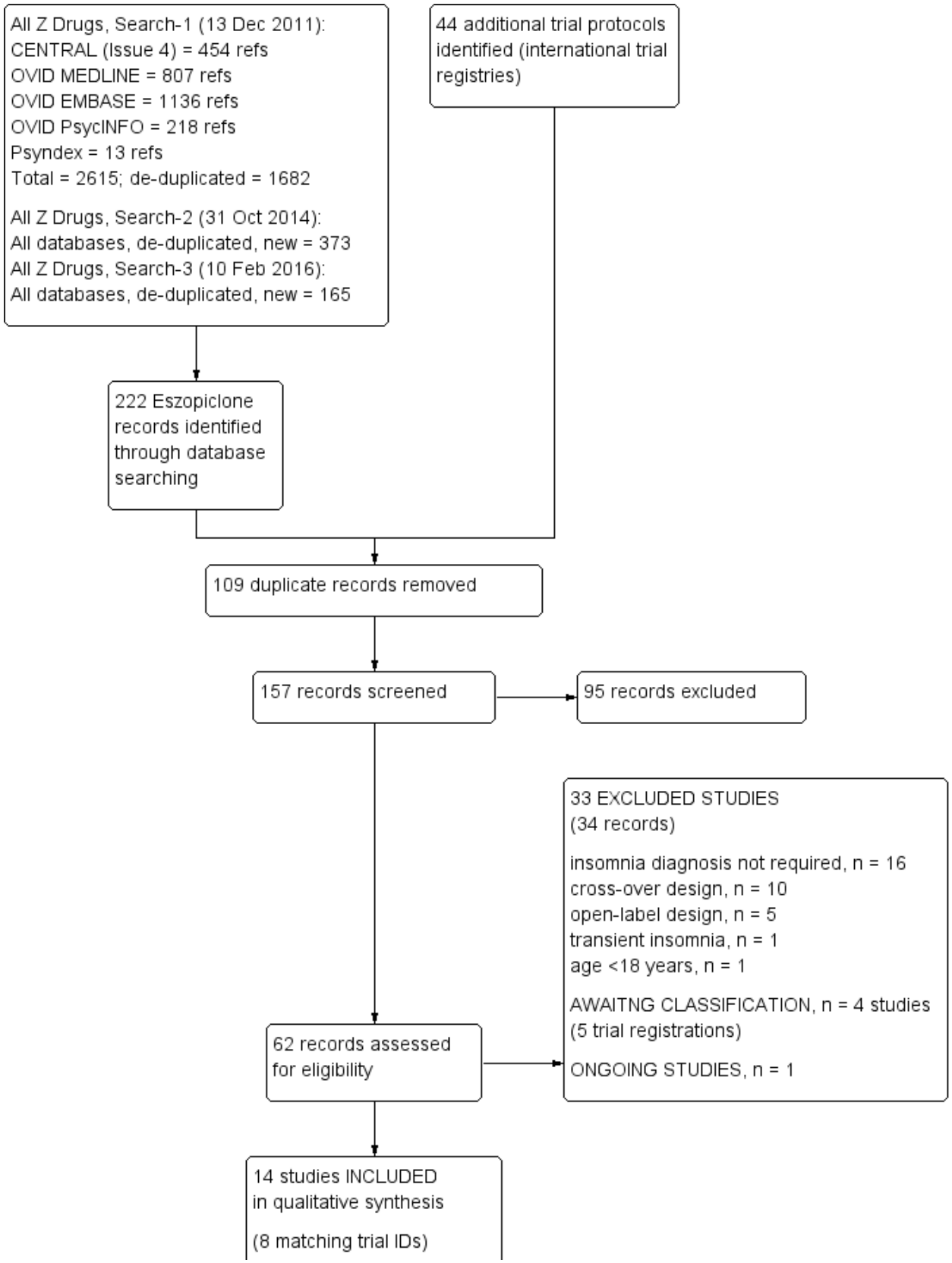
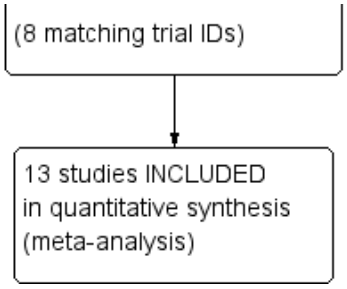


Figure 1. (Continued)



Electronic searches for eszopiclone (only) yielded 222 potentially relevant journal references. Personal communications with investigators and sponsors did not yield further studies. From the 222 yielded references, 94 were recognised as duplicates and removed. For the remaining 128 references, abstracts were screened by two review authors independently (SR, CE and RW, CE). On the basis of information provided in the title and abstracts, a further 80 references were excluded, while for the remaining 48 records, full-text articles were retrieved (where available). Inspection of the study reports led to the exclusion of a further 33 studies (34 reports) and reasons for the exclusions are outlined under Excluded studies.

The search of the international trial registries (to February 2016) identified an additional 44 trial protocols; 15 were excluded as irrelevant and, on closer inspection, 15 were duplicates as they had already been excluded as trial records retrieved from the bibliographic databases search, with the reasons for exclusions outlined under Excluded studies. Of the remaining 14 trial protocols, eight linked to full study reports already included in the review, four were added to 'awaiting classification', one was ongoing and there was one duplicate trial registration.

In keeping with the MECIR conduct standard (c37: re-running searches within 12 months of publication), we ran an update search (21 February 2018) and identified four new studies, two studies (Baran 2017; Buxton 2017) placed in 'studies awaiting classification', one (NCT02456532) placed in ongoing studies and another (retrospectively) excluded (Uchimura 2012b). Thus, including the results of the update search, six studies were categorized as 'studies awaiting classification',two studies as ongoing and a total of 34 excluded studies. A journal article relating to a trial protocol awaiting classification (NCT01100164) was also identified at this time (Pinto 2016).

Finally, 14 RCTs were eligible for the review; of these, 13 RCTs provided data for meta-analytic integrations of sleep efficacy or safety outcomes.

The PRISMA diagram includes details of the search results to 10 February 2016 only (Figure 1).

Acquisition of unreported outcomes

To obtain unreported outcome data for primary efficacy outcomes of the review, correspondence authors of primary studies were contacted by email and requested to provide unreported data. From 10 authors requested, six authors responded, referring to the drug manufacturer, Sunovion (www.sunovion.com/), which did not provide unreported data.

Included studies

Fourteen RCTs (Ancoli-Israel 2010; Fava 2006; Goforth 2014; Krystal 2003; McCall 2006; McCall 2010a; Menza 2010; Pollack 2008; Roth 2009; Scharf 2005; Soares 2006; Spierings 2015; Walsh 2007; Zammit 2004), based on data from 4732 study participants, were included in the review. Table 1 provides an overview of all included studies. Detailed information on study designs, sample characteristics, interventions, and outcomes for each individual trial is presented in the Characteristics of included studies tables.

Design and setting

All trials included in the review were based on a randomised controlled parallel group design. No trials with active controls (new-generation hypnotics, short-acting benzodiazepines, intermediate-acting benzodiazepines, long-acting benzodiazepines) were included, limiting comparisons to 'eszopiclone versus placebo'. Eszopiclone and placebo were provided as home treatment; three of the 14 RCTs (Fava 2006; McCall 2010a; Zammit 2004), additionally included overnight stays in the sleep laboratory. All studies but three Goforth 2014, McCall 2010a, Menza 2010 were based on multicentre designs, including 43 (Roth 2009), and up to 82 (Ancoli-Israel 2010), participating study centres. Thirteen RCTs were undertaken in the United States, and one trial in Canada (Soares 2006) Follow-up after drug discontinuation was considered in ten RCTs, of which seven applied single-blind placebo run-out periods (2 days Zammit 2004, 7 days Roth 2009; Soares 2006 and 14 days Ancoli-Israel 2010; Fava 2006; Pollack 2008; Walsh 2007), two open-label extensions (2 weeks Spierings 2015, 6 months Krystal 2003), and one trial with naturalistic follow-up monthly by telephone for four months after randomised treatment (McCall 2010a). There was a single-blind placebo run-in period to establish baseline values for sleep and daytime functioning and to ensure compliance with the dosing regimen preceded treatment in some trials (Ancoli-Israel 2010; Pollack 2008; Roth 2009; Soares 2006).

Sponsoring, initiation and publication

With the exception of two non-profit funded RCTs (McCall 2010a; Pollack 2008), trials included in the review were financially supported by the pharmaceutical industry. Five of the 14 included RCTs were initiated by the investigator (Goforth 2014; Menza 2010; McCall 2010a; Pollack 2008; Spierings 2015), and the remaining nine RCTs by a sponsor. All trials were published as journal articles.

Sample size

Sample sizes varied from 30 (Menza 2010) to 830 participants (Walsh 2007), with most studies including between 150 to 400 participants

(Ancoli-Israel 2010; McCall 2006; Roth 2009; Scharf 2005; Zammit 2004).

Participants: age

In most RCTs included in the review, participants were recruited from young to middle-aged groups (18 to 64 years), three RCTs defined older age (64 and 85 years) as a criterion of inclusion (Ancoli-Israel 2010; McCall 2006; Scharf 2005), while in the trial of Menza 2010, a broader spectrum of age was considered (35 to 85 years). The mean age of participants varied between 40 and 50 years in most studies; in the studies with elderly participants (Ancoli-Israel 2010; McCall 2006; Scharf 2005), mean age was 71.5 years, and in the trial with the broader age range (Menza 2010), mean age of participants was 56 years.

Participants: gender

RCTS were based on mixed-gender samples, apart from one trial testing eszopiclone after menopausal transition (Soares 2006), thus exclusively including only female participants. In mixed-gender samples, females constituted the majority of participants by representing 63% and 67% of the sample. A higher proportion of females was seen in the trials focusing on comorbid rheumatoid arthritis (86.9%; Roth 2009) and migraineurs (82.5%; Spierings 2015), and a lower proportion in the trial with comorbid Parkinson's disease (20%; Menza 2010).

Participants: insomnia diagnosis

Participants of included trials either met DSM-5 or DSM-4-TR criteria for primary insomnia (Ancoli-Israel 2010; Krystal 2003; McCall 2006; Scharf 2005; Spierings 2015; Walsh 2007; Zammit 2004), or DSM-5 criteria for insomnia associated with a comorbid psychiatric or medical condition (Fava 2006; Goforth 2014; McCall 2010a; Menza 2010; Pollack 2008; Roth 2009; Soares 2006).

The study conducted by Spierings 2015, including participants with primary insomnia and suffering migraine, took an intermediate position between primary insomnia studies and comorbidity trials. Total sleep time (TST) was required to be lower than six hours in two studies (Ancoli-Israel 2010; Soares 2006), or 6.5 hours (Fava 2006; Goforth 2014; Krystal 2003; McCall 2006; Menza 2010; Pollack 2008; Roth 2009; Scharf 2005; Spierings 2015; Walsh 2007; Zammit 2004), and wake time after sleep onset (WASO) had to be at least 30 minutes (Fava 2006; Goforth 2014; Krystal 2003; McCall 2006; McCall 2010a; Menza 2010; Pollack 2008; Scharf 2005; Walsh 2007; Zammit 2004), or 45 minutes (Ancoli-Israel 2010; Roth 2009; Soares 2006). Insomnia symptoms had to occur at least three nights per week (Ancoli-Israel 2010; Fava 2006; McCall 2010a; Menza 2010; Pollack 2008; Roth 2009; Scharf 2005; Spierings 2015), on a typical night (Goforth 2014; Walsh 2007), or each night during the last month (Krystal 2003; McCall 2006; Scharf 2005; Zammit 2004).

Participants: comorbidity

Comorbid conditions associated with insomnia included major depression (Fava 2006; McCall 2010a), general anxiety disorder (Pollack 2008), chronic low back pain (Goforth 2014), Parkinson's`s disease (Menza 2010), rheumatoid arthritis (Roth 2009), and complaints in the context of the menopausal transition (Soares 2006). Some trials demanded that comorbid symptoms must either have predated insomnia (Soares 2006; Roth 2009), or postdated insomnia less than four weeks (Goforth 2014) or 10 weeks (Fava 2006). In the remaining studies considering comorbidity, no temporal relationship between insomnia and comorbid disorders was required (McCall 2010a; Menza 2010; Pollack 2008). Individuals with another primary or secondary sleep disorder (e.g. sleep apnea, restless legs syndrome, periodic leg movement disorder) or with a known or suspected acute medical or psychiatric condition that impacted or was likely to impact sleep, were excluded.

A lifetime history of substance abuse or dependence was a criterion of exclusion in five of 14 RCTs (Krystal 2003; Pollack 2008; Soares 2006; Walsh 2007; Zammit 2004), while other studies excluded participants only if substance abuse or dependence occurred within the last 12 months (Goforth 2014), five years (Spierings 2015), or was present at screening (McCall 2010a). Some trials also defined positive urine screening for drugs or alcohol (Fava 2006), drinking more than two standard drinks per day (Krystal 2003; McCall 2006; Scharf 2005; Soares 2006; Spierings 2015; Zammit 2004) or more than 14 drinks per week (Krystal 2003; McCall 2006) as a criterion of exclusion. Even so, four RCTs (McCall 2006; Menza 2010; Roth 2009; Scharf 2005) did not mention substance use or substance use disorders as a criterion of exclusion.

Intervention: comparisons and doses

Twelve of the 14 RCTs used a two-armed design, testing eszopiclone dosed as recommended (3 mg for non-elderly, 2 mg for elderly participants) against placebo, and two RCTs (Scharf 2005; Zammit 2004) compared recommended doses of eszopiclone with lower dose groups (2 mg for non-elderly in Zammit 2004; 1 mg for elderly participants in Scharf 2005) using a three-armed design. From these trials, only the initially recommended dose groups (3 mg for non-elderly, 2 mg for elderly participants) were included in the meta-analytic integration. For home treatment, participants were instructed to take study medication at bedtime, in the sleep laboratory condition (McCall 2006; Zammit 2004), or a single bedtime dose was administered 30 minutes before lights out.

Intervention: comedication

Eszopiclone was coadministered with open-label fluoxetine (starting dose 20 mg; dose range: 20 to 40 mg/day) in participants with coexisting major depressive disorder (Fava 2006; McCall 2010a), open-label escitalopram (10 mg) in participants with comorbid generalised anxiety disorder (Pollack 2008), naproxen (50 mg open-label; twice daily) and lansoprazole (15 mg open-label; once daily) in participants with low back pain (Goforth 2014), open-label hormones for menopause symptoms (Soares 2006) or open-label disease-modifying medications for Parkinson's`s disease (Menza 2010) and rheumatoid arthritis (Roth 2009).

Intervention: treatment duration

Single-blind placebo run-in periods were used to establish baseline values for sleep and daytime functioning and to ensure compliance with the dosing regimen in some trials (Ancoli-Israel 2010; Pollack 2008; Roth 2009; Soares 2006). Duration of treatment with eszopiclone and placebo varied from two weeks (McCall 2006; Scharf 2005) to 24 weeks (Krystal 2003; Walsh 2007), including short-term treatment of insomnia (≤ four weeks; Goforth 2014; McCall 2006; Menza 2010; Roth 2009; Scharf 2005; Soares 2006), medium-term treatment (> four weeks ≤ six months; Ancoli-Israel 2010; Fava 2006; McCall 2010a; Pollack 2008; Spierings 2015; Zammit 2004) and long-term treatment (> six months; Krystal 2003; Walsh 2007). Length of follow-up intervals was two days (Zammit 2004), one week (Roth 2009; Soares 2006) or two weeks (Ancoli-

Israel 2010; Fava 2006; Pollack 2008; Walsh 2007; Spierings 2015) for placebo run-out periods, and four months (McCall 2010a) or six months (Krystal 2003) for open-label or naturalistic follow-up extensions.

Outcomes: sleep efficacy

Sleep efficacy outcomes (SOL, WASO, TST) constituted the primary efficacy endpoints in all but one trial focusing on health-related quality of life (McCall 2010a). Besides latency to persistent sleep (LPS), WASO and TST, Zammit 2004 additionally analysed time and percentage of time spent in the different sleep stages. Sleep efficacy outcomes were either provided as mean change from baseline values (McCall 2006; Pollack 2008; Soares 2006; Scharf 2005) or mean values defined as the average over a defined time interval or the entire double-blind treatment period (Ancoli-Israel 2010; Goforth 2014; Krystal 2003; Menza 2010; Scharf 2005; Spierings 2015; Zammit 2004). Due to the skewed distribution of data, for some trials medians were exclusively (Fava 2006; Roth 2009; Walsh 2007) or additionally reported (Goforth 2014; Krystal 2003; McCall 2006; Pollack 2008; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004). The trial focusing on quality of life (McCall 2010a) reported ß-, SE and t-values for repeated measures mixed modelling. Sleep efficacy outcomes were assessed through participant self-reports in all but three RCTs (McCall 2006; McCall 2010a; Zammit 2004) which included both participant-reported and objective measures of sleep. Objective sleep measures were assessed via polysomnography (PSG) recording during overnight stays in the sleep laboratory (McCall 2006; Zammit 2004) and via actigraphy (McCall 2010a), where participants continuously wore an actigraph unit on their non-dominant wrist for the duration of the study. Participant self-reports on sleep were assessed with paper sleep diaries (Spierings 2015) or electronic sleep diaries (Ancoli-Israel 2010; Pollack 2008; Menza 2010) completed in the morning or with the aid of an interactive voice response system (IVRS; Fava 2006; Krystal 2003; McCall 2006 McCall 2010a; Menza 2010; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004) that had either to be called daily (McCall 2006 McCall 2010a; Menza 2010; Scharf 2005; Soares 2006; Zammit 2004) or weekly (Fava 2006; Krystal 2003; Walsh 2007) in the morning to report the previous night's sleep.

Outcomes: discontinuation effects

Rebound effects, assessed through change from baseline for sleep efficacy outcomes during placebo run-out period, were provided for seven RCTs (Ancoli-Israel 2010; Fava 2006; Pollack 2008; Roth 2009; Soares 2006; Walsh 2007; Zammit 2004). One RCT provided means for change from baseline for each single day during placebo run-out (Ancoli-Israel 2010), the remaining trials either reported median change values (Fava 2006; Pollack 2008; Roth 2009; Walsh 2007; Zammit 2004) or referred to the significance of effects without providing outcome statistics (Soares 2006). Prevalence of new or worsening of adverse events (Pollack 2008; Roth 2009; Soares 2006) or central nervous system-related adverse events (Ancoli-Israel 2010; Fava 2006; Pollack 2008; Zammit 2004) reflecting withdrawal effects were provided by seven RCTs (Ancoli-Israel 2010; Fava 2006; Krystal 2003; Pollack 2008; Roth 2009; Soares 2006; Zammit 2004). In two trials (Ancoli-Israel 2010; Walsh 2007), withdrawal effects were evaluated with the Benzodiazepine Withdrawal Symptom Questionnaire (Tyrer 1990) administered following the discontinuation period.

Outcomes: next-day functioning

Daytime functioning was recorded in the evening with electronic wake diaries (Ancoli-Israel 2010; Pollack 2008; Menza 2010) or by evening calls to the interactive voice response system (Fava 2006; Krystal 2003; McCall 2006 McCall 2010a; Menza 2010; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004). Next-day functioning was rated on an 11-point Likert scale (0 to 10), with higher scores indicating improved functioning (Ancoli-Israel 2010; Krystal 2003; McCall 2006; Menza 2010; Roth 2009; Scharf 2005; Spierings 2015; Zammit 2004, in one RCT (Zammit 2004), next-day residual effects were additionally evaluated with the Digit-Symbol Substitution Test (DSST; Wechsler 1955).

Excluded studies

Thirty-four studies were excluded on the basis of full-text papers. Among reasons for exclusion, insomnia diagnosis not being mandatory for including subjects in the primary study (Attarian 2011; Demanuele 2014; Dimsdale 2011b; Eckert 2011; Lettieri 2008; NCT00460993; NCT00511134; NCT00616655; NCT00685269; NCT00811746; NCT00813735; NCT00826111; NCT01102270; NCT01641900; Tek 2014, Huang 2015) was most common (n = 16). Further reasons for exclusion were the use of a cross-over design (Boyle 2008; Boyle 2012; Erman 2008; NCT00120250; NCT00368056; NCT00374192; NCT00900159; Pollack 2011; Rosenberg 2007; Uchimura 2012a; Uchimura 2012b), an open-label design (Gross 2011; NCT00889200; NCT00900159; NCT01710631; Peng 2013), the inclusion of healthy subjects passing through a model of transient insomnia (Rosenberg 2005) and younger age participants (< 18 years) (Sangal 2014). Individual trials excluded from the review and the corresponding reasons for exclusion are outlined under Characteristics of excluded studies.

Ongoing studies

Searches in registry databases (WHO trials portal; ClinicalTrials.gov) (to February 2016) yielded one trial (Emiko 2015) in the stage of 'currently recruiting', which seemed to meet the inclusion criteria of the review. In this randomised study, conducted at the School of Medicine at Nihon University, efficacy and safety of eszopiclone was examined for the treatment of insomnia complicated with nocturnal awakenings. The other ongoing study, under consideration after the update search in February 2018, was (NCT02456532).

Studies awaiting classification

A total of six studies have been identified as 'awaiting classification'.

The search in February 2016 identified four RCTs (NCT00392041; NCT00435279; NCT00374556; Pinto 2016/NCT01100164) with a completed or unknown recruitment status in registry databases (WHO trials portal; ClinicalTrials.gov); no study publications were identified at this time. Accordingly, eligibility of the trials could not be conclusively assessed on the basis of published materials and requests to investigators. These studies included RCTs on eszopiclone in the treatment of insomnia associated with fibromyalgia (NCT00392041), with major depressive disorder (NCT00435279), with osteoarthritis (NCT00374556), and of primary insomnia according to DSM-4 (Pinto 2016). Accordingly, the eligibility of the studies will be checked again in updates of the review.

The update search in February 2018 identified a further two studies awaiting classification (Baran 2017) and (Buxton 2017) (see Results of the search).

Risk of bias in included studies

For details of the risk of bias judgements for each study, see Characteristics of included studies. Graphical representations of the overall risk of bias in included studies are presented in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

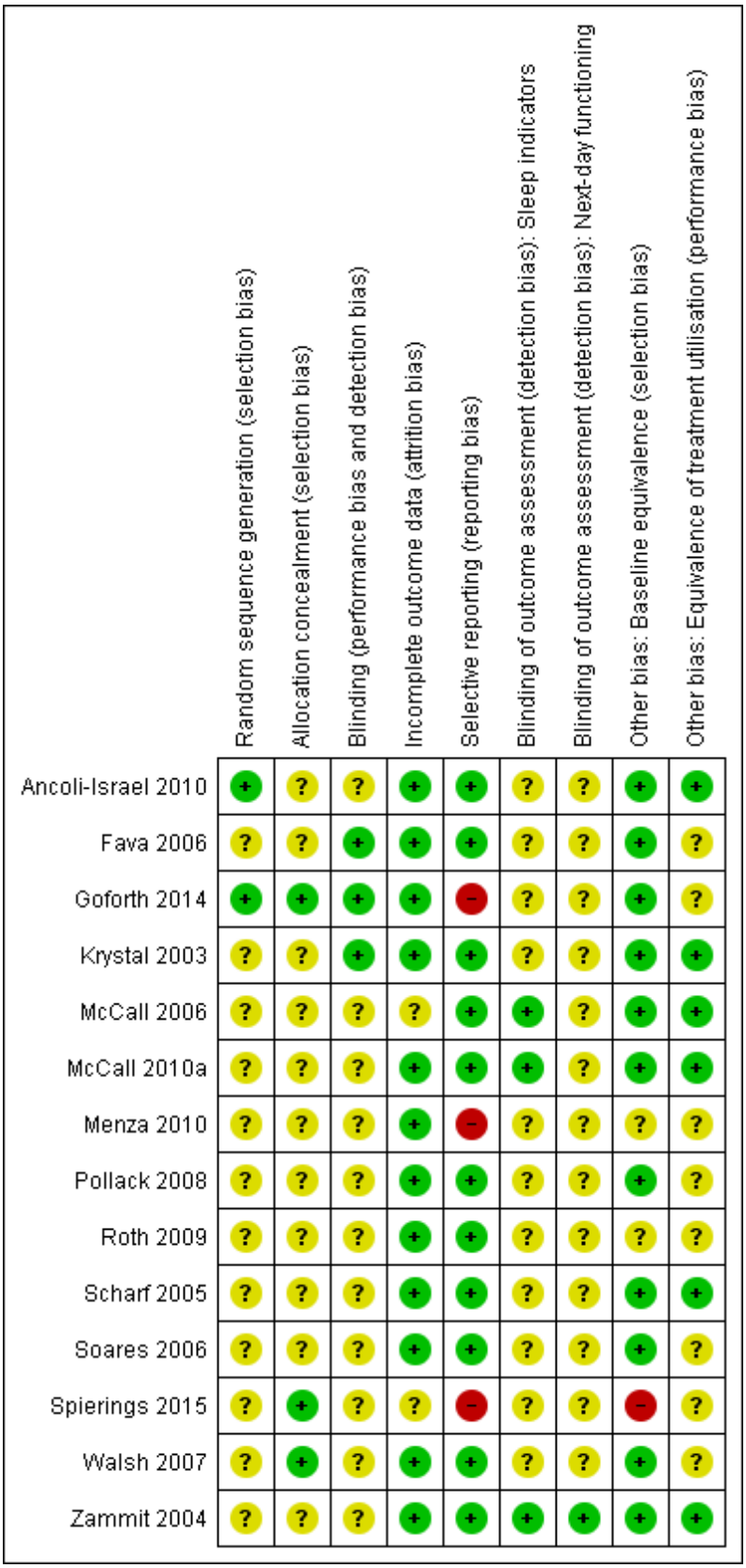
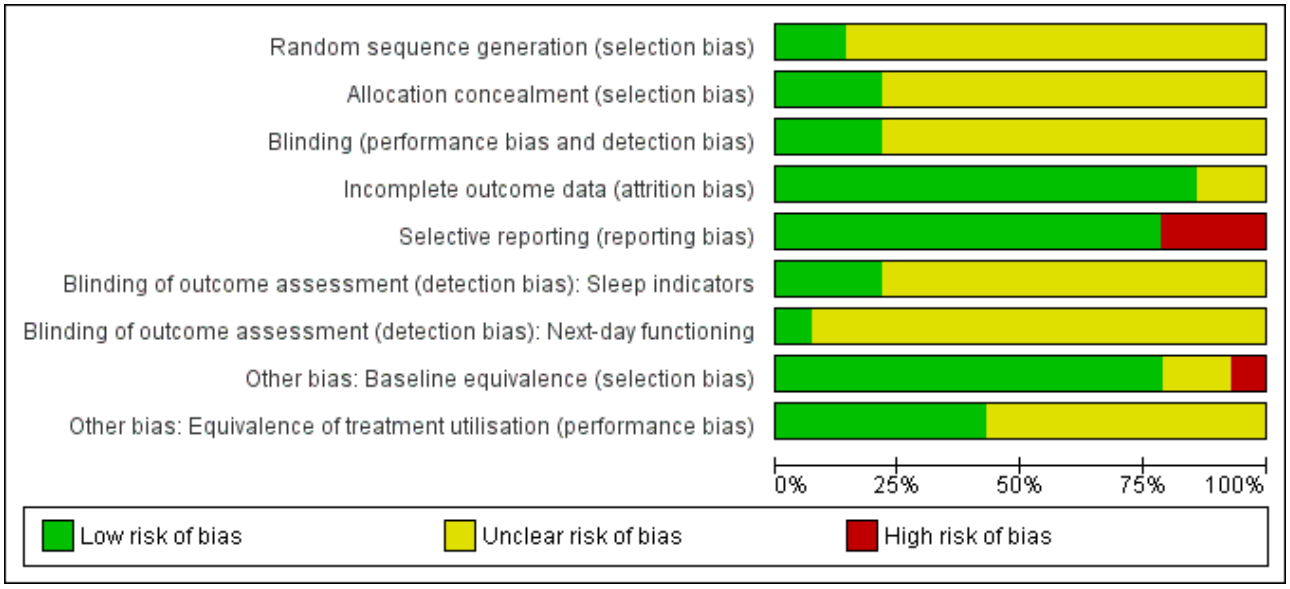


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

Methods used for sequence generation were specified in two RCTs (Ancoli-Israel 2010; Goforth 2014), describing the generation of the random allocation schedule as being based on an internet randomisation system (Ancoli-Israel 2010) and a computer-driven pseudo-random number generator (Goforth 2014). Accordingly, methods used for sequence generation were rated as being adequate in two RCTs (Ancoli-Israel 2010; Goforth 2014) and unclear for the remaining 12 studies.

Allocation concealment

Randomisation was described as centralised and conducted by an independent support unit remote from participant recruitment centres in three RCTs (Goforth 2014; Spierings 2015; Walsh 2007). Goforth 2014 additionally reported that drug capsules were supplied by the sponsor in sequentially numbered pill containers and that the random allocation sequence was only provided to the investigators after all subjects had completed the study. The remaining 11 RCTs did not specify methods used for allocation concealment. Applying our criteria for adequate allocation concealment (centralised drug preparation performed remote from the participant recruitment), risk of bias in the randomisation process was rated as being low in three of 14 RCTs (Goforth 2014; Spierings 2015; Walsh 2007).

Baseline equivalence

Baseline equivalence for age, gender, and indicators of sleep initiation and maintenance are were confirmed in 10 of 14 RCTs (Ancoli-Israel 2010; Fava 2006; Goforth 2014; Krystal 2003; McCall 2006; McCall 2010a; Pollack 2008; Scharf 2005; Soares 2006; Walsh 2007) and in one trial (Zammit 2004), gender differences between treatment groups were detected, but adequately controlled in the statistical analyses. In all RCTs including insomnia associated with comorbid conditions, baseline equivalence for comorbid symptoms was tested and confirmed (Fava 2006; Goforth 2014; McCall 2010a; Pollack 2008; Roth 2009; Soares 2006) or, if differences were shown (Menza 2010), these were controlled in the statistical analyses. All in all, three RCTs did not fulfil our criteria for baseline equivalence (baseline equivalence or control for age, gender, sleep initiation, sleep maintenance, and comorbidity), including two RCTs (Menza 2010; Roth 2009), which did either not provide information on gender or baseline sleep initiation and one RCT (Spierings 2015) identifying a significant group difference for sleep latency at baseline, which was not reported to be controlled.

Blinding

Blinding integrity was described as being tested and confirmed in one trial (Goforth 2014), and two trials (Fava 2006; Krystal 2003) tested adherence and treatment success of participants who perceived an unpleasant taste and found consistent results for the entire sample. Accordingly, the risk of unmasking blinding was rated as being low in three RCTs (Fava 2006; Goforth 2014; Krystal 2003), while for the remaining 11 RCTs, the risk was judged as being uncertain.

Incomplete outcome data

Two RCTs included in the review did not provide information on the principles of analysis used in the study (McCall 2006) or applied further criteria such as compliance at least five days per week for the first two weeks (Spierings 2015). For the remaining 12 of 14 RCTs, it was reported that statistical analyses were conducted according to the intention-to-treat principle, analysing all randomised participants (Krystal 2003; McCall 2010a; Menza 2010; Soares 2006) or those who have received at least one dose of treatment (treatment-received analysis; Ancoli-Israel 2010; Fava 2006; Goforth 2014; Pollack 2008; Roth 2009; Scharf 2005; Walsh 2007; Zammit 2004) in the group they had been allocated to by randomisation. When analysing the ITT (intention-to-treat) population comprising all randomised participants, the last-observation-carried-forward (LOCF) technique was used to impute missing data in seven studies (Ancoli-Israel 2010; Fava 2006; Goforth 2014; Krystal 2003; McCall 2010a; Pollack 2008; Walsh 2007). All in

all, 12 of 14 RCTs (Krystal 2003; McCall 2010a; Menza 2010; Soares 2006; Ancoli-Israel 2010; Fava 2006; Goforth 2014; Pollack 2008; Roth 2009; Scharf 2005; Walsh 2007; Zammit 2004) met our criteria for an adequate handling of incomplete outcome data.

Selective reporting

Outcomes listed in the methods section were adequately reported and properly interpreted in all but one trial (Spierings 2015), which mentioned TST during the run-out period as a secondary outcome in the methods section, but did not provide results in the result section. All trials included in the review considered both indicators of sleep induction and sleep maintenance as primary or secondary endpoints. Nevertheless, outcome diversity was limited in two trials (Goforth 2014; Menza 2010), which had a study duration assumed to be sufficient to conclusively assess withdrawal and rebound insomnia, while these variables had not been assessed or at least reported as being assessed. Accordingly, 11 of 14 RCTs (Ancoli-Israel 2010; Fava 2006; Krystal 2003; McCall 2006; McCall 2010a; Pollack 2008; Roth 2009; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004) fulfilled our criteria of adequate outcome reporting and outcome diversity.

Other potential sources of bias

Performance bias

Nine of 14 RCTs tested and confirmed the equivalence of medication compliance between groups (Ancoli-Israel 2010; Fava 2006; Krystal 2003; McCall 2006; McCall 2010a; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004), while the remaining five RCTs (Goforth 2014; Menza 2010; Pollack 2008; Roth 2009; Spierings 2015) did not provide such information. With the exception of one trial (Goforth 2014), studies permitting comedication for comorbid conditions tested and confirmed the equivalence of medication for comorbid conditions between groups (Fava 2006; McCall 2010a; Menza 2010; Pollack 2008; Roth 2009; Soares 2006; Spierings 2015); in two of the comorbidity studies with the option of dose titration for antidepressive comedication (Fava 2006; McCall 2010a), differences in titrations were tested between groups. The use of further medication was allowed in some studies (Ancoli-Israel 2010; Fava 2006; Menza 2010; Roth 2009; Scharf 2005; Walsh 2007); three of these (Ancoli-Israel 2010; Roth 2009; Scharf 2005) compared the use of concomitant medication and confirmed the equivalence between groups. All trials including elderly participants (Ancoli-Israel 2010; McCall 2006; Scharf 2005) compared daytime napping between groups to control for the occurrence of compensatory sleep. Applying all criteria for an equivalent treatment utilisation (equivalence of medication compliance, use of further medications and daytime napping) simultaneously, six of 14 RCTs (Ancoli-Israel 2010; Krystal 2003; McCall 2006; McCall 2010a; Scharf 2005; Zammit 2004) were rated to have a low risk of performance bias.

General susceptibility to bias

Eleven of 14 RCTs assessed sleep efficacy outcomes exclusively on the basis of participant reports using an electronic sleep diary (Ancoli-Israel 2010; Pollack 2008; Menza 2010), paper sleep diary (Spierings 2015), or interactive voice response system (IVRS; Krystal 2003; McCall 2006 McCall 2010a; Menza 2010; Scharf 2005; Soares 2006; Walsh 2007; Zammit 2004), while three RCTs McCall 2006; McCall 2010a; Zammit 2004) combined self-report measures with polysomnography (PSG) (McCall 2006; McCall 2010a; Zammit 2004) and actigraphy recording (McCall 2010a). Thus, susceptibility to bias effects for sleep outcomes was rated as being low for three of 14 RCTs (McCall 2006; McCall 2010a; Zammit 2004) and as being uncertain for the remaining 11 RCTs (Ancoli-Israel 2010; Fava 2006; Goforth 2014; Krystal 2003; Menza 2010; Pollack 2008; Roth 2009; Scharf 2005; Soares 2006; Spierings 2015; Walsh 2007). With the exception of one RCT (Zammit 2004), which assessed next-day functioning by self-reports and the Digit-Symbol Substitution Test (DSST), RCTs included in the review measured functioning during the next day on the basis of participant reports. Accordingly, susceptibility to bias effects for next-day functioning was rated as being low in Zammit 2004 and as being uncertain in the remaining 13 RCTs (Ancoli-Israel 2010; Fava 2006; Goforth 2014; Krystal 2003; McCall 2006; McCall 2010a; Menza 2010; Pollack 2008; Roth 2009; Scharf 2005; Soares 2006; Spierings 2015; Walsh 2007).

Publication bias

By plotting of the mean differences against their standard error for the primary efficacy outcomes SOL (Figure 4) and WASO (Figure 5), we did not identify asymmetry, but note that the interpretation of funnel plot graphs was impeded by the small number of included studies, limiting the conclusiveness of the funnel plot method.

Figure 4. Funnel plot of comparison: 1 Eszopiclone versus placebo, outcome: 1.1 Sleep onset latency (SOL).

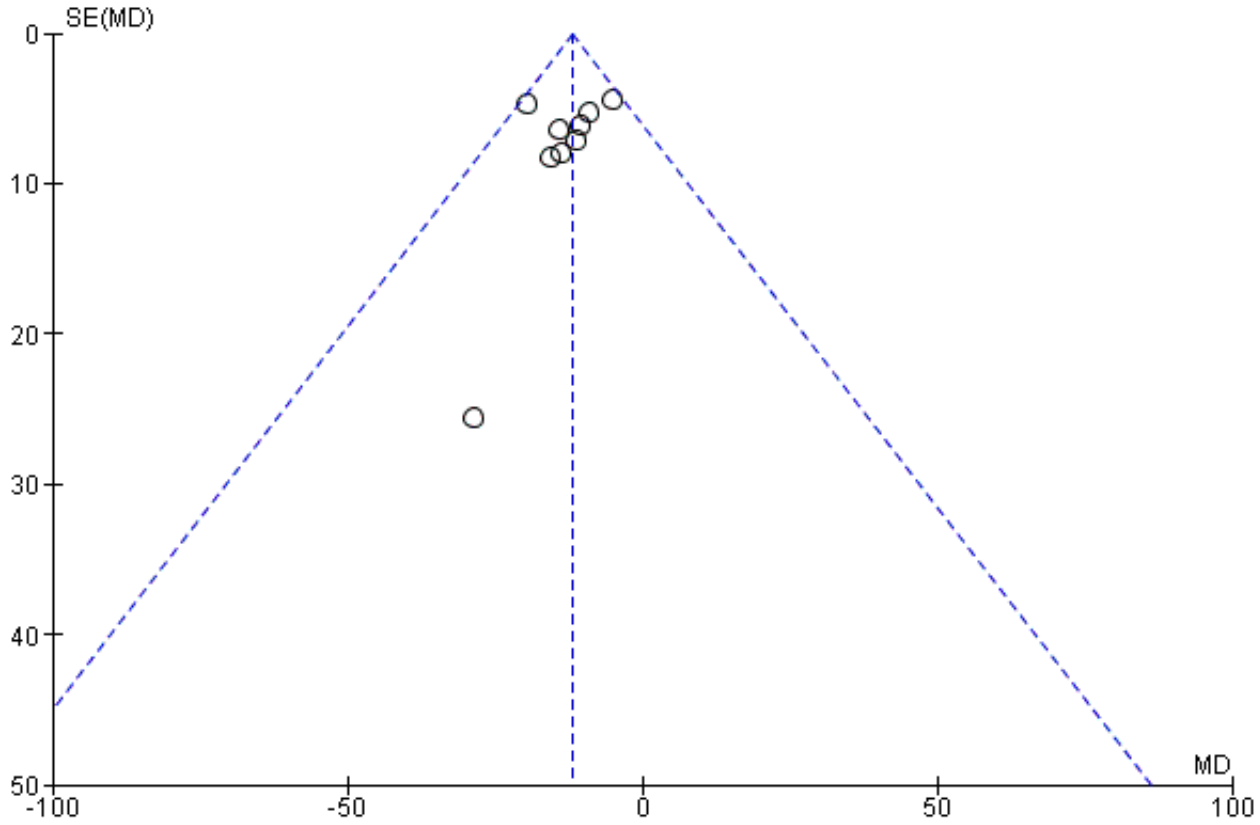
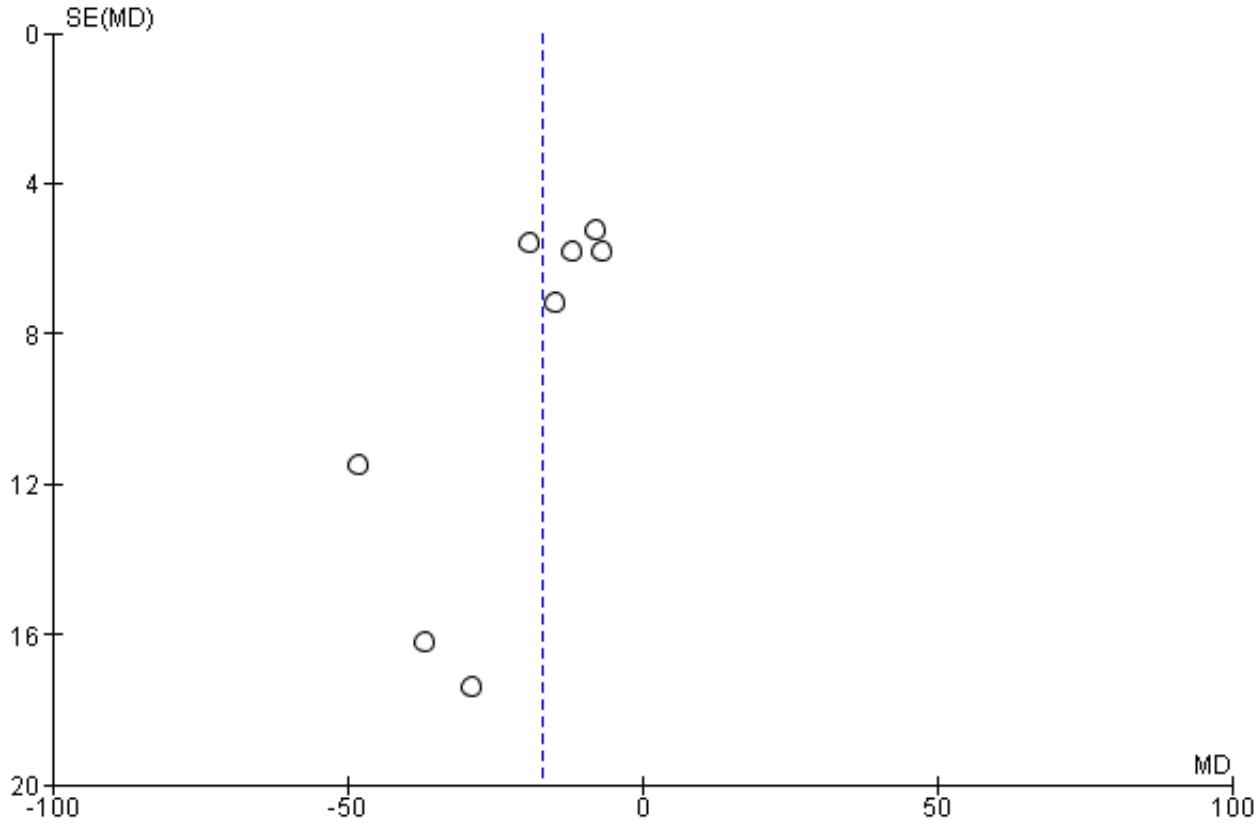


Figure 5. Funnel plot of comparison: 1 Eszopiclone versus placebo, outcome: 1.2 Wake time after sleep onset (WASO).



Effects of interventions

See: **Summary of findings for the main comparison** Eszopiclone for insomnia

Comparison 1: Eszopiclone versus placebo

Of 14 RCTs included in the review, 13 RCTs contributed to the meta-analysis. One RCT (McCall 2010a) provided statistics for repeated measures mixed model analyses, which could not be integrated into meta-analyses. From the two RCTs using a three-armed design (Scharf 2005; Zammit 2004), only the study arms with eszopiclone under recommended dosing (3 mg for non-elderly, 2 mg for elderly participants) and placebo were included. Results for the primary and secondary outcomes of the review are described below and outlined for the most important findings in the Summary of findings for the main comparison.

Primary outcomes

1.1 Sleep onset latency (SOL)

Meta-analyses of participant-reported data show that eszopiclone significantly decreased length of time after lights-out until sleep by approximately 12 minutes (Mean Difference (MD) -11.94 min, 95% confidence interval (CI) -16.03 to -7.86; participants = 2890; studies = 9; I^2 = 0%; moderate quality evidence; Analysis 1.1) compared to placebo.

1.2 Wake time after sleep onset (WASO)

Compared to placebo, eszopiclone significantly reduced participant-reported wake time after sleep onset by about 17 minutes (MD -17.02 min, 95% CI -24.89 to -9.15; participants = 2295; studies = 8; I^2 = 55%; moderate quality evidence; Analysis 1.2).

1.3 Withdrawal symptoms

Following drug discontinuation during single-blind placebo run-out periods, a total of 22 new or deteriorated adverse events were documented from seven RCTs with 3125 participants (Analysis 1.3). The overall risk of being affected by withdrawal symptoms did not differ between the eszopiclone and the placebo group (RD 0.00, 95% CI -0.03 to 0.04; participants = 2103; studies = 5; I^2 = 42%). Accidental injury, agitation, anxiety, back pain, dizziness, headache, nausea, pharyngitis, and pain were listed in more than one study, with headache being the most frequently reported symptom (RD 0.00, 95% CI -0.01 to 0.01; participants = 2237; studies = 6; I^2 = 0%; Analysis 1.3). Nevertheless, for the 22 adverse events reported during the single-blind placebo run-out, the risk difference was not shown to significantly differ between groups.

1.4 Rebound insomnia

Mean change from baseline values for the primary efficacy outcomes SOL (MD 17.00 min, 95% CI -4.29 to 38.29; participants = 291; studies = 1; I^2 and T^2: not applicable; low quality evidence) and WASO (MD -6.71, 95% CI -21.25 to 7.83; participants = 291; studies = 1; I^2 and T^2: not applicable; low quality evidence) averaged

over the first three nights of the single-blind run-out period did not indicate worsening of sleep after drug discontinuation (Analysis 1.4). Negative signs of change from baseline values, shown for each single night during the discontinuation period in the eszopiclone group as well as the placebo group (data not shown), indicated that hypnotic efficacy measures improved after treatment, irrespective of treatment condition.

Secondary outcomes

1.5 Total sleep time (TST)

Compared to placebo, eszopiclone significantly increased total sleep time by about 28 minutes (MD 27.70 min, 95% CI 20.30 to 35.09; participants = 2965; studies = 10; I^2 = 39%; moderate quality evidence; Analysis 1.5).

1.6 Next-day alertness

Meta-analytic results showed that next-day alertness during double-blind treatment was rated as being significantly higher in the eszopiclone than in the placebo group (MD 0.46, 95% CI 0.28 to 0.63; participants = 2061; studies = 8; I^2 = 31%; low quality evidence; Analysis 1.6).

1.7 Adverse events

Compared to participants in the placebo group, participants treated with eszopiclone did not significantly differ in their risk of dropping out from treatment due to adverse events (RD 0.01, 95% CI -0.01 to 0.02; participants = 4007; studies = 11; I^2 = 52%; moderate quality evidence; Analysis 1.7). Among a total of 34 adverse events, headache (n = 10), unpleasant taste (n = 9) and somnolence (n = 8) were most commonly reported, followed by accidental injury and dizziness (n = 7) as well as and back pain and dry mouth (each reported in six RCTs). Significant risk differences were demonstrated for unpleasant taste (RD 0.18, 95% CI 0.14 to 0.21; NNTH = 5.6, 95% CI 4.8 to 7.1; participants = 3787; studies = 9; I^2 = 72%), dry mouth (RD 0.04, 95% CI 0.02 to 0.06; NNTH = 25, 95% CI 16.7 to 50.0; participants = 2802; studies = 6; I^2 = 11%), somnolence (RD 0.04, 95% CI 0.02 to 0.06; NNTH = NNTH = 25, 95% CI 16.7 to 50.0; participants = 3532; studies = 8; I^2 = 10%) and dizziness (RD 0.03, 95% CI 0.01 to 0.05; NNTH = 33.3, 95% CI 20.0 to 100.0; participants = 2933; studies = 7; I^2 = 48%).

Serious adverse events occurred in eight of 12 RCTs (Ancoli-Israel 2010; Fava 2006; Krystal 2003; McCall 2006; Pollack 2008; Roth 2009; Scharf 2005; Walsh 2007). There was no significant difference between groups in the occurrence of serious adverse events (RD 0.00, 95% CI -0.01 to 0.01; participants = 4289; studies = 12; I^2 = 0%; T^2 = 0.00). Serious adverse events observed in the eszopiclone groups included suicide and death due to arteriosclerotic heart disease (Ancoli-Israel 2010), anxiety and confusion (Fava 2006), gastrointestinal disorder (Krystal 2003), moderate to severe chest pain (Krystal 2003; Roth 2009; Scharf 2005), accidental injury due to a fall (McCall 2006), asthma, cholelithiasis, concussion with multiple fractures and loss of consciousness (Pollack 2008) and cerebrovascular accident (Walsh 2007). With the exception of one RCT, in which serious adverse events in 0.34% of participants (2/593) taking eszopiclone over the 6-month treatment were considered to be “possibly related” to therapy (Krystal 2003), serious adverse events in further trials were not considered by the investigators to be treatment-related. Also, where accidental injury due to a fall occurred two days after the end of treatment (McCall 2006) or due to slipping on a wet floor in the late afternoon (Pollack 2008), investigators classified these serious events as unrelated to treatment.

Subgroup analyses

Primary versus comorbid insomnia

Subgroup analyses for different types of insomnia showed significant effects for eszopiclone in samples with primary insomnia (SOL: MD -15.14 minutes, 95% CI -21.13 to -9.15; participants = 1803; studies = 5; I^2 = 0%; WASO: MD -15.76 min, 95% CI -25.60 to -5.92; participants = 1803; studies = 5; I^2 = 68%; TST: MD 30.04 min, 95% CI 19.09 to 40.98; participants = 1878; studies = 6; I^2 = 52%) and comorbid insomnia as well (WASO: MD -21.20 min, 95% CI -40.76 to -1.65; participants = 462; studies = 2; I^2 = 36%; TST: MD 23.37 min, 95% CI 12.61 to 34.12; participants = 462; studies = 2; I^2 = 0%), except for SOL, which did not reach statistical significance in the comorbid insomnia sample (SOL: MD -8.10 min, 95% CI -17.77 to 1.57; participants = 462; studies = 2; I^2 = 24%).

Sleep efficacy outcomes, separately analysed for primary insomnia and comorbid insomnia subgroups, are shown in Analysis 1.8 for SOL, Analysis 1.9 for WASO, and Analysis 1.10 for TST.

Young to middle-aged versus older age

Analyses for the subgroups of young to middle-aged and older age individuals demonstrated significant effects in samples aged between 18 to 64 years (SOL: MD -13.08 minutes, 95% CI -19.15 to -7.00; participants = 2049; studies = 5, I^2 = 25%; WASO: MD -12.20 minutes, 95% CI -19.02 to -5.37; participants = 1454; studies = 4; I^2 = 5%; TST: MD 29.66 minutes, 95% CI 21.60 to 37.72; participants = 2124; studies = 6; I^2 = 30%) and samples with an age over 64 years (SOL: MD -11.41 minutes, 95% CI -20.37 to -2.45; participants = 811; studies = 3; I^2 = 0%; WASO: MD -22.16 minutes, 95% CI -40.70 to -3.63; participants = 811; studies = 3; I^2 = 81%; TST: MD 27.01 minutes, 95% CI 11.83 to 42.18; participants = 811; studies = 3; I^2 = 49%). Sleep efficacy outcomes separately analysed for different age subgroups are shown in Analysis 1.8 for SOL, Analysis 1.9 for WASO, and Analysis 1.10 for TST.

Next-day alertness was significantly increased by 0.56 points on the 11-point Likert scale in young to middle-aged individuals (MD 0.56, 95% CI 0.37 to 0.75; participants = 1220; studies = 4; I^2 = 0%) and 0.34 points in the elderly (MD 0.34, 95% CI 0.01 to 0.67; participants = 811; studies = 3; I^2 = 58%). Analyses of serious adverse events, limited to the subgroup of elderly participants, did not show a difference between the eszopiclone and placebo condition (RD 0.00, 95% CI -0.01 to 0.02; participants = 804; studies = 3; I^2 = 58%). Serious adverse events in the elderly included suicide and death due to arteriosclerotic heart disease (Ancoli-Israel 2010), moderate to severe chest pain (Scharf 2005) and accidental injury due to a fall, which occurred two days after the end of treatment (McCall 2006) and was classified by the investigator as unrelated to treatment. Compared to participants in the placebo group, elderly participants treated with eszopiclone did not significantly differ in their risk of dropping out from treatment due to adverse events (RD -0.00, 95% CI -0.03 to 0.03; participants = 811; studies = 3; I^2 = 30%). Among a total of 19 adverse events reported in participants aged over 64 years, significant risk differences were demonstrated for unpleasant taste (RD 0.11, 95% CI 0.08 to 0.15; participants = 811;

studies = 3; I^2 = 0%), dry mouth (RD 0.07, 95% CI 0.02 to 0.12; participants = 264; studies = 1), and dizziness (RD 0.03, 95% CI 0.01 to 0.06; participants = 652; studies = 2; I^2 = 0%). For an overview of adverse events analyses in elderly subgroups, see Analysis 1.15.

Study initiation

Subgroup analyses for type of study initiation showed significant effects in investigator-initiated trials (SOL: MD -8.29 minutes, 95% CI -14.24 to -2.34; participants = 677; studies = 3; I^2 = 0%) (WASO: MD -33.29 minutes, 95% CI -56.47 to -10.10; participants = 82; studies = 2; I^2 = 0%) and sponsor-initiated trials (SOL: MD -15.21 min, 95% CI -20.83 to -9.59; participants = 2213; studies = 6; I^2 = 0%) (WASO: MD -15.31 min, 95% CI -23.50 to -7.11; participants = 2213; studies = 6; I^2 = 61%) (TST: MD 28.40 min, 95% CI 19.60 to 37.21; participants = 2288; studies = 7; I^2 = 48%), except for TST, which was not significant in investigator-initiated trials (TST: MD 21.04 minutes, 95% CI -4.19 to 46.27; participants = 677; studies = 3; I^2 = 41%).

Sleep efficacy outcomes, separately analysed for sponsor-initiated versus investigator-initiated, are shown in Analysis 1.16 for SOL, Analysis 1.17 for WASO and Analysis 1.18 for TST.

Sensitivity analyses

Assessment of sleep outcomes

Effect estimates based on objective assessment methods such as polysomnography and actigraphy were slightly lower in their magnitude (SOL: MD -15.50 min, 95% CI -19.89 to -11.11; participants = 468; studies = 2; WASO: MD -12.37 min, 95% CI -18.61 to -6.13; participants = 468; studies = 2; I^2 = 0%) (TST: MD 28.60 min, 95% CI 18.14 to 39.06; participants = 264; studies = 1) than participant-reported outcomes, while still reaching statistical significance. Accordingly, the demonstration of effects of eszopiclone on sleep efficacy outcomes did not seem to depend on type of measurement (Analysis 1.19).

Assessment of withdrawal

Withdrawal assessed with the BWSQ scale (SMD -0.06, 95% CI -0.26 to 0.14; participants = 1218; studies = 2) did not indicate a significant difference between the eszopiclone and placebo group, confirming the findings on reported events (Analysis 1.20).

DISCUSSION

Summary of main results

A total of 14 RCTs with 4732 participants were included in this review. Most RCTs included in the review covered short-term (≤ four weeks; six RCTs) and medium-term treatment with eszopiclone (> four weeks ≤ six months; five RCTs), with three RCTs having a treatment duration of 12 months or more. Eszopiclone was provided in a dose of 3 mg for non-elderly and 2 mg for elderly individuals.

Meta-analyses of participant-reported data on sleep efficacy outcomes demonstrated a 12-minute decrease of SOL, a 17-minute decrease of WASO and an approximate 28-minute increase of TST for eszopiclone compared to placebo. There were no significant changes from baseline to the first night after drug discontinuation for SOL and WASO in the majority of trials and no significant differences between groups in the prevalence of new or worsening adverse events. Participant-reported data also indicated that next-day alertness significantly improved under eszopiclone compared to placebo, while adverse events, documented significantly more frequently under eszopiclone compared to placebo, included unpleasant taste, dry mouth, somnolence, and dizziness.

Subgroup analyses indicated that eszopiclone improved most sleep efficacy outcomes irrespective of insomnia type (primary and comorbid insomnia), age groups (young to middle-aged and elderly individuals) and study initiation (investigator initiation and sponsor initiation). The statistical and qualitative integration of evidence from RCTS indicated moderate, but robust, therapeutic effects of eszopiclone on sleep efficacy outcomes. Nevertheless, safety should be determined on the base of individual risk patterns and monitored closely during treatment.

When counterbalancing risks against benefits, a half an hour increase of sleep time per night might not seem much at first glance. However, it represents a mean value averaged over nights of poor sleep and good nights` sleep, both contributing to the night-to-night variability of sleep in insomniacs (Valieres 2005). A limitation of eszopiclone intake to nights of poor sleep according to 'treatment as needed' can be expected to clearly exceed demonstrated effects. Intermittent dosing or 'treatment as needed' with eszopiclone might be an alternative to daily scheduled treatment and bring about advantages in terms of habituation and discontinuation effects that has to be tested in further trials.

Overall completeness and applicability of evidence

Through including insomnia as a primary or a comorbid condition, the review concerns a wide range of insomniac problems and approximates the distribution of insomniac conditions in the general population (Katz 1998). In addition, with a mean age between 40 and 50 years and the percentage of women varying between 63% and 67%, the distribution of age and gender in the primary studies corresponds with the larger insomnia population (Delahaye 1990; Zammit 2004). Contextual factors, such as length of treatment and comedications use, further contribute to the variety of treatment conditions. Nevertheless, due to reasons of safety and accessibility, certain subgroups of individuals might be underrepresented in clinical studies with eszopiclone. This concerns elderly participants with cognitive and psychomotor impairments, shown to have an increased risk for falls, serious injury, and hip fractures (Berry 2013) and individuals with substance use disorder, who might be at increased risk of using eszopiclone in an unrecommended way. Further limitations in the external validity might arise from the cultural context of clinical research. With the exception of one trial (Soares 2006), study sites were exclusively located in the United States. Even though post hoc analyses of studies with eszopiclone indicated the generalisability of findings across different ethnicities (McCall 2006), cultural differences in values, norms, and health-related beliefs might play a role in treatment utilisation, length of use, dosing, and compliance. With placebo as a comparator, integrated evidence on eszopiclone is only applicable to therapeutic decisions that concern eszopiclone versus 'no treatment', while for recommendations concerning the relative efficacy and safety of eszopiclone compared to other available interventions, no direct evidence is available.

All in all, the nonrestrictive definition of inclusion criteria in terms of comorbidity, gender, age, and treatment conditions contributes to the external validity of the review and increases the

applicability of findings to everyday clinical practice. Limitations in the variability of participant characteristics and treatment conditions originating from the cultural context, criteria of inclusion, differences in accessibility to clinical research and the monitoring of treatment implementation in clinical trials, have to be taken into consideration when determining the applicability of evidence. Thus, a weighting of risks and benefits for prescribing eszopiclone has always been made against the background of individual participant characteristics, particularly those associated with a patients' vulnerability to adverse events and those influencing medication-taking behaviour. As placebo was the only comparator considered in RCTs with eszopiclone, available evidence did not allow conclusions on the superiority or inferiority of eszopiclone compared to alternative therapeutic options.

Quality of the evidence

Applying GRADE criteria for down- and upgrading the quality of evidence, we rated the overall quality as being moderate for sleep efficacy outcomes and adverse events and as being low for rebound effects and next-day functioning. We downgraded quality to moderate because of threats to bias resulting from incomplete reporting of certain design features and unmatched taste of eszopiclone. Downgrading quality of evidence for rebound insomnia to a low grade was based on the poor study design of most studies for assessing discontinuation effects, while for next-day functioning, the assumed inadequacy of subjective reporting for representing clinically relevant qualities of functioning caused downgrading of the evidence. Thus, due to methodological limitations, such as the open-label design of run-out intervals in some trials and a potential lack of sensitivity to subjective measures for detecting psychomotor and cognitive impairments, safety conclusions of the review concerning rebound insomnia and next-day functioning might be of limited validity. Quality rating for each outcome is shown in the summary of findings table (Summary of findings for the main comparison), and the rating of single GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision, publication bias) is outlined in detail in the following.

Risk of bias: efficacy outcomes

Various design characteristics of the RCTs included in the review ensured the methodological quality of evidence. Most studies (12 of 14 RCTs) stated that participants were randomly assigned to treatment groups to prevent selection bias and to ensure equivalence between groups at baseline, and treatment and placebo groups were compared for age, gender and for indicators of sleep initiation and sleep maintenance (11 of 14 RCTs). All participants, or at least those who have received at least one dose of treatment, were analysed in the group they had been allocated to by randomisation (12 of 14 RCTs) to avoid attrition bias, while the risk of performance bias was limited by ensuring the equivalence between groups in the use of concomitant medication for comorbid disorders (seven of eight RCTs), in the use of substances with a secondary effect on sleep (three of six RCTs) and in medication compliance (nine of 14 RCTs). In addition, all RCTs including elderly participants compared treatment groups for daytime napping to control the occurrence of compensatory sleep as a further risk of performance bias. Outcomes listed in the method sections were adequately reported and properly interpreted and all RCTs included in the review considered both indicators of sleep induction and sleep maintenance as endpoints of the statistical analyses at the same time.

Despite these measures, some uncertainties persisted. Since specific features of the study design were omitted from most trial reports, it remained unclear whether these had not been implemented or whether these had been implemented, but not reported. Frequently omitted information concerned the specification of methods used for sequence generation, allocation concealment, and blinding procedures. Unclear concealment, has repeatedly been shown to be associated with bias effects in various fields of clinical research (Huwiler-Muntener 2002; Pildal 2007; Schulz 1995). In addition, subject-specific threats to bias might have arisen from eszopiclone`s unpleasant taste, which was reported by a considerable proportion of participants treated with eszopiclone (see Table 2). Drug characteristics, revealing the identity of medication to participants or investigators and their impact on estimates of efficacy, have strikingly been shown in the example of antidepressants drugs (Moncrieff 2004). Even though perception of unpleasant taste has not been significantly associated with treatment adherence or success in selected studies (Fava 2006; Krystal 2003), the evidence removed all doubts. Accordingly, we downgraded the quality of evidence to a moderate degree for sleep efficacy outcomes and adverse events.

Risk of bias: rebound effects

For rating the quality of evidence on discontinuation effects, methodological features of the interval subsequent to the randomised controlled treatment period were taken into consideration. Seven of the 12 RCTs exceeding the threshold duration of two weeks for assessing discontinuation effects applied a single-blind placebo run-out period to assess change from baseline for sleep efficacy outcomes, while the remaining five RCTs (with a duration > two weeks) applied open-label extensions, naturalistic follow-up, or no follow-up. Considering the latter as not being appropriate for controlling bias effects, we downgraded the quality of evidence for rebound insomnia outcomes to a low degree.

Inconsistency

Even though some inconsistency of results has been shown for the primary efficacy outcome WASO, heterogeneity appeared to be mainly attributable to one trial (Scharf 2005), whose exclusion resulted into a I^2 reduction from 55% to 6%. Additionally, considering the low to moderate heterogeneity of results shown for further outcomes of the review (SOL: 0%; serious adverse events: 0%; TST: 31%; next-day alertness: 31%), consistency of results was considered as not being serious.

Indirectness

With placebo as a comparator, integrated evidence on eszopiclone was only applicable to therapeutic decisions that concerned eszopiclone versus 'no treatment', while for recommendations concerning the relative efficacy and safety of eszopiclone compared to other available interventions, no direct evidence was available. On the other hand, study samples, features of the therapeutic interventions (duration, dosing, etc.), and outcomes of the RCTs included in the review contributed to the directness of evidence in terms of population, intervention, comparator and efficacy outcomes, not raising considerable uncertainty about the applicability of the evidence to the relevant questions of

daily practice. Thus, we did not rate limitations in directness of evidence as being serious for sleep efficacy outcomes and discontinuation effects. In contrast, we downgraded evidence due to indirectness for subjective next-day functioning. In contrast to subjective efficacy outcomes, it was expected that the objective rather than the subjective measures of next-day functioning might have determined the risk of harm, including injuries and accidents. Thus, questioning the clinical relevance of subjective next-day functioning (compared to objective measures only applied in one RCT), we rated the directness of evidence for next-day functioning as being limited and downgraded the evidence for next-day functioning to low-quality.

Imprecision

Eleven of 14 RCTs included in the review were multicentre trials based on large study samples that allowed precise estimations of eszopiclone`s efficacy and safety; thus we did not judge the quality of evidence to be lowered by imprecision.

Publication and funding bias

With the exception of two non-profit funded RCTs (McCall 2010a; Pollack 2008), trials included in the review were financially supported by the pharmaceutical industry. As subgroup analyses according to 'sponsoring type' would not be conclusive, due to the imbalance of sample size between non-profit sponsored (two RCTs) and industry-sponsored (10 RCTs) subgroups, we formed subgroups according to the type of study initiation. Comparisons of effects from investigator- versus sponsor-initiated trials did not demonstrate statistically significant differences (Analysis 1.16; Analysis 1.17; Analysis 1.18). Plotting of the mean differences against standard errors for SOL (Figure 4) and WASO (Figure 5) did not indicate asymmetry, but, due to the small number of included studies, the conclusiveness of the funnel plot method was limited (see Other potential sources of bias). Nevertheless, a suspicion of funding bias (Lexchin 2003) remained due to the overweight of industry-sponsored trials.

Potential biases in the review process

Even though, according to the standards of the Cochrane Collaboration, various strategies have been implemented in the planning and conduction of the review to limit bias in the review process and to increase research transparency, a number of methodological decisions were left to the authors and are discussed for their impact on efficacy and safety conclusions of the review in the following comments.

We decided to exclude studies with a cross-over design due to the fact that sleep stabilising effects of eszopiclone have been reported even after drug discontinuation (Zammit 2004), making it difficult to control carry-over effects by wash-out. We identified two studies with a cross-over design fulfilling further inclusion criteria of our review (Erman 2008; Joffe 2010), both confirming the sleep-promoting effects of eszopiclone. Accordingly, we assumed that our decision to include parallel group studies was unlikely to have affected the efficacy and safety conclusions of the review.

Treatment effectiveness was assessed through two outcomes: 1. 'sleep onset latency' (SOL) defined as the length of time (in minutes) after lights-out until sleep onset, and 2. 'wake time after sleep onset' (WASO), defined as the length of time (in minutes) of wakefulness after the onset of persistent sleep. The consideration of two effectiveness outcomes was reasoned by their conceptual distinctiveness, with SOL measuring a drug's impact on sleep onset, and WASO measuring its potential to improve sleep maintenance. Thereby, the former reflected its suitability for the treatment of sleep-onset insomnia and the latter for sleep-maintenance insomnia (see Description of the condition). Even though assessed on the base of conceptual distinctive outcomes, sleep efficacy outcomes of the review might not have captured the full extent of insomnia. Nevertheless, to control for Type I error and to ensure clarity and comprehensibility of the review, outcomes were limited on the base of theoretical considerations.

A further important methodological decision concerned the 'type of participants' considered as eligible for the review. The original protocol had limited 'type of participants' to patients with primary insomnia. A careful weighing of the available evidence and a reconsideration of the referees` comments made us extend the inclusion criteria by including both primary and secondary insomnia. Our arguments for doing so are outlined in the section Differences between protocol and review. Primary and comorbid insomnia was considered as criteria for subgroup analyses (Analysis 1.8; Analysis 1.9; Analysis 1.10), allowing a statistical analysis of the impact that type of insomnia diagnosis had on efficacy outcomes of the review.

A limitation arose from the asymmetric distribution of primary sleep efficacy data and the provision of outcome statistics as medians in some studies, which had to be excluded from pooling of continuous data (Hozo 2005). The problem marginally concerned sleep efficacy outcomes, provided as means in the majority of studies (Ancoli-Israel 2010; Goforth 2014; Krystal 2003; McCall 2010a; Menza 2010; Pollack 2008; Scharf 2005; Soares 2006; Spierings 2015; Zammit 2004), but affected rebound effects to a more considerable extent. Effect estimations for change from baseline during run-out intervals were based on only one trial (Ancoli-Israel 2010), while outcomes from the remaining trials were provided as medians (Fava 2006; Pollack 2008; Roth 2009; Walsh 2007) or p-values (Soares 2006; Zammit 2004). Table 3 compared information of significance between studies providing means and medians. Only one trial (Roth 2009), not included in the statistical pooling of data, found a small, non-significant increase in WASO on day one and three of the run-out period and a significant decrease in TST on day one.

A strength of the review might have come from the nonrestrictive definition of inclusion criteria and from analysing the impact of potentially effect-determining factors on the basis of subgroup and sensitivity analyses. A further strength was owed to the support we received from the primary investigators and further experts (see Acknowledgements), who checked the completeness of our study search and who provided feedback on design characteristics and outcome statistics. Nevertheless, no unpublished trials and data could be included. This, together with the overweight of industry-sponsored studies, clearly increased the risk of overestimating effects due to funding bias (Lexchin 2003).

Finally, to limit the influence of reviewers interests and expectations, all outcome statistics were extracted by at least two reviewers independently (SR & CE, CE & RW), and disagreements were resolved in consensus discussions between three reviewers (SR, CE, RW). To additionally prevent confirmation bias (Nickerson 1998), at least one author, who had not been involved in insomnia research before, participated in each review step.

Agreements and disagreements with other studies or reviews

Efficacy conclusions of the review largely agree with those of previous reviews and meta-analyses (Buscemi 2007; Huedo-Medina 2012; Sateia 2017), suggesting that eszopiclone is an effective therapeutic option in the treatment of insomnia. With a reduction of SOL by about 12 minutes, a decrease of WASO by about 17 minutes and an increase of TST by about 28 minutes, effects are comparable in their magnitude with those shwon by Sateia 2017 for SOL and TST in the 2 mg eszopiclone dosing group (SOL: MD = -17.78; 95% CI -28.52 to -7.04; TST: MD = 27.53; 95% CI 18.29 to 36.76) and for WASO in the 3 mg dosing group (WASO: MD = -14.49; 95% CI -17.68 to -11.69). In contrast to the review at hand, Sateia 2017 included cross-over trials and provided separate analyses for 2 mg and 3 mg dosing groups. Furthermore, our review excluded medians from pooling of continuous data as suggest by Hozo 2005, which did not allow the inclusion of the largest trial (Walsh 2007) into meta-analyses of primary sleep efficacy outcomes.

Adverse events identified in the review like unpleasant taste (RD 0.18, 95% CI 0.14 to 0.219), dry mouth (RD 0.04, 95% CI 0.02 to 0.06), somnolence (RD 0.04, 95% CI 0.02 to 0.06) and dizziness (RD 0.03, 95% CI 0.01 to 0.05) have been reported formerly (e.g. Hair 2008; Najib 2006) and are listed in the Lunesta package insert (Lunesta 2004 [pers comm]). In contrast to case-control studies (Berry 2013; Diem 2014), subgroup analyses of adverse events in samples of the elderly did not identify an increased risk for serious adverse events like falls, injury, and hip fractures, which might be due to the more controlled conditions in clinical trials compared to everyday life. The exclusion of certain participant subgroups and the monitoring of treatment implementation in clinical research might also explain the absence of central nervous system (CNS) side effects of eszopiclone, such as amnesia or hallucinations, which have previously been reported in case studies for racemic zopiclone (Elko 1998; Toner 2000; Tsai 2003) and eszopiclone (Duggal 2007), occurring preferably if hypnotic drugs were taken in high doses or if combined with other psychoactive substances.

Meta-analyses of participant-reported next-day alertness (MD = 0.46; 95% CI 0.28 to 0.63; 8 RCTs; 2061 participants) did not identify residual effects as currently shown in a randomised, double-blind cross-over study (Boyle 2012). Reasons for divergent results might be found from a lack of the sensitivity of subjective measures in displaying psychomotor and cognitive impairments or the application of sleep restriction protocols in the cross-over study. Nevertheless, as a restricted sleep protocol might adequately represent 'likely scenarios in insomniacs' (Gunja 2013), significant weight might be given to the findings of the cross-over study (Boyle 2012).

Finally, the review did not identify withdrawal symptoms and distinct rebound effects after eszopiclone was discontinued, supporting the conclusion that, if taken as recommended, eszopiclone has a low potential to cause dependence and withdrawal. Findings from randomised placebo-controlled studies with racemic zopiclone, which failed to demonstrate polysomnographic withdrawal effects after a four-week treatment in a recommended dose range (Vorderholzer 2001) and did not show abuse-like effects in drug-naive participants (Licata 2008), are consistent with our conclusion. Nevertheless, withdrawal symptoms, craving, and severe rebound insomnia associated with the high dose use of zopiclone in individuals with preexisting chemical abuse or psychiatric disorders, as documented in case reports (Cimolai 2007), suggests that safety conclusions might only be valid for the use of eszopiclone in the recommended dose range and without contraindicated substances.

AUTHORS' CONCLUSIONS

Implications for practice

The review of 14 RCTs with 4732 participants showed significant effects of eszopiclone on primary and secondary sleep efficacy outcomes. Compared to placebo, eszopiclone was shown to reduce time to fall asleep by about 12 minutes and wake time after sleep onset by about 17 minutes, contributing to a more or less half an hour increase of total sleep time per night. Efficacy of eszopiclone on sleep has been shown to cover different age groups and insomnia types, including insomnia as a primary and comorbid condition. Evidence from two six-month trials indicated that therapeutic benefits can be maintained over medium- to long-term treatment periods. Participants taking eszopiclone may subjectively experience better functioning the next day than participants taking placebo, although the effect is likely to be small. Participants in the eszopiclone group reported more often unpleasant taste, dry mouth, somnolence, and dizziness. Discontinuation of eszopiclone after several weeks and months of treatment did not result in withdrawal symptoms, while rebound effects were occasionally reported, but not observed in the majority of RCTs.

However, these implications for practice should not be made without refering to potential limitations in the quality and generalisability of evidence. First of all, due to the open-label design of run-out intervals (see Quality of the evidence), the risk of rebound insomnia after the discontinuation of eszopiclone might be underestimated by some trials. In addition, the exclusion of certain participant groups, such as elderly participants with cognitive and psychomotor impairments or individuals with high dose or combined use from clinical trials, might limit the safety conclusions of the review (see Overall completeness and applicability of evidence).

The review suggests that in healthy individuals who use the drug as prescribed for a limited time, eszopiclone can be considered a safe and efficacious treatment for insomnia. Intermittent dosing or 'treatment as needed' might be an alternative to daily scheduled treatment, but the risk-benefit profile has to assessed by future research (see Implications for research).

Implications for research

The RCTs included in the review showed various methodological strengths, which might serve as standards for future research. Such standards include baseline comparisons in sleep indicators between study groups to prevent selection bias, and the monitoring of medication compliance and of concomitant drugs as a strategy to control the risk of performance bias. Comparisons between groups for daytime napping have been implemented in studies with elderly subjects only, but might be equally helpful to control compensatory sleep in all age group samples. The consideration of both types of outcomes, SOL and WASO, allows a simultaneous assessment of distinctive drug effects on sleep onset and sleep maintenance and the identification of potential shifts in the efficacy profile of a hypnotic drug.

At the same time, a stricter adherence to methodological standards of reporting, as outlined in the CONSORT statement (Schulz 2010), would help to remove prevailing doubts and uncertainties resulting from an incomplete description of methods used for sequence generation, allocation concealment, and blinding procedures. Moreover, eszopiclone`s specific taste properties, which can potentially reveal the identity of the medication to participants or investigators (see Moncrieff 2004), constitute the need to taste-match placebo to the active comparator drug in future RCTs. Finally, single-blind run-out periods should be routinely applied after treatment discontinuation in hypnotic drug trials to allow a valid assessment of withdrawal and rebound effects, which in turn serve as indicators of chronic use and dependence (Vorderholzer 2001).

Despite the wide range of methods and conditions considered in RCTs, some issues were left for future research. One of these concerns the relative effectiveness and safety of eszopiclone compared to other hypnotic drugs. While findings from RCTs comparing eszopiclone with placebo are applicable to the question: 'Can this intervention work?' (Krishnan 2011), and the therapeutic decision whether to use eszopiclone or not, it is the evidence from active-controlled trials that clinicians refer to when deciding which of the available treatment options to prefer.

A further unresolved problem concerns the identification of appropriate treatment strategies for participant subgroups with an increased vulnerability to adverse events. The exclusion of specific samples from RCTs, such as participants with substance use disorders, contrasts with the high occurrence of insomnia in these groups of individuals and the potential impact insomnia has on substance use. In participants with comorbid alcohol dependence - a group of individuals known to often use alcohol for self-medicating sleeping problems - insomnia was not only shown to significantly determine the severity of alcohol problems, but also the risk of a relapse to drinking during alcohol recovery (Arnedt 2007; Brower 2001; Conroy 2006; Foster 1999; Kaplan 2014). The exclusion of these participant subgroups from RCTs, a decision justified from a safety perspective, might bear the risk of adhering to higher risk treatments (Brunette 2003) or to treatments with unclear indications and effectiveness (Friedmann 2003).

In conclusion, to ensure that efficacy research meets the needs of every day clinical practice, relevant samples (e.g. elderly with impairments, individuals with substance use disorders) and treatment conditions (e.g. as-needed dosing regimen; Hajak 2002a; Hajak 2002b), flexible strategies have to be included in high quality research. Available RCTs that consider longer treatment durations point in the right direction, while the conclusiveness of results might be increased by elaborate study designs to assess withdrawal and rebound effects. Such studies would not only provide credible answers to urgent questions, but might also serve as further examples illustrating that clinical relevance does not necessarily preclude internal validity.

ACKNOWLEDGEMENTS

We thank the Federal Ministry of Education and Research (BMBF Germany) for the financial support (FKZ:01KG0727). The authors are pleased to acknowledge the team of the Cochrane Common Mental Disorders Group (CCMD) for their support in the preparation of this review and **Yoon Loke** (University of East Anglia, UK, Co-Convenor of the Cochrane Adverse Effects Methods Group (CAEMG)), who provided feedback on the analyses of adverse events.

Furthermore, we give thanks to **Hrayr Attarian**, Department of Neurology, Circadian Rhythms and Sleep Research Lab, Chicago, Illinois, USA; **Joel E. Dimsdale**, University of California, San Diego, CA, USA; **Todd A. Grinnell**, Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc, Marlborough, MA, USA; **Tara Lauriat**, Dept. of Psychiatry, Steward St, Elizabeth's Medical Center, Boston, MA, USA; **Egilius Spierings**, Craniofacial Pain Center, Tufts University School of Dental Medicine, Boston, MA, USA; **Rose Nourse**, formerly Lehigh Center for Clinical Research, Allentown, PA, USA; **Sergio Tufik**, **Cristina Jorge**, Departamento de Psicobiologia, Universidade Federal de São Paulo, São Paulo, Brasil; **Sinan Guloksuz**, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; **Michael T. Smith**, John Hopkins University School of Medicine, Center for Sleep Related Symptom Science, Baltimore, MD, USA for the provision of information on their studies; and with special thanks to **Hrayr Attarian** (see above) for supplying unreported outcomes from his primary study.

We also thank **R Bart Sangal**, Clinical Neurophysiology Services, Sterling Heights, MI, USA; J**ames K. Walsh**, Sleep Medicine and Research Center, St. Luke's Hospital, Chesterfield, MO, USA; **Gary Zammit,** Cliniclabs, NY, USA; and **Thomas Roth**, Henry Ford Hospital, Detroit, MI, USA; for providing contact and further information.

CRG Funding Acknowledgement:
The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Common Mental Disorders Group.

Disclaimer:
The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS, or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ancoli-Israel 2010

Methods	**Design:** parallel group randomised trial
	Principle of analysis: ITT (treatment-received analysis)

Ancoli-Israel 2010 *(Continued)*

	Setting: outpatient **Study sites:** 82 **Country:** USA
Participants	**N** = 388 **Diagnosis:** primary insomnia (DSM-4-TR) **Sample:** elderly participants **Age:** M = 72 years (SD = 5.1; range: 65 to 85 years) **Gender:** 63 % female **Sleep-related criteria of inclusion:** TST≤ 6 hours, WASO ≥ 45 min (for ≥ 3 nights per week in the last month); further inclusion criteria: run-in compliance ≥ 4 doses **Exclusion criteria:** OSRD, OCAS, SAM (e.g. antidepressants on a stable dose), HSAD (6 months before screening)
Interventions	**Experimental:** ESZ (2 mg); n = 194 **Control:** PBO; n = 194 **Treatment duration:** 12 weeks **Run-out:** 4 weeks (2 weeks single-blind PBO; 2 weeks no drug period) **Run-in:** 1 (+1) week single-blind PBO for compliance assessment **Dosing:** nightly
Outcomes	**Primary outcomes:** TST **Secondary outcomes:** SOL, WASO, ISI (Bastien 2001); **next day functioning:** alertness, ability to function, well-being, ability to concentrate, **rebound insomnia, withdrawal effects; adverse events; further outcomes:** SF-36 (Ware 1993); BWSQ (Tyrer 1990)
Financial support	Sepracor, Marlborough, Massachusetts; sponsored phase-IV study
Data assessment	**Timepoints for assessment:** clinic visits at 3-week intervals **Quantitative sleep measures:** daily, participant reports (electronic sleep/wake diary) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** mean SOL, TST and WASO change from baseline for each day of the two week run-out period **Withdrawal effects:** Benzodiazepine Withdrawal Symptom Questionnaire (Tyrer 1990); new or worsening central nervous system or psychiatric adverse events that occurred during the follow-up period **Tolerance:** reduction of treatment effects throughout the study **Compliance:** pill count
Treatment adherence	**Dropout:** 24.2 % (ESZ); 23.7 % (PBO); group difference: ns **Compliance:** 97.3 % (ESZ); 97.6 % (PBO); group difference: ns
Notes	**Declaration of interest:** Trial investigators have served as consultants or advisory board members to Sepracor, have received research support from Sepracor or were Sepracor employees. **Further publi-**

Ancoli-Israel 2010 *(Continued)*

cations: A further publication concerned the evaluation of predictors of response to eszopiclone (Marshall 2011a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with internet based randomisation system
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 12.4% in the ESZ group and 1.5% in the PBO group reported an unpleasant taste; **testing of blinding integrity:** explicitly stated that blinding integrity was not tested
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** LOCF
Selective reporting (reporting bias)	Low risk	**Reporting:** primary and secondary endpoints adequately listed, reported and interpreted; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender:yes; sleep initiation: yes; sleep maintenance: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of SAM:** tested for various substances; no significant difference between groups; slightly more participants in the PBO group used analgesics, but the difference was not statistically significant; **occurrence of compensatory sleep:** a significantly greater decrease in naps per week was noted over the first three weeks of treatment with eszopiclone, but not at week 6, 9, or 12; napping endpoints were also analysed in ITT

Fava 2006

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** outpatient; sleep laboratory (night 1, 15, 29, 45, 46), **Study sites:** 67 **Country:** USA

Fava 2006 *(Continued)*

Participants	**N** = 545 **Diagnosis:** 1. insomnia (DSM-4); 2. major depressive disorder (MDD; DSM-4); insomnia symptoms must not have predated MDD > 10 weeks **Sample:** depressive comorbidity **Age:** 41.0 years (SD = 11.0; range: 21 to 64 years) **Gender:** 66.6% female **Sleep-related criteria of inclusion:** SOL ≧ 30 min, TST ≤ 6.5 hours, WASO ≧ 45 min (for ≥ 3 nights per week in the last month) **Exclusion criteria:** OSRD, OCAS, SAM (chronic prescription medication on a stable dose, over-the-counter (OTC) medications not intended for soporific use allowed), HSAD (6 months before screening) or positive urine test at screening
Interventions	**Experimental:** ESZ (3 mg); n = 270 **Control:** PBO; n = 275 **Treatment duration:** 8 weeks **Run-out:** 2 weeks single-blind PBO **Dosing:** nightly **Comedication:** fluoxetine (20 mg open-label; with the option of dose titration to 40 mg)
Outcomes	**Primary outcomes:** WASO **Secondary outcomes:** SOL, TST, HAM-D-17 (Maier 1985); **next day functioning:** daytime alertness; **tolerance; rebound insomnia; withdrawal effects; adverse events; further outcomes:** sleep quality, sleep depth, daytime functioning, physical well-being
Financial support	Sepracor Inc.
Data assessment	**Timepoints for assessment:** weekly**,** **Quantitative sleep measures:** participant reports (IVRS, morning questionnaire) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function); DSST **Rebound insomnia:** SOL, WASO and TST median change from baseline for each night during 14 days run-out period **Withdrawal effects:** new or worsening CNS and CNS-related adverse events during ESZ run-out period **Tolerance:** no information on tolerance assessment provided: **compliance:** pill count; **adverse events:** any event, regardless of its relation to the study drug, was recorded
Treatment adherence	**Dropout:** 6.3 % (ESZ); 7.7 % (PBO); group difference: ns **Compliance:** 96 to 100%; no group specific values provided; presumably ns
Notes	**Declaration of interest:** Trial investigators have served as consultants or advisory board members to Sepracor, have received research support from Sepracor or were Sepracor employees. **Further publications:** Further publications of the study concerned the evaluation of discontinuation (Krystal 2007) and antidepressant effects (Fava 2011). The study was also included in a post hoc analysis (Krystal 2012b), comparing effect sizes of primary insomnia samples and medical and psychiatric comorbidity samples from 5 RCTs on eszopiclone (Fava 2006; Pollack 2008; Roth 2009; Soares 2006; Walsh 2007).

Fava 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 22.7% in the ESZ group and 0.7% in the PBO group reported unpleasant taste; **testing of blinding integrity:** reanalysis of data in participants who did not experience unpleasant taste was consistent with the efficacy results of the entire sample
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** LOCF
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes; no differences in depression as measured by the Hamilton Rating Scale for depression (HAM-D-17; Hamilton 1960) were found between groups
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** yes; **concomitant use of comorbidity medication:** tested for fluoxetine dose titration from 20 mg to 40 mg, which significantly differed between the ESZ-group (44.7%) and the PBO group (53.7%) at week 4, but not at the end; further medication (on a stable dose, not tested); **concomitant use of further SAM:** not reported

Goforth 2014

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** outpatient **Study sites:** 1 **Country:** USA
Participants	**N** = 58

Goforth 2014 *(Continued)*

	Diagnosis: 1. insomnia (DSM-4-TR); 2. chronic low back pain (LBP); insomnia did not predate LBP onset > 4 weeks **Sample:** participants with chronic low back pain (LBP) **Age:** M = 43.5 years (SD = 11.7; range: 65 to 85 years) **Gender:** 63 % female **Sleep-related criteria of inclusion:** TST < 6.5 hours, SOL > 30 min (on a usual night in the last month) **Exclusion criteria:** OSRD, OCAS, SAM, HSAD (12 months before screening)
Interventions	**Experimental:** ESZ (3 mg); n = 33 **Control:** PBO; n = 25 **Treatment duration:** 4 weeks **Dosing:** nightly **Comedication:** naproxen (50 mg open-label; twice daily), lansoprazole (15 mg; once daily)
Outcomes	**Primary outcomes:** TST **Secondary outcomes:** SOL, WASO, SE, ISI (Bastien 2001); **further outcomes:** Roland Morris Disability Questionnaire (RMDQ; Roland 1983); Hamilton Rating Scale for depression (Hamilton 1960)
Financial support	investigator-initiated study; sponsored by Sunovion Coropration (then Sepracor Corporation)
Data assessment	**Timepoints for assessment:** week 1, 2 and 4 **Quantitative sleep measures:** daily, sleep diaries **Compliance:** pill count
Treatment adherence	**Dropout:** 12.1 % (ESZ); 32.0 % (PBO); **excluded from analyses:** 3% (ESZ); 20% (PBO) **Compliance:** not reported
Notes	**Declaration of interest:** One trial investigator has received research support from Sunovion/Sepracor; the other authors have indicated no financial conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation schedule based on computer-driven pseudo-random number generator
Allocation concealment (selection bias)	Low risk	The sponsor supplied identical ESZ and PBO capsules and provided the investigator with sequentially numbered pill containers in order to implement the random allocation sequence. The random allocation sequence was only provided to the investigators after all subjects have completed the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	**Participants blinded:** double-blind; all investigators and study personal were blinded; **placebo appearance:** identical to ESZ capsules; no information on unpleasant taste provided; **testing of blinding integrity:** all investigators and study personal were shown to remain blind to treatment assignment throughout the study

Goforth 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** LOCF
Selective reporting (reporting bias)	High risk	**Reporting:** primary and secondary endpoints were adequately listed, reported and interpreted; **outcome diversity**: limited; no data on rebound insomnia or withdrawal symptoms provided
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes; no differences in pain and back pain severity were found between groups
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** not reported; **concomitant use of comorbidity medication:** differences in use of analgesics between groups was not reported; **concomitant use of SAM:** not allowed (see criteria of exclusion)

Krystal 2003

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT **Setting:** outpatient **Study sites:** 70 **Country:** USA
Participants	**N** = 788 **Diagnosis:** primary insomnia (DSM-4) **Age:** 44 years (SD = 11; range 21 to 65 years) **Gender:** 63% female **Sleep-related criteria of inclusion:** SOL > 30 min, TST< 6.5 hours **(each night in the last month)** **Exclusion criteria:** OSRD, OCAS, SAM, HSAD (lifetime), ALC > SDU per day or > 14 SDU per week
Interventions	**Experimental:** ESZ (3 mg); n = 595 **Control:** PBO; n = 196 **Treatment duration:** 6 months (randomised, double-blind design) **Treatment continuation:** 6-month open-label with 3 mg ESZ after the randomised period (available to all participants) **Dosing:** nightly
Outcomes	**Primary outcomes:** SOL

Krystal 2003 *(Continued)*

	Secondary outcomes: TST, WASO;**next day functioning:** ability to function, daytime alertness, physical well-being, ability to concentrate; **further outcomes: tolerance, withdrawal symptoms; adverse events**
Financial support	Sepracor-sponsored phase-III study
Data assessment	**Timepoints for sleep indicator assessment:** weekly (value reported once a week for average nightly values during that week) **Timepoints for safety and compliance assessment:** monthly, termination visit 5 to 7 days after the last dose **Quantitative sleep measures:** participant reports (IVRS) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** not considered **Withdrawal effects:** new events following drug discontinuation **Tolerance:** reduction of treatment effects throughout the study **Compliance:** pill count
Treatment adherence	**Dropout:** 39.5 % (ESZ); 43.4% (PBO); group difference: ns **Compliance:** 94.4% (ESZ); 90.6% (PBO); group difference: ns
Notes	**Declaration of interest:** Trial investigators have served as consultants or advisory board members to Sepracor, have received research support from Sepracor or were Sepracor employees. **Further publications:** Further publication of the study concerned the evaluation of the open-label period (Roth 2005), cost-effectiveness analyses (Botteman 2007; Snedecor 2009) and WASO-subgroup effects (Krystal 2012a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 26.1% in the ESZ group and 5.6% in the PBO group reported an unpleasant taste; **testing of blinding integrity:** a comparison between participants who perceived unpleasant taste and those who did not, did not indicate differences in adherence and treatment success.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT; **handling of missing data:** LOCF (sensitivity of results to handling of missing data methods (ITT, PP) was tested and shown to be robust)
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia)
Blinding of outcome assessment (detection bias)	Unclear risk	No objective measures of sleep provided

Krystal 2003 *(Continued)*

Sleep indicators		
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of SAM:** not allowed (see criteria of exclusion)

McCall 2006

Methods	**Design:** parallel group randomised trial **Principle of analysis:** not reported **Setting:** sleep laboratory (night 1, 2, 13, 14); outpatient (night 3 to 12) **Study sites:** 49 **Country:** USA
Participants	**N** = 264 **Diagnosis:** primary insomnia (DSM-4) **Sample:** elderly participants **Age:** 71.1 years (SD = 5.1; range: 64 to 84 years) **Gender:** 67.4% female **Sleep-related criteria of inclusion:** SOL > 30 min, TST ≤ 6.5 hours (each night in the last month), PSG screening **Exclusion criteria:** OSRD, OCAS, SAM, ALC > 2 (14) SDU per day (week)
Interventions	**Experimental:** ESZ (2 mg); n = 136 **Control:** PBO; n = 128 **Treatment duration:** 2 weeks **Run-out:** not considered **Dosing:** nightly
Outcomes	**Primary outcomes:** LPS, SE **Secondary outcomes:** WASO, NAW, WTPS, WTDS, CWT, ISI (Bastien 2001); **next day functioning:** morning sleepiness, QOS, depth of sleep, sense of well-being; **further outcomes:** SF-36 (Ware 1992); % stage 1 sleep; time spent in slow wave/REM sleep; adverse events
Financial support	Sepracor-sponsored phase-III study: it was reported that the sponsor did not place limitations on the data analyses, interpretation of results, and manuscript writing.
Data assessment	**Timepoints for sleep indicator assessment:** daily

McCall 2006 *(Continued)*

	Timepoints for safety and compliance assessment: 4 visits **Quantitative sleep measures:** 1. PSG (night 1, 2, 13, 14); 2. participant reports (IVRS questionnaire) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** not considered **Withdrawal effects:** not considered **Tolerance: compliance:** dosing cards; **adverse events:** personal interviews and reports
Treatment adherence	**Dropout:** 2.2% (ESZ); 4.6% (PBO); group differences: ns **Compliance:** 99.3% (ESZ); 99.2% (PBO); group difference: ns
Notes	**Declaration of interest:** Trial investigators have served as consultants or advisory board members to Sepracor, have received research support from Sepracor or were Sepracor employees. Further authors have indicated no financial conflicts of interest. **Further publications:** Erman 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 12.5% in the ESZ group and 0% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Principle of analysis:** not reported
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, next-day functioning) *rebound insomnia not required because of 2-week treatment duration
Blinding of outcome assessment (detection bias) Sleep indicators	Low risk	PSG assessments (4 nights) and participant reports (10 nights) came to consistent effectiveness conclusions except for NAW, which only reached statistical significance for participant-reported data
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of SAM:** not allowed (see criteria of exclusion); **occurrence of compensatory sleep:** daytime napping was nearly 50% in both groups: number and duration of naps was higher in the PBO than in the ESZ, but did not reach statistical significance (P = 0.07)

McCall 2010a

Methods	**Design:** parallel group randomised trial **Principle of analysis:** not reported **Setting:** outpatient **Study sites:** 1 **Country:** USA
Participants	**N** = 60 **Diagnosis:** 1. insomnia (Research Dignostic Criteria; Edinger 2004)); 2. major depressive episode (DSM-4); no temporal relationship between insomnia and major depressive episode required **Sample:** depressive comorbidity **Age:** 41.2 years (SD = 12.5; range: 18 to 70 years) **Gender:** 66.7% female **Sleep-related criteria of inclusion:** SOL > 30 min; SE (sleep efficiency) < 85% at least 4 nights per week in the last month; PSG screening **Exclusion criteria:** OSRD, OCAS, SAM, absence of substance abuse (current)
Interventions	**Experimental:** ESZ (3 mg); n = 30 **Control:** PBO; n = 30 **Treatment duration:** 8 weeks **Run-out:** not considered (naturalistic follow-up conducted monthly by telephone for 4 months after treatment) **Dosing:** nightly **Comedication:** fluoxetine (20 mg open-label; with the option of dose titration to 40 mg)
Outcomes	**Primary outcomes:** Health-related quality of life (HRQOL) **Secondary outcomes:** SL, WASO, TST, number of naps, nap time, SE, NAW, ISI (Bastien 2001); **next day functioning:** daily living and role functional subscale of the BASIS-32 (Eisen 1994) was considered as the primary outcome
Financial support	Not industry-supported study. Funded by NIH MH70821; M01-RR07122. Medications from Sepracor Inc, material support from Mini Mitter
Data assessment	**Timepoints for sleep indicator assessment:** daily **Timepoints for safety and compliance assessment:** 4 visits **Quantitative sleep measures:** 1. actigraphy (Mini Mitter Actiwatch); 2. sleep diary **Next-day functioning:** HRQOL; BASIS-32 (Eisen 1994) **Rebound insomnia:** not considered **Withdrawal effects:** not considered **Tolerance: compliance: adverse events:** open-ended questions
Treatment adherence	**Dropout:** 16.6% (ESZ); 13.3% (PBO); group differences: ns

McCall 2010a *(Continued)*

	Compliance: not reported; group difference: ns
Notes	**Declaration of interest:** Trial investigators have participated in speaking engagement for Sepracor or have received research support from Sepracor, further authors have indicated no financial conflicts of interest. **Further publications:** Further publications assessed effects of eszopiclone on quality of life (McCall 2009), insomnia severity as an indicator of suicidal ideation (McCall 2010b), analyses of the placebo effect (McCall 2011a), and the comparison between actigraphic and diary sleep measurements (McCall 2011b; McCall 2012).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 46% in the ESZ group reported an unpleasant taste (placebo rate of unpleasant taste not provided); **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT; **handling of missing data:** information provided for naturalistic follow-up, for which missing data appeared to be missing at random, so a mixed linear model was used to compare groups
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia)
Blinding of outcome assessment (detection bias) Sleep indicators	Low risk	PSG was assessed at the beginning and the end of treatment, actigraphic monitoring throughout the entire duration of the study. Pre-post PSG differences failed to reveal an advantage for ESZ for either latency to the first epoch and to persistent sleep; a comparison between actigraphic monitoring and sleep diaries indicated differences between objective and subjective sleep measurements in depressed insomniacs (McCall 2012); the results of this study found that, overall, actigraphic sleep measurements demonstrated significantly increased sleep time and decreased wake time in the laboratory relative to the home environment
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of comorbidity medication:** tested for fluoxetine dose titration from 20 mg to 40 mg, which did not significantly differ between the ESZ and PBO group; **concomitant use of SAM:** not allowed (see criteria of exclusion)

Menza 2010

Methods	**Design:** parallel group randomised trial

Menza 2010 *(Continued)*

	Principle of analysis: ITT **Setting:** outpatient **Study sites:** 5 **Country:** USA
Participants	**N** = 30 **Diagnosis:** 1. insomnia; 2. Parkinson's disease; no temporal relationship between insomnia and parkinson's disease required **Sample:** Parkinson's`s disease comorbidity **Age:** 56 years (range: 35 to 85 years) **Gender:** 20% female **Sleep-related criteria of inclusion:** SOL > 30 min, TST < 6.5 hours (in ≥ 3 from 7 nights in the last month), PSG screening **Exclusion criteria:** OSRD, OCAS (PSG), SAM (antidepressants on a stable dose, benzodiazepines taken during the day, Parkinson's medication (e.g. levodopa, COMT inhibitor, MAO inhibitor were allowed)
Interventions	**Experimental:** ESZ (3/2 mg); n = 15 (dose stratified by age; 3 mg for age < 65 years; 2 mg for age ≥ 65 years) **Control:** PBO; n = 15 **Treatment duration:** 6 weeks **Run-out:** not considered **Dosing:** nightly
Outcomes	**Primary outcomes:** TST **Secondary outcomes:** WASO, NAW; **next day functioning; next day alertness; adverse events; further outcomes:** Parkinson's severity; QOL and motor functioning
Financial support	Investigator-initiated study; not sponsored by Sepracor besides providing study medication
Data assessment	**Timepoints for sleep indicator assessment:** daily **Timepoints for safety and compliance assessment:** weeks 0, 2, 4 and 6 **Quantitative sleep measures:** sleep diary (National Sleep Foundation Sleep Diary) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function); **QOL**: assessed with the short version of the Parkinsons Disease Questionnaire (PDQ-8; Jenkinson 1997) **Rebound insomnia:** not considered **Tolerance:** reduction of treatment effects throughout the study; **compliance:** not reported
Treatment adherence	**Dropout:** 20% (ESZ); 53.3% (PBO); group differences: not reported **Compliance:** not reported
Notes	**Declaration of interest:** Some trial investigators have received research support from Sepracor; further authors have indicated no financial conflicts of interest.

Menza 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** equal appearance to eszopiclone pill; none of the participants reported an unpleasant taste (see discussion); **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT; **handling of missing data:** no information provided
Selective reporting (reporting bias)	High risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: limited; no data on rebound insomnia or withdrawal symptoms provided
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided (except: PSG baseline evaluation)
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Unclear risk	**Baseline equivalence:** age: not reported; gender: yes; sleep initiation: not reported; sleep maintenance: yes; baseline scores indicated a higher severity of Parkinson's disease in the eszopiclone group; covariate comprised participant age, gender, and the score at baseline of a Parkinson's disease rating scale
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** not reported; **concomitant use of comorbidity medication:** equivalence of Parkinson's medication confirmed; **concomitant use of SAM:** concomitant medications were listed in the outcome section, but no group-specific values were provided

Pollack 2008

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** outpatient **Study sites:** 69 **Country:** USA
Participants	**N** = 595

Pollack 2008 *(Continued)*

	Diagnosis: 1. insomnia (DSM-4-TR); 2. general anxiety disorder (GAD; DSM-4-TR); insomnia was defined as being related to GAD, while no requirement for a particular temporal relationship between the onset of GAD and insomnia was required **Sample:** general anxiety disorder comorbidity **Age:** 40.0 years (range: 18 to 64 years) **Gender:** 66% female **Sleep-related criteria of inclusion:** SOL ≥ 30 min; TST ≤ 6.5 hours (for ≥ 3 nights per week in the last month); 70% compliance and diary entries in the run-in period **Exclusion criteria:** OSRD, OCAS, SAM, HSAD
Interventions	**Experimental:** ESZ (3 mg); n = 294 **Control:** PBO; n = 301 **Treatment duration:** 8 weeks **Run-in:** 10-day single-blind PBO (compliance ensured) **Run-out:** 2 weeks single-blind PBO (rebound, withdrawal effects) **Dosing:** nightly **Comedication:** escitalopram (open label; 10 mg daily)
Outcomes	**Primary outcomes:** SOL **Secondary outcomes:** TST, WASO, NAW, TST, QOS, DOS, ISI (Bastien 2001); **next-day functioning:** ability to function, ability to concentrate, daytime alertness, physical well-being; **severity of insomnia; tolerance; rebound insomnia; withdrawal effects; adverse events; further outcomes: anxiety** (Hamilton Anxiety Scale (HAM-A; Hamilton 1959).
Financial support	Investigator-initiated study, not sponsored by Sepracor
Data assessment	**Timepoints for assessment:** weeks 1, 2, 4, 6, 8 and 10 **Quantitative sleep measures:** daily participant reports (electronic diary) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** SOL, TST, WASO change to baseline for each day during the 2 week ESZ run-out period **Withdrawal effects:** adverse events and central nervous events during run-out period **Tolerance:** significance reduction of treatment effects throughout the study **Compliance:** pill count **Adverse events:** medical event calendar
Treatment adherence	**Dropout:** 20.1% (ESZ); 21.3% (PBO); group differences: ns **Lost to follow-up:** ESZ: 6%; PBO: 5.8%; group differences: ns **Compliance:** not reported (only participants who took at least 70% of the required doses in the single-blind run-in period were included in the randomisation)
Notes	**Declaration of interest:** Trial investigators have served as consultants or advisory board members to Sepracor, or have received research support from Sepracor. **Further publications:** The study was included in a post hoc analysis (Krystal 2012b), comparing effect sizes of primary insomnia samples and

Pollack 2008 *(Continued)*

medical and psychiatric comorbidity samples from 5 RCTs on eszopiclone (Fava 2006; Pollack 2008; Roth 2009; Soares 2006; Walsh 2007).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** matched to ESZ; 24.1% in the ESZ group and 3.7% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** LOCF
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes; furthermore, no differences in depression as measured with the Hamilton Rating Scale for depression (HAM-A; Hamilton 1959) were found between groups
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** not reported; **concomitant use of comorbidity medication:** tested for escitalopram, which did not significantly differ between the ESZ-group (45%) and the PBO group (41%); **concomitant use of further SAM:** not allowed (see criteria of inclusion)

Roth 2009

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** outpatient **Study sites:** 43 **Country:** USA

Roth 2009 *(Continued)*

Participants	**N** = 153 **Diagnosis:** 1. insomnia (DSM-4); 2. rheumatoid arthritis; the diagnosis of rheumatoid arthritis must have predated the onset of insomnia symptoms **Age:** 52.1 years (SD = 8.8; range: 25 to 64 years) **Gender:** 86.9% female **Sleep-related criteria of inclusion:** TST < 6.5 hours, WASO ≥ 45 min (for ≥ 3 nights per week in the last month) **Exclusion criteria:** OSRD, OCAS, SAM (SSRI on a stable dose, selected medications in the event of an exacerbation of rheumatoid arthritis symptoms were allowed)
Interventions	**Experimental:** ESZ (3 mg); n = 77 **Control:** PBO; n = 76 **Treatment duration:** 4 weeks **Run-in:** 3 to 7 days single-blind PBO **Run-out:** 2 weeks single-blind PBO **Dosing:** nightly
Outcomes	**Primary outcomes:** WASO **Secondary outcomes:** SOL,TST, QOS, DOS; **next-day functioning:** ability to function, daytime alertness, physical well-being, ability to concentrate; **rebound insomnia: withdrawal symptoms; adverse events; further outcomes:** QOL (SF-36; Ware 1992); HAQDI
Financial support	Sepracor-sponsored phase-IIIb study
Data assessment	**Timepoints for assessment:** weeks 0, 2 and 4 **Quantitative sleep measures:** daily; participant reports (IVRS) **Severity of insomnia:** ISI **Next-day functioning:** 11 point scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** SOL, TST, WASO change to baseline during ESZ run-out period **Withdrawal effects:** new or worsening adverse events during ESZ run-out period **Compliance:** not reported **Quality of life:** SF-36 (Ware 1992) **Time of assessment:** morning administration; **frequency of assessment:** daily
Treatment adherence	**Dropout:** 5.2 % (ESZ); 9.2 % (PBO); group difference: ns **Compliance:** not reported
Notes	**Declaration of interest:** Trial investigators have served as consultants to Sepracor, were Sepracor employees, or stock shareholders in Sepracor. One investigator reported no financial or other affiliations relevant to the subject of the study. **Further publications**: Schnitzer 2005
Risk of bias	

Roth 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 27.3% in the ESZ group and 0% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** no imputation methods used for missing data
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Unclear risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: not reported; sleep maintenance: not reported
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** not reported; **concomitant use of SAM and comorbidity medication:** no group differences in dose increase or new prescription of either pain or disease-modifying medications between groups observed

Scharf 2005

Methods	**Design:** parallel group randomised trial
	Principle of analysis: ITT (treatment-received analysis)
	Setting: outpatient
	Study sites: multicentre (number not specified)
	Country: USA
Participants	**N** = 231
	Diagnosis: primary insomnia (DSM-4)
	Sample: elderly participants
	Age: 72.3 years (SD = 5.1; range 64 to 85 years)
	Gender: 57.8% female

Scharf 2005 *(Continued)*

	Sleep-related criteria of inclusion: SOL > 30 min, TST ≤ 6.5 hours **(each night in the last month)** **Exclusion criteria:** OSRD, OCAS, SAM, alcohol use was permitted but limited to 2 or fewer drinks per day
Interventions	**Experimental 1:** ESZ (2 mg); n = 79 **Experimental 2:** ESZ (1 mg); n = 72 **Control:** PBO; n = 80 **Treatment duration:** 2 weeks **Dosing:** nightly * 1 mg dosing group was not included in the MA
Outcomes	**Primary outcome:** SOL **Secondary outcomes:** TST, WASO, NAW, QOS, DOS; **next-day functioning:** daytime alertness, daytime ability to function, sense of well-being; number and duration of naps; **adverse events; tolerance; QOL**
Financial support	Sepracor-sponsored phase-III study
Data assessment	**Timepoints for assessment:** weekly **Quantitative sleep measures:** daily, participant reports (IVRS) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** not considered **Withdrawal effects:** not considered **Tolerance:** significance of effects in week 1 and 2 **Compliance:** pill count
Treatment adherence	**Dropout:** 2.5 % (ESZ 2 mg); 6.3 % (PBO); group difference: ns **Compliance:** 98.7% (ESZ 2 mg); 98.2%; group difference: ns
Notes	**Declaration of interest:** Trial investigators have received research support from Sepracor or were Sepracor employees. Data were analysed by Sepracor Inc; the paper was written by the authors with the assistance of Sepracor Inc. Reporting was excellent.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 11.4% in the ESZ group and 1.3% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided

Scharf 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** not reported
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, next-day functioning); *rebound insomnia not required because of 2-week treatment duration
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of SAM:** tested for various substances; no significant difference between groups; **occurrence of compensatory sleep:** participants in the eszopiclone group had significantly fewer daytime naps compared to PBO

Soares 2006

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT **Setting:** outpatient **Study sites:** multicentre (number not specified) **Country:** Canada
Participants	**N** = 410 **Diagnosis:** insomnia (DSM-4) **Sample:** women in peri- or early postmenopausal stage; the onset of menopausal transition must have predated insomnia **Age:** 49.1 years (SD = 4.0; range 40 to 60 years) **Gender:** 100% female **Sleep-related criteria of inclusion:** SOL > 45 min and TST ≤ 6 hours (at least 3 nights per week in the last month) **Exclusion criteria:** OSRD, OCAS, HSAD (lifetime), ALC > 2 (14) SDU per day (week); SAM (except hormone therapy on a stable dose allowed); PSY
Interventions	**Experimental:** ESZ (3 mg); n = 201 **Control:** PBO; n = 209 **Treatment duration:** 4 weeks

Soares 2006 *(Continued)*

	Run-in: 3 to 7 day single-blind PBO **Run-out:** 1 week single-blind PBO **Dosing:** nightly
Outcomes	**Primary outcome:** SOL **Secondary outcomes:** TST, WASO, NAW, QOS; **next-day functioning:** daytime alertness, daytime ability to function, daytime ability to concentrate, sense of well-being; **adverse events; rebound insomnia; withdrawal effects; further outcomes:** menopause-related symptoms, menopause-specific quality of life
Financial support	Sepracor-sponsored phase-IIIb study
Data assessment	**Timepoints for assessment:** weekly **Quantitative sleep measures:** daily, participant reports (IVRS) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** SOL, TST and WASO change to baseline during run-out period (data not shown) **Withdrawal effects:** adverse events during run-out week **Tolerance:** significance of effects in week 1 and 2 **Quality of life:** Shehan Disbility Scale (menopause-specific quality of life scale)
Treatment adherence	**Dropout:** 11.9 % (ESZ); 12.9 % (PBO); group difference: ns **Compliance:** not reported; group difference: ns
Notes	**Declaration of interest:** Trial investigators have served as consultants to Sepracor, were Sepracor employees, or stock shareholders in Sepracor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 17.6% in the ESZ group and 0.5% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT; **handling of missing data:** not reported
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)

Soares 2006 *(Continued)*

Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep initiation: yes; sleep maintenance: yes; no differences in symptoms of menopause were found between groups
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** yes; **concomitant use of comorbidity medication:** a subgroup analysis was prospectively analysed between baseline hormone users and non-users; **concomitant use of comorbidity medication:** not allowed (see exclusion criteria)

Spierings 2015

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (modified) **Setting:** outpatient **Study sites:** 5 (investigator information) **Country:** USA
Participants	**N** = 75 (randomised: N = 79) **Diagnosis:** 1. primary insomnia (DSM-4); 2. migraine (IHS-ICHD II) **Sample:** participants suffering migraine **Age:** 44.4 years (SD = 10.8; range: 18 to 64 years) **Gender:** 82.5% female **Sleep-related criteria of inclusion:** TST ≤ 6.5 hours **Exclusion criteria:** SAM (with the exception of preventive migraine treatment with beta-blockers or calcium-entry blockers; treatment of insomnia for 2 weeks prior to screening), HSAD (last 5 years), ALC > 2 SDU per day on average
Interventions	**Experimental:** ESZ (3 mg); n = 35 **Control:** PBO; n = 40 **Treatment duration:** 6 weeks **Baseline-period:** 2 weeks **Run-out:** 2 weeks open-label run-out period (information on blindness reported by the primary investigator) **Dosing:** nightly
Outcomes	**Primary outcomes:** TST (averaged over 6 weeks)

Spierings 2015 *(Continued)*

	Secondary outcomes: TST (2-week intervals; change from baseline)**,** SOL, NAW, **next-day functioning:** daytime alertness, functioning, fatigue; sleep quality; headache frequency, duration, intensity
Financial support	Investigator initiated trial; study was conducted with a grant from Sunovian Pharmaceuticals
Data assessment	**Timepoints for assessment:** weekly **Quantitative sleep measures:** paper sleep diary (every morning) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** TST change from baseline (not included in the meta-analysis due to the open-label design of the run-out period) **Withdrawal effects:** not considered **Tolerance:** not considered;**compliance:** pill count; **adverse events:** not considered
Treatment adherence	**Dropout:** not reported (4 randomised subjects, 3 taking medication for less than 2 weeks, 1 lost-to-follow-up) were not included in the analyses **Compliance:** not reported
Notes	**Declaration of interest:** No conflict of interest reported; study was conducted with a grant from Sunovian Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	The sponsor provided blinded study-drug kits, each containing three bottles with a 2-week supply of tablets. The kits were packaged in blocks of four, each provided with a subject number, and were dispensed as much as possible in sequential order to ensure even distribution.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** eszopiclone and placebo tablets were identical-looking, plain white tablets and contained all the ingredients of the verum other than eszopiclone; rates of unpleasant taste were not provided**; testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Principle of analysis:** ITT-modified, including all subjects who took study medication at least 5 days per week for the first 2 weeks; **handling of missing data:** not reported
Selective reporting (reporting bias)	High risk	**Reporting:** TST during the run-out period was mentioned as a secondary outcome in the methods section, but not reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided

Spierings 2015 *(Continued)*

Other bias: Baseline equivalence (selection bias)	High risk	**Baseline equivalence:** age: yes; gender: yes; sleep maintenance: yes; sleep initiation: no (statistically significant difference for sleep latency, which was higher in the eszopiclone group compared to placebo); no differences in headache frequency, intensity, and duration were found between groups
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** not reported;**concomitant use of comorbidity medication:** not reported; **concomitant use of SAM:** not allowed (see criteria of exclusion)

Walsh 2007

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** outpatient **Study sites:** 54 **Country:** USA
Participants	**N** = 830 **Diagnosis:** primary insomnia (DSM-4) **Age:** 46 years (SD = 11.8; range 21 to 64 years) **Gender:** 61% female **Sleep-related criteria of inclusion:** SOL > 30 min and TST ≤ 6.5 hours (on a typical night in the last month) **Exclusion criteria:** OSRD, OCAS, HSAD (lifetime), SAM (exception: certain OTC medications and chronic prescription medication if taken on a stable dose allowed)
Interventions	**Experimental:** ESZ (3 mg); n = 550 **Control:** PBO; n = 280 **Treatment duration:** 6 months **Run-out:** 2 weeks single-blind PBO **Dosing:** nightly
Outcomes	**Primary outcome:** SOL **Secondary outcomes:** WASO, TST; **next-day functioning:** daytime alertness; **adverse events; rebound insomnia; withdrawal symptoms; further outcomes: quality of life; work limitations**
Financial support	Sepracor-sponsored phase-IV study; it was reported that the sponsor placed no limitations on the data analyses, interpretation, and manuscript publication.
Data assessment	**Timepoints for assessment:** baseline visit, 6-monthly visits, final visit **Quantitative sleep measures:** daily, participant reports (IVRS) **Next-day functioning:** Likert scale (0 to 10; higher scores indicating improved function) **Rebound insomnia:** SOL, TST and WASO change from baseline during run-out period

Walsh 2007 *(Continued)*

	Withdrawal: Benzodiazepine Withdrawal Symptom Questionnaire (Tyrer 1990) **QOL:** SF-36 (Leger 2001); Work Limitations Questionnaire (Lerner 2001) **Adverse events:** COSTART dictionary (Version 5.0, 1995) **Compliance:** pill count
Treatment adherence	**Dropout:** 37.1 % (ESZ); 52.1 % (PBO) **Compliance:** rates not reported; group difference: ns
Notes	**Declaration of interest:** Trial investigators have received research support from Sepracor or were Sepracor employees. **Further publications:** A further publication concerned the evaluation of predictors of response to eszopiclone (Marshall 2011b).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Drug preparation and randomisation were performed centralised by the sponsor
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind including participants, research and sponsor personnel; **placebo appearance:** ESZ and PBO were of identical appearance; 19.7% in the ESZ group and 1.1% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** LOCF; dropouts were shown not to differ from trial completers in baseline characteristics, compliance rates and outcome measures
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Unclear risk	No objective measures of sleep provided
Blinding of outcome assessment (detection bias) Next-day functioning	Unclear risk	No objective measures of next-day functioning provided
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: yes; sleep maintenance: yes; sleep initiation: yes; duration of insomnia: yes
Other bias: Equivalence of treatment utilisation (performance bias)	Unclear risk	**Compliance equivalence:** yes; **concomitant use of SAM medication:** not reported

Zammit 2004

Methods	**Design:** parallel group randomised trial **Principle of analysis:** ITT (treatment-received analysis) **Setting:** sleep laboratory (night 1, 15, 29, 45, 46), outpatient (41 nights) **Study sites:** multicentre (number not specified) **Country:** USA
Participants	**N** = 308 **Diagnosis:** primary insomnia (DSM-4) **Age:** 39.4 years (SD = 11.7; range 21 to 64 years **Gender:** 65% female **Sleep-related criteria of inclusion:** SOL > 30 min and TST ≤ 6.5 hours **(each night during the last month)** **Exclusion criteria:** OSRD, OCAS, SAM, HSAD (lifetime), ALC > 2 SDU per day
Interventions	**Experimental 1:** ESZ (3 mg); n = 105 **Experimental 2:** ESZ (2 mg)*; n = 104 **Control:** PBO; n = 99 **Treatment duration:** 6 weeks **Run-out:** 2 days single-blind PBO **Dosing:** nightly * 2 mg dosing group was not included in the MA
Outcomes	**Primary outcome:** SOL, LPS **Secondary outcomes:** WASO, TST; **next-day functioning:** daytime alertness; DSST; **tolerance; rebound insomnia; withdrawal effects; adverse events; further outcomes:** SE, stage 1, 3, 4 and REM sleep
Financial support	Sepracor-sponsored phase-III study
Data assessment	**Timepoints for assessment:** **Quantitative sleep measures:** 1. PSG (nights 1, 15, 29, 45, 46); 2. participant reports (IVRS), daily **Next-day functioning:** 1. Likert scale (0 to 10; higher scores indicating improved function); 2. DSST **Rebound insomnia:** LPS, SE and WASO change from baseline for each of 2 nights during run-out period **Withdrawal:** New CNS and CNS-related adverse events in the week after treatment discontinuation **Tolerance:** PSG measures for LPS, SE and WASO on nights 1, 15, and 29; **Adverse events:** COSTART dictionary (Version 5.0, 1995) **Compliance:** pill count
Treatment adherence	**Dropout:** 5% (no group-specific values provided) **Compliance:** ESZ: 98.2%; PBO: 97.8%; group difference: ns

Zammit 2004 *(Continued)*

Notes	**Declaration of interest:** not provided; **Further publications:** A conference publication described effects of eszopiclone on stage 2 sleep (Zammit 2009)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	**Participants blinded:** double-blind; no further information provided; **placebo appearance:** no information on appearance provided; 33.3% in the ESZ group and 3% in the PBO group reported unpleasant taste; **testing of blinding integrity:** no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Principle of analysis:** ITT (treatment-received analysis); **handling of missing data:** not reported
Selective reporting (reporting bias)	Low risk	**Reporting:** all primary and secondary endpoints listed in the methods section were adequately reported in the results section; **outcome diversity**: adequate (sleep induction, sleep maintenance, rebound insomnia, withdrawal symptoms)
Blinding of outcome assessment (detection bias) Sleep indicators	Low risk	PSG assessments (3 nights) and participant reports came to consistent effectiveness conclusions
Blinding of outcome assessment (detection bias) Next-day functioning	Low risk	Digit-Symbol Substitution Test (DSST) and participant reports of next-day functioning came to consistent conclusions concerning next-day impairments
Other bias: Baseline equivalence (selection bias)	Low risk	**Baseline equivalence:** age: yes; gender: no (65% female; ESZ > PBO); sleep initiation: yes; sleep maintenance: yes; gender differences were included as covariates in the efficacy analysis mode
Other bias: Equivalence of treatment utilisation (performance bias)	Low risk	**Compliance equivalence:** yes; **concomitant use of SAM medication:** not allowed (see criteria of exclusion)

ALC: alcohol
BASIS: Behaviour and Symptom Identification Scale
BWSQ: Benzodiazepine Withdrawal Symptom Questionnaire
CGI: Clinical Global Impression scale
CNS: central nervous system
COMT: Catechol-O-methyltransferase
COSTART: Coding Symbols for a Thesaurus of Adverse Reaction Terms
CWT: continous wavelet transform
DOS: duration of sleep
DSM: Diagnostic and Statistical Manual of Mental Disorders
DSST: digital symbol substitution test
ESZ: eszopiclone
GAD: generalised anxiety disorder
HAM: Hamilton Rating Scale for Depression

HAQDI: Health Assessment Questionnaire without Didability Index
HRQOL: Health-Related Quality of Life
HSAD: hydrolase
ICHD: International Classification of Headache Disorders
IHS: idiopathic hyperinsomnia
ISI: Insomnia Severity Index
ITT: intention-to-treat
IVRS: interactive voice response system
LBP: low back pain
LOCF: last-observation-carried-forward
LPS: latency to persistent sleep
M: Mean
MA: meta-analysis
MAO: monoamine oxidase inhibitors
MDD: major depressive disorder
mg: milligram
min: minute
n: number
NAW: number of nighttime awakenings
NIH: National Institute of Health
ns: not significant
OCAS: oral contraceptive agents
OSRD: other primary or secondary sleep disorders than insomnia such as sleep apnea, restless legs syndrome, periodic leg movement
OTC: over the counter
PBO: placebo
PDQ: Parkinson's Disease Questionnaire
PP: Per Protocol
PSG: polysomnography
PSY: psychiatric disorders
QOL: quality of life
QOS: quality of sleep
RCT: randomised controlled trial
REM: rapid eye movement
RMDQ: Roland-Morris Disability Questionnaire
SAM: sleep-affecting medication
SD: sleep duration
SDU: standard drink units
SE: sleep efficiency
SF-36: Short Form (36) Health Survey
SL: sleep latency
SOL: sleep onset latency
SSRI: selective serotonin reuptake inhibitors
TST: total sleep time
WASO: wake time after sleep onset
WTDS: wake time during sleep
WTPS: wake time before persistent sleep

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Attarian 2011	Insomnia diagnosis was not required for inclusion
Boyle 2008	Cross-over design

Study	Reason for exclusion
Boyle 2012	Cross-over design; healthy volunteers
Demanuele 2014	Insomnia diagnosis was not required for inclusion; patients with schizophrenia
Dimsdale 2011b	Insomnia diagnosis was not required for inclusion (according to investigator information); patients with mucositis associated with hematologic malignancies
Eckert 2011	Insomnia diagnosis was not required for inclusion; patients with obstructive sleep apnoea (OSA)
Erman 2008	Cross-over design
Gross 2011	Open-label design; control: mindfulness meditation training
Huang 2015	Insomnia diagnosis was not required for inclusion; patients with schizophrenia
Joffe 2010	Cross-over design
Lettieri 2008	Insomnia diagnosis was not required for inclusion; patients with sleep-disordered breathing (SDB)
NCT00120250	Cross-over design
NCT00368056	Cross-over design
NCT00374192	Cross-over design; participants were peri- and postmenopausal women
NCT00460993	Insomnia diagnosis was not required for inclusion; nursing home patients with low sleep quality; no further information available
NCT00511134	Insomnia diagnosis was not required for inclusion; smokers with sleep problems related to smoking cessation
NCT00616655	Insomnia diagnosis was not required for inclusion; patients with generalised anxiety disorder
NCT00685269	Insomnia diagnosis was not required for inclusion (according to investigator information); patients with obstructive sleep apnea syndrome (OSA)
NCT00811746	Insomnia diagnosis was not required for inclusion; patients with obstructive sleep apnea syndrome (OSA)
NCT00813735	Insomnia diagnosis was not required for inclusion; Insomnia Severity Index > 15 (according to register information)
NCT00826111	Insomnia diagnosis was not required for inclusion (according to investigator information); participants had to score above a threshold score of the Insomnia Severity Index (Bastien 2001)
NCT00889200	Open-label design
NCT00900159	Cross-over design
NCT01102270	Insomnia diagnosis was not required for inclusion; patients with obstructive sleep apnea syndrome (OSA)
NCT01641900	Insomnia diagnosis was not required for inclusion; effects on brain activity during sleep and memory in patients with schizophrenia

Study	Reason for exclusion
NCT01710631	Open-label extension of a six-months phase-II study (Krystal 2003)
Peng 2013	Open-label; no placebo or active drug control group (control: eszopiclone without psychotherapy)
Pollack 2011	Cross-over design; insomnia diagnosis was not required for inclusion (sleep disturbance)
Rosenberg 2005	Healthy subject model of transient insomnia
Rosenberg 2007	Cross-over design; insomnia diagnosis was not required for inclusion; patients with obstructive sleep apnea syndrome (OSA))
Sangal 2014	Sample: children and adolescents (< 18 years)
Tek 2014	Insomnia diagnosis was not required for inclusion; patients with schizophrenia or schizoaffective disorder according to DSM-4; sleep problems twice per week in the proceeding month, Insomnia Severity Index rating > 10
Uchimura 2012a	Cross-over design; no placebo or active drug control group (control: different dose groups (1 mg, 2 mg, 3 mg))
Uchimura 2012b	Cross-over design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Baran 2017

Methods	Polysomnography study on coordination of slow waves with sleep spindles in schizophrenia
Participants	Schizophrenia participants and matched healthy controls
Interventions	Eszopiclone 3 mg versus placebo
Outcomes	spindle-coordination, sleep-dependent memory consolidation
Notes	—

Buxton 2017

Methods	Randomised, double-blind, placebo-controlled trial to test effects of pharmacological treatment on glucose metabolism in primary insomnia
Participants	Adult men and women meeting clinical criteria for primary insomnia
Interventions	Eszopiclone 3 mg versus placebo
Outcomes	Change in glucose metabolism
Notes	NCT00900159; status: completed; study publication available: Buxton 2017

NCT00374556

Methods	Insomnia and osteoarthritis study
Participants	Osteoarthritis Insomnia
Interventions	Eszopiclone 3 mg versus placebo
Outcomes	WASO, pain sensitivity
Notes	NCT00374556; status: completed; no publications provided; study was terminated early due to recruitment issues (according to Sunovion) Principal Investigator: Michael T. Smith, Ph.D, Johns Hopkins University

NCT00392041

Methods	Eszopiclone in the treatment of insomnia and fibromyalgia
Participants	ACR criteria for fibromyalgia; L Allen requested
Interventions	Eszopiclone 3 mg versus placebo
Outcomes	TST, WASO, sleep quality, fibromyalgia symptoms
Notes	NCT00392041; status: completed; no publications provided

NCT00435279

Methods	Study of eszopiclone coadministered with venlafaxine in subjects with major depressive disorder and insomnia
Participants	Major depressive disorder
Interventions	Eszopiclone 3 mg versus placebo
Outcomes	Depression score
Notes	NCT00435279; status: completed; no publications provided; no further information available (Sunovion)

Pinto 2016

Methods	A non-inferiority study with two treatment arms, eszopiclone 3 mg versus zopiclone 7.5 mg, for the treatment of insomnia
Participants	Diagnosis of primary insomnia according to DSM-4
Interventions	Eszopiclone 3 mg; zopiclone 7.5 mg
Outcomes	LPS, WASO, NAW

Pinto 2016 *(Continued)*

Notes	NCT01100164; status: completed; study publication available: Pinto 2016

ACR: American College of Rheumatology
DSM: Diagnostic and Statistical Manual of Mental Disorders
LPS: Latency to persistent sleep
mg: milligram
NAW: number of nighttime awakenings
SE: sleep efficiency
SOL: sleep onset latency
TST: total sleep time
WASO: wakefulness after sleep onset

Characteristics of ongoing studies *[ordered by study ID]*

Emiko 2015

Trial name or title	Efficacy and safety of eszopiclone in the treatment of insomnia complicated with nocturnal awakenings associated with urination
Methods	Parallel group randomised controlled trial
Participants	Subjects with insomnia complicated with nocturnal awakenings associated with urination
Interventions	Eszopiclone, no treatment
Outcomes	Primary outcome: quality of life
Starting date	Date of first enrolment: 6/2016
Contact information	matsui.tsuyoshi@nihon-u.ac.jp
Notes	ICTRP: JPRN-UMIN000013808

NCT02456532

Trial name or title	Safety and efficacy of chronic hypnotic use 2
Methods	Parallel group randomised controlled trial
Participants	Subjects with chronic insomnia
Interventions	Eszopiclone, zolpidem, placebo
Outcomes	Primary outcomes: change in number capsules chosen, discontinuation difficulty
Starting date	7/2015
Contact information	Gail Koshorek, BS; gkoshor1@hfhs.org
Notes	Sponsor: Henry Ford Health System

DATA AND ANALYSES

Comparison 1. Eszopiclone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sleep onset latency (SOL)	9	2890	Mean Difference (IV, Fixed, 95% CI)	-11.94 [-16.03, -7.86]
2 Wake time after sleep onset (WASO)	8	2295	Mean Difference (IV, Random, 95% CI)	-17.02 [-24.89, -9.15]
3 Withdrawal symptoms	7		Risk Difference (M-H, Random, 95% CI)	Subtotals only
3.1 Abdominal pain	1	478	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.00, 0.03]
3.2 Accidental injury	3	1068	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.01]
3.3 Agitation	2	701	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
3.4 Anxiety	2	590	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
3.5 Arthritis	1	153	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.01, 0.09]
3.6 Backpain	3	1058	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.03]
3.7 Dizziness	4	1291	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
3.8 Dysmenorrhea	1	359	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.01]
3.9 Headache	6	2237	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
3.10 Hyperesthesia	1	204	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
3.11 Infection	1	478	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.00, 0.04]
3.12 Insomnia	1	386	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
3.13 Memory impairment	1	386	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
3.14 Nausea	2	590	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.03, 0.02]
3.15 Neurosis	1	204	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
3.16 Nightmares	1	204	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.05]
3.17 Paresthesia	1	410	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.01]
3.18 Pharyngitis	2	878	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.02, 0.01]
3.19 Photosensivity	1	204	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.04, 0.02]
3.20 Pain	4	1417	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.01]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.21 Pruritis	1	410	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.03]
3.22 Tremor	1	153	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.02, 0.07]
3.23 Any	5	2103	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.03, 0.04]
4 Rebound insomnia	1	873	Mean Difference (IV, Random, 95% CI)	-1.76 [-18.55, 15.04]
4.1 Rebound - SOL	1	291	Mean Difference (IV, Random, 95% CI)	17.0 [-4.29, 38.29]
4.2 Rebound - WASO	1	291	Mean Difference (IV, Random, 95% CI)	-6.71 [-21.25, 7.83]
4.3 Rebound - TST	1	291	Mean Difference (IV, Random, 95% CI)	-14.30 [-36.42, 7.82]
5 Total sleep time (TST)	10	2965	Mean Difference (IV, Random, 95% CI)	27.70 [20.30, 35.09]
6 Next-day alertness	8	2061	Mean Difference (IV, Random, 95% CI)	0.46 [0.28, 0.63]
7 Adverse events	13		Risk Difference (M-H, Random, 95% CI)	Subtotals only
7.1 Serious adverse events	12	4289	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
7.2 Dropout	11	4007	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
7.3 Chest pain	1	58	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.14, 0.06]
7.4 Accidental injury	7	3374	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
7.5 Anxiety	2	652	Risk Difference (M-H, Random, 95% CI)	0.02 [0.00, 0.04]
7.6 Abdominal pain	2	1381	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.06, 0.05]
7.7 Arthralgia	1	264	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
7.8 Asthenia	3	1484	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
7.9 Backpain	6	2647	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
7.10 Confusion	1	153	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.02, 0.07]
7.11 Coughing	1	153	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.02, 0.08]
7.12 Decreased libido	1	593	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.00, 0.06]
7.13 Diarrhea	2	1381	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.04]
7.14 Dry mouth	6	2802	Risk Difference (M-H, Random, 95% CI)	0.04 [0.02, 0.06]
7.15 Dizziness	7	2933	Risk Difference (M-H, Random, 95% CI)	0.03 [0.01, 0.05]
7.16 Dyspepsia	5	2728	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.17 Edema	1	264	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.05]
7.18 Fatigue	1	593	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.01, 0.06]
7.19 Hallucinations	1	388	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
7.20 Headache	10	4124	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
7.21 Infection	3	2159	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.02, 0.10]
7.22 Memory impairment	2	652	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.00, 0.03]
7.23 Mood changes	1	264	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
7.24 Muscle pain	1	828	Risk Difference (M-H, Random, 95% CI)	0.03 [0.00, 0.06]
7.25 Nausea	3	1924	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.06, 0.07]
7.26 Nervousness	5	1552	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
7.27 Nightmares	2	357	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
7.28 Pharyngitis	6	3295	Risk Difference (M-H, Random, 95% CI)	0.02 [0.00, 0.04]
7.29 Pain	5	2833	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
7.30 Poor concentration	1	388	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
7.31 Respiratory infection	3	1156	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.03, 0.04]
7.32 Rhinitis	1	788	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.06]
7.33 Sinusitis	1	788	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.02]
7.34 Skin rash	2	1052	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.04]
7.35 Somnolence	8	3532	Risk Difference (M-H, Random, 95% CI)	0.04 [0.02, 0.06]
7.36 Unpleasant taste	9	3787	Risk Difference (M-H, Random, 95% CI)	0.18 [0.14, 0.21]
8 Subgroups: insomnia type - SOL	7	2265	Mean Difference (IV, Random, 95% CI)	-12.25 [-16.99, -7.50]
8.1 Primary insomnia: SOL	5	1803	Mean Difference (IV, Random, 95% CI)	-15.14 [-21.13, -9.15]
8.2 Comorbid insomnia: SOL	2	462	Mean Difference (IV, Random, 95% CI)	-8.10 [-17.77, 1.57]
9 Subgroups: insomnia type - WASO	7	2265	Mean Difference (IV, Random, 95% CI)	-16.55 [-24.76, -8.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Primary insomnia: WASO	5	1803	Mean Difference (IV, Random, 95% CI)	-15.76 [-25.60, -5.92]
9.2 Comorbid insomnia: WASO	2	462	Mean Difference (IV, Random, 95% CI)	-21.20 [-40.76, -1.65]
10 Subgroups: insomnia type - TST	8	2340	Mean Difference (IV, Random, 95% CI)	28.37 [20.16, 36.58]
10.1 Primary insomnia: TST	6	1878	Mean Difference (IV, Random, 95% CI)	30.04 [19.09, 40.98]
10.2 Secondary insomnia: TST	2	462	Mean Difference (IV, Random, 95% CI)	23.37 [12.61, 34.12]
11 Subgrups: age groups - SOL	8	2860	Mean Difference (IV, Random, 95% CI)	-12.48 [-16.92, -8.04]
11.1 Younger age - SOL	5	2049	Mean Difference (IV, Random, 95% CI)	-13.08 [-19.15, -7.00]
11.2 Older age - SOL	3	811	Mean Difference (IV, Random, 95% CI)	-11.41 [-20.37, -2.45]
12 Subgroups: age groups - WASO	7	2265	Mean Difference (IV, Random, 95% CI)	-16.55 [-24.76, -8.35]
12.1 Younger age - WASO	4	1454	Mean Difference (IV, Random, 95% CI)	-12.20 [-19.02, -5.37]
12.2 Older age - WASO	3	811	Mean Difference (IV, Random, 95% CI)	-22.16 [-40.70, -3.63]
13 Subgroups: age groups - TST	9	2935	Mean Difference (IV, Random, 95% CI)	28.54 [21.81, 35.27]
13.1 Younger age - TST	6	2124	Mean Difference (IV, Random, 95% CI)	29.66 [21.60, 37.72]
13.2 Older age - TST	3	811	Mean Difference (IV, Random, 95% CI)	27.01 [11.83, 42.18]
14 Subgroups: age groups - alertness	7	2031	Mean Difference (IV, Random, 95% CI)	0.44 [0.26, 0.63]
14.1 Younger age: next-day alertness	4	1220	Mean Difference (IV, Random, 95% CI)	0.56 [0.37, 0.75]
14.2 Older age: next-day alertness	3	811	Mean Difference (IV, Random, 95% CI)	0.34 [0.01, 0.67]
15 Subgroups: older participants - adverse events	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only
15.1 Serious adverse events	3	804	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.02]
15.2 Dropout	3	811	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.03, 0.03]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
15.3 Accidental injury	2	652	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
15.4 Anxiety	2	652	Risk Difference (M-H, Random, 95% CI)	0.02 [0.00, 0.04]
15.5 Arthralgia	1	264	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
15.6 Backpain	1	264	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.05]
15.7 Dry mouth	1	264	Risk Difference (M-H, Random, 95% CI)	0.07 [0.02, 0.12]
15.8 Dizziness	2	652	Risk Difference (M-H, Random, 95% CI)	0.03 [0.01, 0.06]
15.9 Dyspepsia	1	159	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.03]
15.10 Edema	1	264	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.05]
15.11 Hallucinations	1	388	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
15.12 Headache	2	547	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.05, 0.07]
15.13 Memory impair-ment	2	652	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.00, 0.03]
15.14 Mood changes	1	264	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.04]
15.15 Nervousness	2	652	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.00, 0.03]
15.16 Pharyngitis	1	388	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.05, 0.04]
15.17 Pain	1	264	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.02, 0.08]
15.18 Poor concentra-tion	1	388	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.01, 0.02]
15.19 Skin rash	1	264	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.04, 0.05]
15.20 Somnolence	2	423	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.03, 0.05]
15.21 Unpleasant taste	3	811	Risk Difference (M-H, Random, 95% CI)	0.11 [0.08, 0.15]
16 Subgroups: study initiation - SOL	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1 Investigator-initi-ated - SOL	3	677	Mean Difference (IV, Random, 95% CI)	-8.29 [-14.24, -2.34]
16.2 Sponsor-initiated - SOL	6	2213	Mean Difference (IV, Random, 95% CI)	-15.21 [-20.83, -9.59]
17 Subgroups: study initiation - WASO	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 Investigator-initi-ated WASO	2	82	Mean Difference (IV, Random, 95% CI)	-33.29 [-56.47, -10.10]

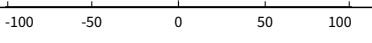
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
17.2 Sponsor-initiated WASO	6	2213	Mean Difference (IV, Random, 95% CI)	-15.31 [-23.50, -7.11]
18 Subgroups: study initiation - TST	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 Investigator-initiated TST	3	677	Mean Difference (IV, Random, 95% CI)	21.04 [-4.19, 46.27]
18.2 Sponsor-initiated TST	7	2288	Mean Difference (IV, Random, 95% CI)	28.40 [19.60, 37.21]
19 Sensitivity: sleep assessment	2	1200	Mean Difference (IV, Fixed, 95% CI)	-9.92 [-13.32, -6.53]
19.1 Sleep onset latency	2	468	Mean Difference (IV, Fixed, 95% CI)	-15.50 [-19.89, -11.11]
19.2 Wake time after sleep onset	2	468	Mean Difference (IV, Fixed, 95% CI)	-12.37 [-18.61, -6.13]
19.3 Total sleep time	1	264	Mean Difference (IV, Fixed, 95% CI)	28.6 [18.14, 39.06]
20 Sensitivity: withdrawal assessment	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Eszopiclone versus placebo, Outcome 1 Sleep onset latency (SOL).

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ancoli-Israel 2010	194	52 (55)	194	62.5 (65.8)		11.45%	-10.5[-22.57,1.57]
Goforth 2014	32	18.4 (14)	20	23.3 (16.9)		21.28%	-4.9[-13.75,3.95]
Krystal 2003	593	46 (47.4)	195	65.7 (61.3)		18.83%	-19.7[-29.11,-10.29]
McCall 2006	136	-40.8 (59.4)	128	-29.5 (55.7)		8.65%	-11.3[-25.18,2.58]
Menza 2010	15	11 (15)	15	20 (14)		15.47%	-9[-19.38,1.38]
Pollack 2008	294	-41.8 (69.8)	301	-27.6 (86.8)		10.44%	-14.15[-26.79,-1.51]
Scharf 2005	79	-70 (175)	80	-41.4 (146)		0.66%	-28.6[-78.73,21.53]
Soares 2006	201	-25.8 (109)	209	-10.1 (42.9)		6.39%	-15.7[-31.85,0.45]
Zammit 2004	105	44.5 (68.8)	99	58.4 (42.9)		6.82%	-13.9[-29.54,1.74]
Total * **	**1649**		**1241**			**100%**	**-11.94[-16.03,-7.86]**

Heterogeneity: $Tau^2=0$; $Chi^2=6.22$, df=8(P=0.62); $I^2=0\%$

Test for overall effect: Z=5.73(P<0.0001)



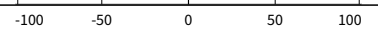
Favours eszopiclone — Favours placebo

Analysis 1.2. Comparison 1 Eszopiclone versus placebo, Outcome 2 Wake time after sleep onset (WASO).

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ancoli-Israel 2010	194	57.8 (55)	194	76.8 (55)		17.11%	-19[-29.95,-8.05]
Goforth 2014	32	41.1 (27.9)	20	78.1 (68.8)		4.98%	-37[-68.66,-5.34]
Krystal 2003	593	43.8 (68.4)	195	55.9 (71.2)		16.64%	-12.1[-23.51,-0.69]
McCall 2006	136	-31.3 (45.7)	128	-24.5 (48.3)		16.69%	-6.8[-18.16,4.56]
Menza 2010	15	17 (50)	15	46 (45)		4.42%	-29[-63.04,5.04]
Scharf 2005	79	-39.9 (79)	80	8.3 (65)		8.27%	-48.2[-70.7,-25.7]
Soares 2006	201	-30.9 (79)	209	-16 (65)		14.11%	-14.9[-28.93,-0.87]
Zammit 2004	105	41.2 (39)	99	49.1 (36.1)		17.78%	-7.9[-18.21,2.41]
Total * **	**1355**		**940**			**100%**	**-17.02[-24.89,-9.15]**

Heterogeneity: Tau^2=63; Chi^2=15.42, df=7(P=0.03); I^2=54.59%

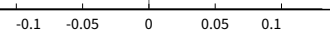
Test for overall effect: Z=4.24(P<0.0001)



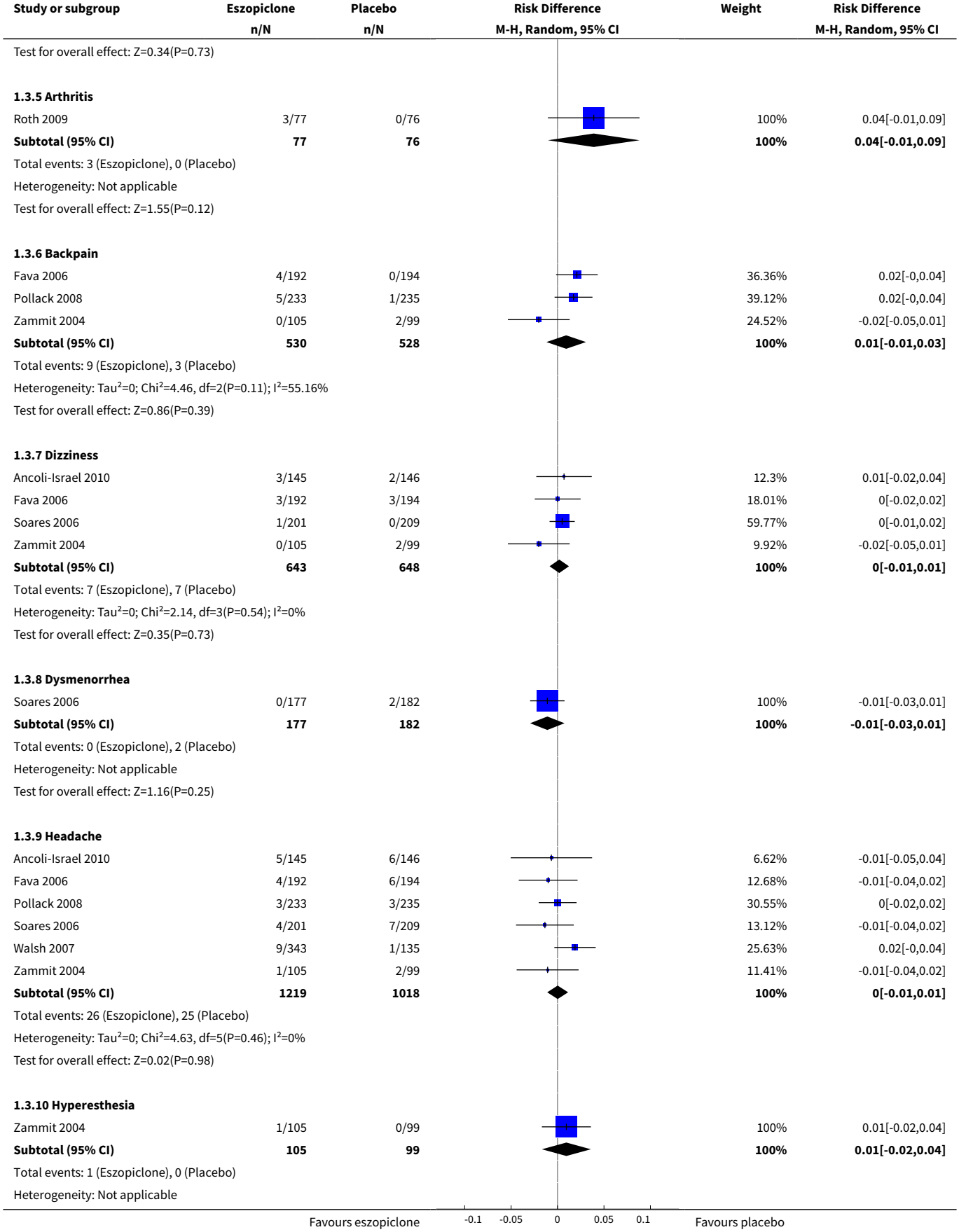
Favours eszopiclone — Favours placebo

Analysis 1.3. Comparison 1 Eszopiclone versus placebo, Outcome 3 Withdrawal symptoms.

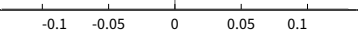
Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.3.1 Abdominal pain					
Walsh 2007	5/343	0/135		100%	0.01[-0,0.03]
Subtotal (95% CI)	**343**	**135**		**100%**	**0.01[-0,0.03]**
Total events: 5 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.71(P=0.09)					
1.3.2 Accidental injury					
Fava 2006	4/192	6/194		28.22%	-0.01[-0.04,0.02]
Walsh 2007	2/343	2/135		58.86%	-0.01[-0.03,0.01]
Zammit 2004	2/105	4/99		12.92%	-0.02[-0.07,0.03]
Subtotal (95% CI)	**640**	**428**		**100%**	**-0.01[-0.03,0.01]**
Total events: 8 (Eszopiclone), 12 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.24, df=2(P=0.89); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					
1.3.3 Agitation					
Ancoli-Israel 2010	1/145	0/146		34.02%	0.01[-0.01,0.03]
Soares 2006	1/201	0/209		65.98%	0[-0.01,0.02]
Subtotal (95% CI)	**346**	**355**		**100%**	**0.01[-0.01,0.02]**
Total events: 2 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
1.3.4 Anxiety					
Fava 2006	1/192	1/194		77.25%	0[-0.01,0.01]
Zammit 2004	1/105	0/99		22.75%	0.01[-0.02,0.04]
Subtotal (95% CI)	**297**	**293**		**100%**	**0[-0.01,0.01]**
Total events: 2 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=1(P=0.52); I^2=0%					



Favours eszopiclone — Favours placebo

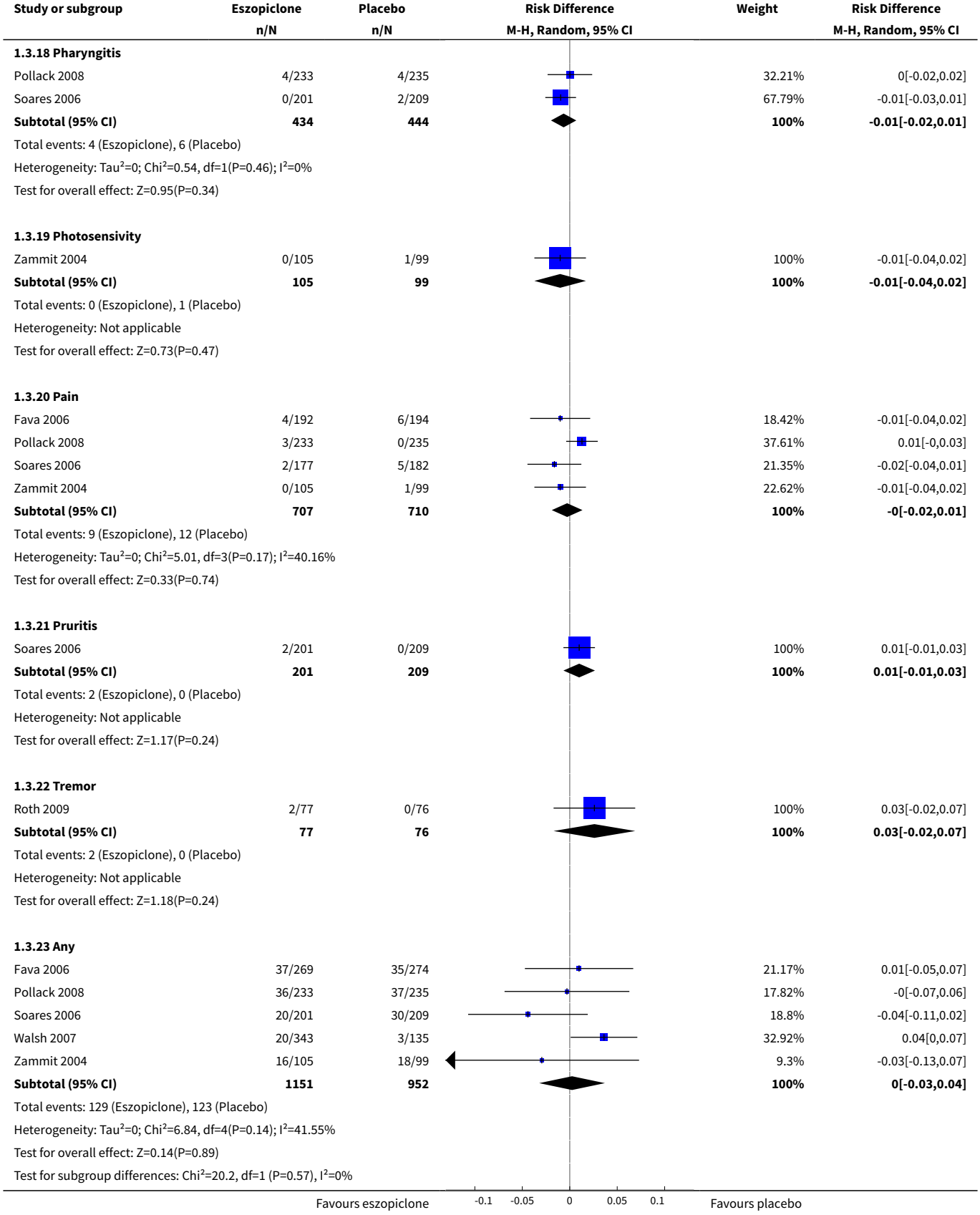


Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Test for overall effect: Z=0.71(P=0.48)					
1.3.11 Infection					
Walsh 2007	6/343	0/135		100%	0.02[-0,0.04]
Subtotal (95% CI)	**343**	**135**		**100%**	**0.02[-0,0.04]**
Total events: 6 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.95(P=0.05)					
1.3.12 Insomnia					
Fava 2006	1/192	1/194		100%	0[-0.01,0.01]
Subtotal (95% CI)	**192**	**194**		**100%**	**0[-0.01,0.01]**
Total events: 1 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
1.3.13 Memory impairment					
Fava 2006	1/192	1/194		100%	0[-0.01,0.01]
Subtotal (95% CI)	**192**	**194**		**100%**	**0[-0.01,0.01]**
Total events: 1 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
1.3.14 Nausea					
Fava 2006	2/192	1/194		64.63%	0.01[-0.01,0.02]
Zammit 2004	0/105	2/99		35.37%	-0.02[-0.05,0.01]
Subtotal (95% CI)	**297**	**293**		**100%**	**-0[-0.03,0.02]**
Total events: 2 (Eszopiclone), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=1(P=0.16); I^2=48.2%					
Test for overall effect: Z=0.29(P=0.77)					
1.3.15 Neurosis					
Zammit 2004	1/105	0/99		100%	0.01[-0.02,0.04]
Subtotal (95% CI)	**105**	**99**		**100%**	**0.01[-0.02,0.04]**
Total events: 1 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
1.3.16 Nightmares					
Zammit 2004	2/105	0/99		100%	0.02[-0.01,0.05]
Subtotal (95% CI)	**105**	**99**		**100%**	**0.02[-0.01,0.05]**
Total events: 2 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.17(P=0.24)					
1.3.17 Paresthesia					
Soares 2006	0/201	1/209		100%	-0[-0.02,0.01]
Subtotal (95% CI)	**201**	**209**		**100%**	**-0[-0.02,0.01]**
Total events: 0 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					



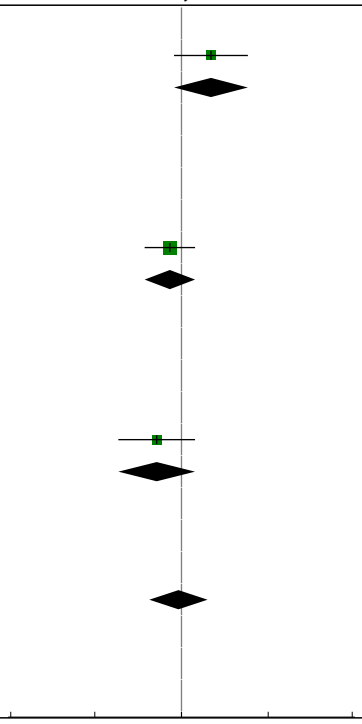
Favours eszopiclone

Favours placebo



Analysis 1.4. Comparison 1 Eszopiclone versus placebo, Outcome 4 Rebound insomnia.

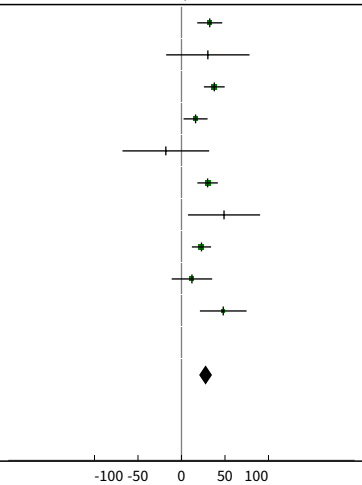
Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.4.1 Rebound - SOL							
Ancoli-Israel 2010	145	-7 (102.3)	146	-24 (81.8)		30.19%	17[-4.29,38.29]
Subtotal ***	**145**		**146**			**30.19%**	**17[-4.29,38.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.56(P=0.12)							
1.4.2 Rebound - WASO							
Ancoli-Israel 2010	145	-28.9 (70.3)	146	-22.1 (55.3)		40.74%	-6.71[-21.25,7.83]
Subtotal ***	**145**		**146**			**40.74%**	**-6.71[-21.25,7.83]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.9(P=0.37)							
1.4.3 Rebound - TST							
Ancoli-Israel 2010	145	34.7 (108.1)	146	49 (82.6)		29.08%	-14.3[-36.42,7.82]
Subtotal ***	**145**		**146**			**29.08%**	**-14.3[-36.42,7.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.27(P=0.21)							
Total ***	**435**		**438**			**100%**	**-1.76[-18.55,15.04]**
Heterogeneity: Tau^2=125.25; Chi^2=4.64, df=2(P=0.1); I^2=56.87%							
Test for overall effect: Z=0.21(P=0.84)							
Test for subgroup differences: Chi^2=4.64, df=1 (P=0.1), I^2=56.87%							



Favours eszopiclone — Favours placebo

Analysis 1.5. Comparison 1 Eszopiclone versus placebo, Outcome 5 Total sleep time (TST).

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ancoli-Israel 2010	194	357.3 (69.3)	194	324.8 (75)		13.87%	32.5[18.13,46.87]
Goforth 2014	32	412.5 (70.7)	20	382.2 (93.9)		2.2%	30.3[-17.59,78.19]
Krystal 2003	593	377.3 (70.5)	195	339.5 (74.7)		16.56%	37.72[25.79,49.65]
McCall 2006	136	48.6 (55)	128	32.4 (59)		14.48%	16.2[2.42,29.98]
Menza 2010	15	342 (69.6)	15	360 (69.6)		2.05%	-18[-67.81,31.81]
Pollack 2008	294	71.4 (66.2)	301	41.3 (79.5)		16.78%	30.02[18.27,41.77]
Scharf 2005	79	87 (142)	80	38.1 (124)		2.87%	48.9[7.44,90.36]
Soares 2006	201	56.6 (55)	209	33.6 (59)		17.66%	23[11.96,34.04]
Spierings 2015	35	378 (54)	40	366 (48)		7.5%	12[-11.27,35.27]
Zammit 2004	105	411.8 (124)	99	363.8 (63.5)		6.03%	48[21.19,74.81]
Total ***	**1684**		**1281**			**100%**	**27.7[20.3,35.09]**
Heterogeneity: Tau^2=48.92; Chi^2=14.86, df=9(P=0.09); I^2=39.43%							
Test for overall effect: Z=7.34(P<0.0001)							



Favours placebo — Favours eszopiclone

Analysis 1.6. Comparison 1 Eszopiclone versus placebo, Outcome 6 Next-day alertness.

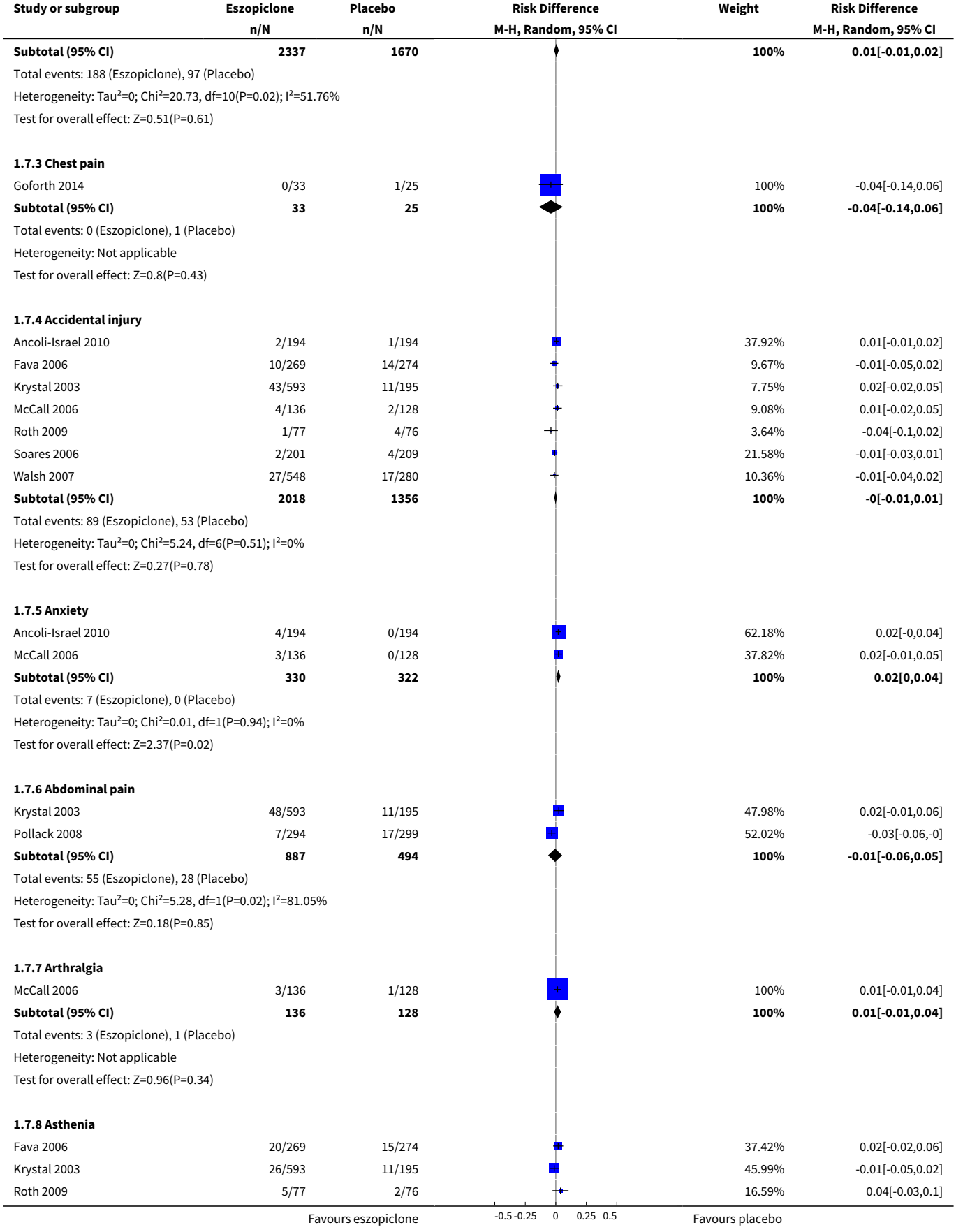
Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ancoli-Israel 2010	194	1 (1.3)	194	0.5 (1.3)		22.33%	0.5[0.24,0.76]
Krystal 2003	593	6.4 (1.7)	195	5.7 (1.7)		21.39%	0.7[0.43,0.97]
McCall 2006	136	7.3 (1.6)	128	7.3 (1.6)		14.04%	0[-0.39,0.39]
Menza 2010	15	6.9 (2)	15	5.9 (1.6)		1.77%	1[-0.3,2.3]
Roth 2009	77	7 (1.6)	76	6.4 (1.6)		9.44%	0.6[0.09,1.11]
Scharf 2005	79	7.3 (1.6)	80	6.8 (1.6)		9.73%	0.5[0,1]
Spierings 2015	35	6.9 (1.3)	40	6.6 (1.2)		7.85%	0.3[-0.27,0.87]
Zammit 2004	105	7 (1.4)	99	6.7 (1.5)		13.44%	0.35[-0.05,0.75]
Total ***	**1234**		**827**			**100%**	**0.46[0.28,0.63]**
Heterogeneity: Tau^2=0.02; Chi^2=10.12, df=7(P=0.18); I^2=30.85%							
Test for overall effect: Z=5.06(P<0.0001)							

Favours placebo — Favours eszopiclone

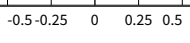
Analysis 1.7. Comparison 1 Eszopiclone versus placebo, Outcome 7 Adverse events.

Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.7.1 Serious adverse events					
Ancoli-Israel 2010	4/194	2/194		4.71%	0.01[-0.01,0.03]
Fava 2006	1/192	1/194		13.81%	0[-0.01,0.01]
Goforth 2014	0/33	0/25		0.64%	0[-0.07,0.07]
Krystal 2003	17/595	2/196		7.51%	0.02[-0,0.04]
McCall 2006	1/136	2/128		4.24%	-0.01[-0.03,0.02]
McCall 2010a	0/30	0/30		0.72%	0[-0.06,0.06]
Pollack 2008	3/294	5/301		8.32%	-0.01[-0.02,0.01]
Roth 2009	1/77	1/76		2.19%	-0[-0.04,0.04]
Scharf 2005	1/72	0/80		2.1%	0.01[-0.02,0.05]
Soares 2006	0/201	0/209		31.34%	0[-0.01,0.01]
Walsh 2007	2/548	3/280		16.58%	-0.01[-0.02,0.01]
Zammit 2004	0/105	0/99		7.84%	0[-0.02,0.02]
Subtotal (95% CI)	**2477**	**1812**		**100%**	**0[-0.01,0.01]**
Total events: 30 (Eszopiclone), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.88, df=11(P=0.81); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					
1.7.2 Dropout					
Ancoli-Israel 2010	14/194	9/194		9.41%	0.03[-0.02,0.07]
Fava 2006	17/270	21/275		10.38%	-0.01[-0.06,0.03]
Krystal 2003	76/593	14/195		9.81%	0.06[0.01,0.1]
McCall 2006	2/136	3/128		12.94%	-0.01[-0.04,0.02]
Menza 2010	0/15	0/15		2.33%	0[-0.12,0.12]
Pollack 2008	16/294	17/301		11.9%	-0[-0.04,0.03]
Roth 2009	2/77	3/76		7.59%	-0.01[-0.07,0.04]
Scharf 2005	2/79	5/80		6.51%	-0.04[-0.1,0.03]
Soares 2006	11/24	3/27		0.69%	0.35[0.12,0.58]
Walsh 2007	48/550	22/280		11.22%	0.01[-0.03,0.05]
Zammit 2004	0/105	0/99		17.22%	0[-0.02,0.02]

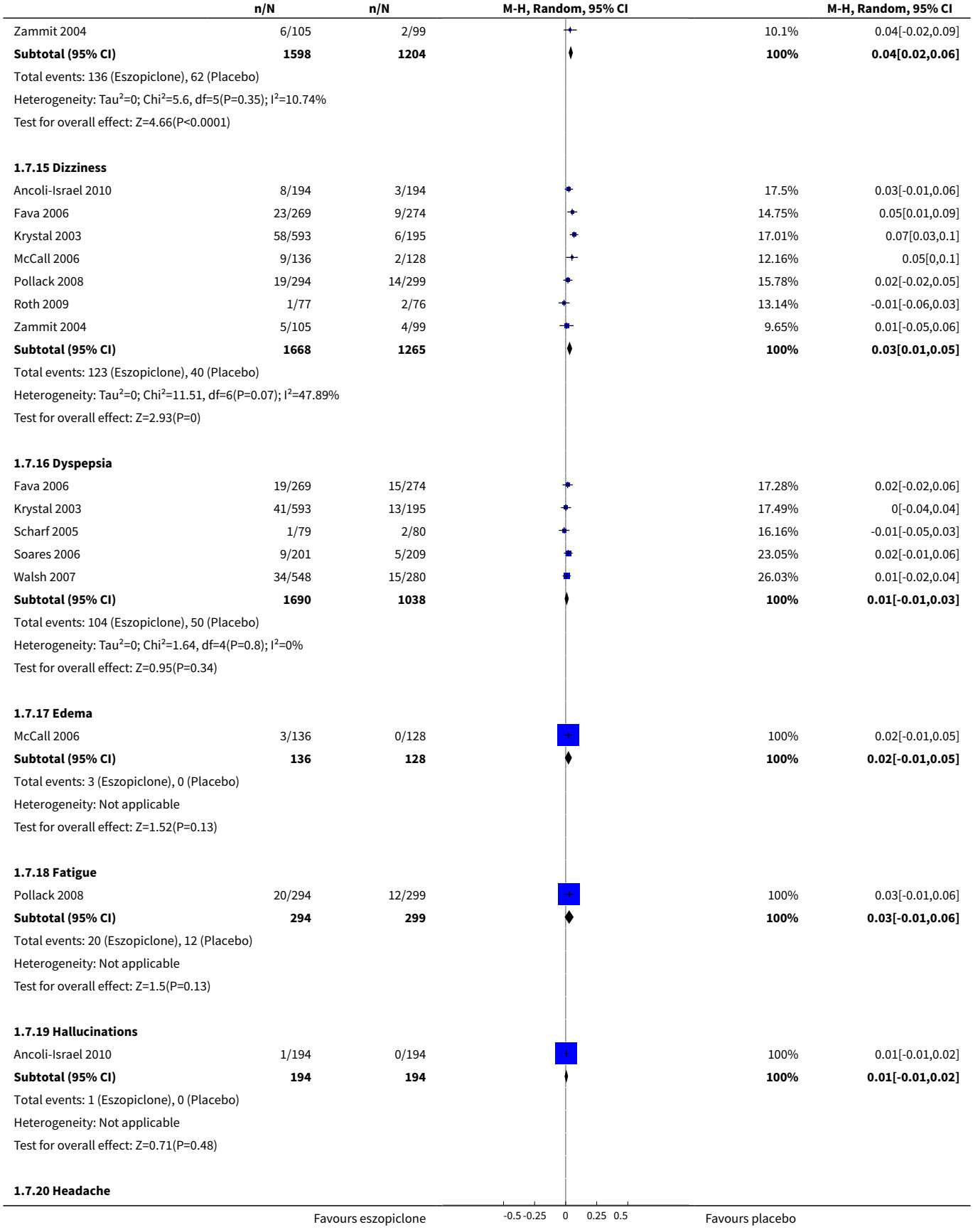
Favours eszopiclone — Favours placebo



Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Subtotal (95% CI)	**939**	**545**		**100%**	**0.01[-0.02,0.04]**
Total events: 51 (Eszopiclone), 28 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.36, df=2(P=0.31); I²=15.24%					
Test for overall effect: Z=0.56(P=0.58)					
1.7.9 Backpain					
Krystal 2003	45/593	6/195		18.98%	0.05[0.01,0.08]
McCall 2006	3/136	0/128		20.87%	0.02[-0.01,0.05]
Roth 2009	1/77	3/76		11.84%	-0.03[-0.08,0.02]
Soares 2006	10/201	4/209		17.53%	0.03[-0,0.07]
Walsh 2007	29/548	20/280		17.45%	-0.02[-0.05,0.02]
Zammit 2004	4/105	2/99		13.32%	0.02[-0.03,0.06]
Subtotal (95% CI)	**1660**	**987**		**100%**	**0.01[-0.01,0.04]**
Total events: 92 (Eszopiclone), 35 (Placebo)					
Heterogeneity: Tau²=0; Chi²=10.55, df=5(P=0.06); I²=52.62%					
Test for overall effect: Z=1.31(P=0.19)					
1.7.10 Confusion					
Roth 2009	2/77	0/76		100%	0.03[-0.02,0.07]
Subtotal (95% CI)	**77**	**76**		**100%**	**0.03[-0.02,0.07]**
Total events: 2 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					
1.7.11 Coughing					
Roth 2009	3/77	1/76		100%	0.03[-0.02,0.08]
Subtotal (95% CI)	**77**	**76**		**100%**	**0.03[-0.02,0.08]**
Total events: 3 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					
1.7.12 Decreased libido					
Pollack 2008	16/294	8/299		100%	0.03[-0,0.06]
Subtotal (95% CI)	**294**	**299**		**100%**	**0.03[-0,0.06]**
Total events: 16 (Eszopiclone), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
1.7.13 Diarrhea					
Krystal 2003	45/593	14/195		48.57%	0[-0.04,0.05]
Pollack 2008	22/294	19/299		51.43%	0.01[-0.03,0.05]
Subtotal (95% CI)	**887**	**494**		**100%**	**0.01[-0.02,0.04]**
Total events: 67 (Eszopiclone), 33 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%					
Test for overall effect: Z=0.52(P=0.6)					
1.7.14 Dry mouth					
Fava 2006	25/269	24/274		11.77%	0.01[-0.04,0.05]
Krystal 2003	39/593	3/195		33.18%	0.05[0.02,0.08]
McCall 2006	12/136	2/128		10.12%	0.07[0.02,0.12]
Pollack 2008	46/294	28/299		9.85%	0.06[0.01,0.12]
Soares 2006	8/201	3/209		24.97%	0.03[-0.01,0.06]

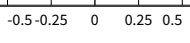


Favours eszopiclone Favours placebo



Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Zammit 2004	6/105	2/99		10.1%	0.04[-0.02,0.09]
Subtotal (95% CI)	**1598**	**1204**		**100%**	**0.04[0.02,0.06]**
Total events: 136 (Eszopiclone), 62 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.6, df=5(P=0.35); I^2=10.74%					
Test for overall effect: Z=4.66(P<0.0001)					
1.7.15 Dizziness					
Ancoli-Israel 2010	8/194	3/194		17.5%	0.03[-0.01,0.06]
Fava 2006	23/269	9/274		14.75%	0.05[0.01,0.09]
Krystal 2003	58/593	6/195		17.01%	0.07[0.03,0.1]
McCall 2006	9/136	2/128		12.16%	0.05[0,0.1]
Pollack 2008	19/294	14/299		15.78%	0.02[-0.02,0.05]
Roth 2009	1/77	2/76		13.14%	-0.01[-0.06,0.03]
Zammit 2004	5/105	4/99		9.65%	0.01[-0.05,0.06]
Subtotal (95% CI)	**1668**	**1265**		**100%**	**0.03[0.01,0.05]**
Total events: 123 (Eszopiclone), 40 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=11.51, df=6(P=0.07); I^2=47.89%					
Test for overall effect: Z=2.93(P=0)					
1.7.16 Dyspepsia					
Fava 2006	19/269	15/274		17.28%	0.02[-0.02,0.06]
Krystal 2003	41/593	13/195		17.49%	0[-0.04,0.04]
Scharf 2005	1/79	2/80		16.16%	-0.01[-0.05,0.03]
Soares 2006	9/201	5/209		23.05%	0.02[-0.01,0.06]
Walsh 2007	34/548	15/280		26.03%	0.01[-0.02,0.04]
Subtotal (95% CI)	**1690**	**1038**		**100%**	**0.01[-0.01,0.03]**
Total events: 104 (Eszopiclone), 50 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=4(P=0.8); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
1.7.17 Edema					
McCall 2006	3/136	0/128		100%	0.02[-0.01,0.05]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.02[-0.01,0.05]**
Total events: 3 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
1.7.18 Fatigue					
Pollack 2008	20/294	12/299		100%	0.03[-0.01,0.06]
Subtotal (95% CI)	**294**	**299**		**100%**	**0.03[-0.01,0.06]**
Total events: 20 (Eszopiclone), 12 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					
1.7.19 Hallucinations					
Ancoli-Israel 2010	1/194	0/194		100%	0.01[-0.01,0.02]
Subtotal (95% CI)	**194**	**194**		**100%**	**0.01[-0.01,0.02]**
Total events: 1 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
1.7.20 Headache					

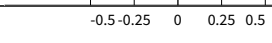
Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Ancoli-Israel 2010	27/194	24/194		10.75%	0.02[-0.05,0.08]
Fava 2006	45/269	40/274		13%	0.02[-0.04,0.08]
Goforth 2014	1/33	1/25		5.21%	-0.01[-0.11,0.09]
Krystal 2003	116/593	37/195		12%	0.01[-0.06,0.07]
Pollack 2008	57/294	45/299		13.19%	0.04[-0.02,0.1]
Roth 2009	8/77	6/76		5.84%	0.02[-0.07,0.12]
Scharf 2005	12/79	12/80		3.92%	0[-0.11,0.11]
Soares 2006	29/201	31/209		10.38%	-0[-0.07,0.06]
Walsh 2007	83/548	42/280		18.33%	0[-0.05,0.05]
Zammit 2004	12/105	8/99		7.38%	0.03[-0.05,0.11]
Subtotal (95% CI)	**2393**	**1731**		**100%**	**0.01[-0.01,0.04]**
Total events: 390 (Eszopiclone), 246 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=9(P=0.99); I^2=0%					
Test for overall effect: Z=1.26(P=0.21)					
1.7.21 Infection					
Fava 2006	12/269	14/274		35.31%	-0.01[-0.04,0.03]
Krystal 2003	94/593	13/195		32.83%	0.09[0.05,0.14]
Walsh 2007	91/548	34/280		31.86%	0.04[-0,0.09]
Subtotal (95% CI)	**1410**	**749**		**100%**	**0.04[-0.02,0.1]**
Total events: 197 (Eszopiclone), 61 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=11.89, df=2(P=0); I^2=83.17%					
Test for overall effect: Z=1.35(P=0.18)					
1.7.22 Memory impairment					
Ancoli-Israel 2010	2/194	0/194		67.32%	0.01[-0.01,0.03]
McCall 2006	2/136	0/128		32.68%	0.01[-0.01,0.04]
Subtotal (95% CI)	**330**	**322**		**100%**	**0.01[-0,0.03]**
Total events: 4 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.77); I^2=0%					
Test for overall effect: Z=1.62(P=0.11)					
1.7.23 Mood changes					
McCall 2006	2/136	0/128		100%	0.01[-0.01,0.04]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.01[-0.01,0.04]**
Total events: 2 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.16(P=0.25)					
1.7.24 Muscle pain					
Walsh 2007	33/548	8/280		100%	0.03[0,0.06]
Subtotal (95% CI)	**548**	**280**		**100%**	**0.03[0,0.06]**
Total events: 33 (Eszopiclone), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.22(P=0.03)					
1.7.25 Nausea					
Fava 2006	35/269	35/274		31.6%	0[-0.05,0.06]
Krystal 2003	67/593	11/195		35.84%	0.06[0.02,0.1]
Pollack 2008	30/294	44/299		32.56%	-0.05[-0.1,0.01]
Subtotal (95% CI)	**1156**	**768**		**100%**	**0.01[-0.06,0.07]**
Total events: 132 (Eszopiclone), 90 (Placebo)					



Favours eszopiclone

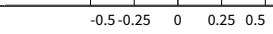
Favours placebo

Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=9.51, df=2(P=0.01); I²=78.96%					
Test for overall effect: Z=0.2(P=0.84)					
1.7.26 Nervousness					
Ancoli-Israel 2010	3/194	0/194		37.24%	0.02[-0,0.04]
Fava 2006	22/269	15/274		12.59%	0.03[-0.02,0.07]
McCall 2006	5/136	2/128		14.97%	0.02[-0.02,0.06]
Roth 2009	1/77	1/76		16.51%	-0[-0.04,0.04]
Zammit 2004	0/105	2/99		18.7%	-0.02[-0.05,0.01]
Subtotal (95% CI)	**781**	**771**		**100%**	**0.01[-0.01,0.02]**
Total events: 31 (Eszopiclone), 20 (Placebo)					
Heterogeneity: Tau²=0; Chi²=5.23, df=4(P=0.26); I²=23.46%					
Test for overall effect: Z=1.02(P=0.31)					
1.7.27 Nightmares					
Roth 2009	1/77	0/76		53.72%	0.01[-0.02,0.05]
Zammit 2004	2/105	2/99		46.28%	-0[-0.04,0.04]
Subtotal (95% CI)	**182**	**175**		**100%**	**0.01[-0.02,0.03]**
Total events: 3 (Eszopiclone), 2 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.3, df=1(P=0.59); I²=0%					
Test for overall effect: Z=0.49(P=0.63)					
1.7.28 Pharyngitis					
Ancoli-Israel 2010	11/194	12/194		13.85%	-0.01[-0.05,0.04]
Fava 2006	17/269	12/274		19.91%	0.02[-0.02,0.06]
Krystal 2003	59/593	10/195		18.79%	0.05[0.01,0.09]
Pollack 2008	28/294	29/301		13.7%	-0[-0.05,0.05]
Roth 2009	8/77	2/76		5.62%	0.08[0,0.15]
Walsh 2007	33/548	11/280		28.13%	0.02[-0.01,0.05]
Subtotal (95% CI)	**1975**	**1320**		**100%**	**0.02[0,0.04]**
Total events: 156 (Eszopiclone), 76 (Placebo)					
Heterogeneity: Tau²=0; Chi²=5.95, df=5(P=0.31); I²=15.98%					
Test for overall effect: Z=2.33(P=0.02)					
1.7.29 Pain					
Fava 2006	13/269	15/274		22.46%	-0.01[-0.04,0.03]
Krystal 2003	67/593	12/195		19.27%	0.05[0.01,0.09]
McCall 2006	8/136	4/128		15.53%	0.03[-0.02,0.08]
Soares 2006	9/201	5/209		23.78%	0.02[-0.01,0.06]
Walsh 2007	48/548	29/280		18.96%	-0.02[-0.06,0.03]
Subtotal (95% CI)	**1747**	**1086**		**100%**	**0.01[-0.01,0.04]**
Total events: 145 (Eszopiclone), 65 (Placebo)					
Heterogeneity: Tau²=0; Chi²=6.54, df=4(P=0.16); I²=38.86%					
Test for overall effect: Z=1.23(P=0.22)					
1.7.30 Poor concentration					
Ancoli-Israel 2010	1/194	0/194		100%	0.01[-0.01,0.02]
Subtotal (95% CI)	**194**	**194**		**100%**	**0.01[-0.01,0.02]**
Total events: 1 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					



Favours eszopiclone Favours placebo

Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.7.31 Respiratory infection					
Pollack 2008	19/294	12/299		41.82%	0.02[-0.01,0.06]
Roth 2009	3/77	7/76		14%	-0.05[-0.13,0.02]
Soares 2006	7/201	6/209		44.19%	0.01[-0.03,0.04]
Subtotal (95% CI)	**572**	**584**		**100%**	**0.01[-0.03,0.04]**
Total events: 29 (Eszopiclone), 25 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.18, df=2(P=0.2); I^2=37.2%					
Test for overall effect: Z=0.34(P=0.73)					
1.7.32 Rhinitis					
Krystal 2003	42/593	9/195		100%	0.02[-0.01,0.06]
Subtotal (95% CI)	**593**	**195**		**100%**	**0.02[-0.01,0.06]**
Total events: 42 (Eszopiclone), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
1.7.33 Sinusitis					
Krystal 2003	25/593	11/195		100%	-0.01[-0.05,0.02]
Subtotal (95% CI)	**593**	**195**		**100%**	**-0.01[-0.05,0.02]**
Total events: 25 (Eszopiclone), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.77(P=0.44)					
1.7.34 Skin rash					
Krystal 2003	31/593	6/195		67.75%	0.02[-0.01,0.05]
McCall 2006	5/136	4/128		32.25%	0.01[-0.04,0.05]
Subtotal (95% CI)	**729**	**323**		**100%**	**0.02[-0.01,0.04]**
Total events: 36 (Eszopiclone), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=1.29(P=0.2)					
1.7.35 Somnolence					
Fava 2006	23/269	20/274		12.01%	0.01[-0.03,0.06]
Krystal 2003	54/593	5/195		21.95%	0.07[0.03,0.1]
McCall 2006	9/136	7/128		7.81%	0.01[-0.05,0.07]
Pollack 2008	31/294	22/299		11.78%	0.03[-0.01,0.08]
Roth 2009	3/77	2/76		8.11%	0.01[-0.04,0.07]
Scharf 2005	3/79	2/80		8.67%	0.01[-0.04,0.07]
Walsh 2007	48/548	9/280		22.7%	0.06[0.02,0.09]
Zammit 2004	8/105	3/99		6.98%	0.05[-0.02,0.11]
Subtotal (95% CI)	**2101**	**1431**		**100%**	**0.04[0.02,0.06]**
Total events: 179 (Eszopiclone), 70 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.78, df=7(P=0.35); I^2=10.05%					
Test for overall effect: Z=4.55(P<0.0001)					
1.7.36 Unpleasant taste					
Ancoli-Israel 2010	24/194	3/194		12.58%	0.11[0.06,0.16]
Krystal 2003	155/593	11/195		12.77%	0.2[0.16,0.25]
McCall 2006	17/136	0/128		11.69%	0.13[0.07,0.18]
Pollack 2008	71/294	11/299		12.11%	0.2[0.15,0.26]
Roth 2009	21/77	0/76		7.21%	0.27[0.17,0.37]
Scharf 2005	9/79	1/80		9.71%	0.1[0.03,0.18]



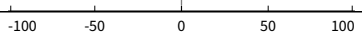
Favours eszopiclone Favours placebo

Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Soares 2006	35/201	1/209		12.13%	0.17[0.12,0.22]
Walsh 2007	108/548	3/280		14.23%	0.19[0.15,0.22]
Zammit 2004	35/105	3/99		7.58%	0.3[0.21,0.4]
Subtotal (95% CI)	**2227**	**1560**		**100%**	**0.18[0.14,0.21]**
Total events: 475 (Eszopiclone), 33 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.37, df=8(P=0); I^2=71.8%					
Test for overall effect: Z=9.72(P<0.0001)					
Test for subgroup differences: Chi^2=145.76, df=1 (P<0.0001), I^2=75.99%					

Favours eszopiclone | Favours placebo

Analysis 1.8. Comparison 1 Eszopiclone versus placebo, Outcome 8 Subgroups: insomnia type - SOL.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.8.1 Primary insomnia: SOL							
Ancoli-Israel 2010	194	52 (55)	194	62.5 (65.8)		15.46%	-10.5[-22.57,1.57]
Krystal 2003	593	46 (47.4)	195	65.7 (61.3)		25.41%	-19.7[-29.11,-10.29]
McCall 2006	136	-40.8 (59.4)	128	-29.5 (55.7)		11.68%	-11.3[-25.18,2.58]
Scharf 2005	79	-70 (175)	80	-41.4 (146)		0.9%	-28.6[-78.73,21.53]
Zammit 2004	105	44.5 (68.8)	99	58.4 (42.9)		9.2%	-13.9[-29.54,1.74]
Subtotal ***	**1107**		**696**			**62.65%**	**-15.14[-21.13,-9.15]**
Heterogeneity: Tau^2=0; Chi^2=2.06, df=4(P=0.72); I^2=0%							
Test for overall effect: Z=4.95(P<0.0001)							
1.8.2 Comorbid insomnia: SOL							
Goforth 2014	32	18.4 (14)	20	23.3 (16.9)		28.72%	-4.9[-13.75,3.95]
Soares 2006	201	-25.8 (109)	209	-10.1 (42.9)		8.63%	-15.7[-31.85,0.45]
Subtotal ***	**233**		**229**			**37.35%**	**-8.1[-17.77,1.57]**
Heterogeneity: Tau^2=14.16; Chi^2=1.32, df=1(P=0.25); I^2=24.28%							
Test for overall effect: Z=1.64(P=0.1)							
Total ***	**1340**		**925**			**100%**	**-12.25[-16.99,-7.5]**
Heterogeneity: Tau^2=0; Chi^2=5.78, df=6(P=0.45); I^2=0%							
Test for overall effect: Z=5.06(P<0.0001)							
Test for subgroup differences: Chi^2=1.47, df=1 (P=0.23), I^2=32.03%							

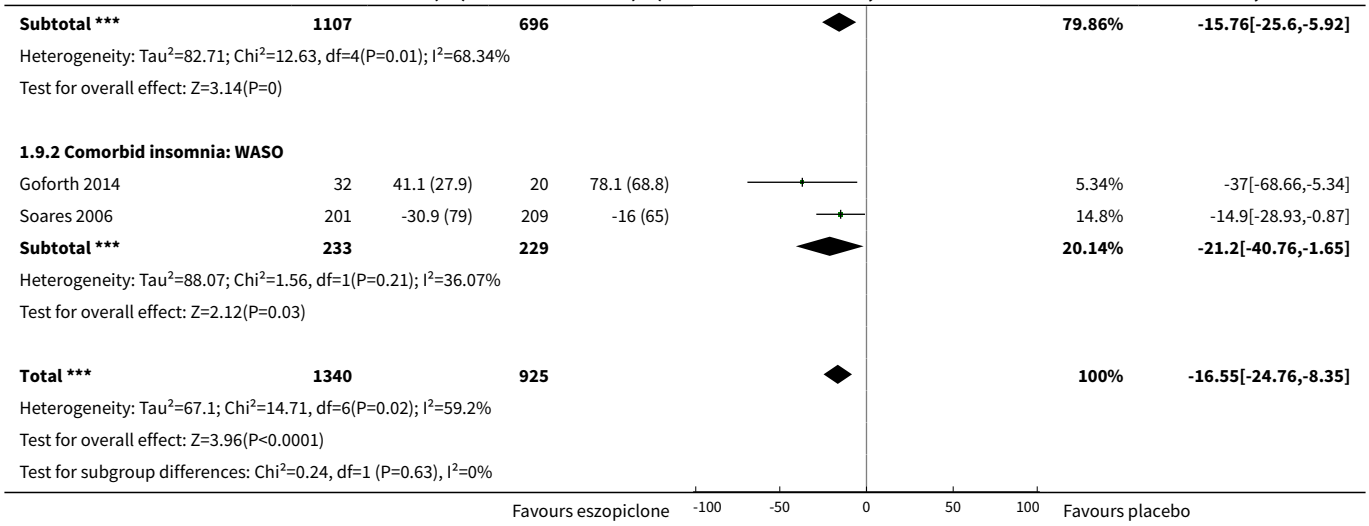


Favours eszopiclone | Favours placebo

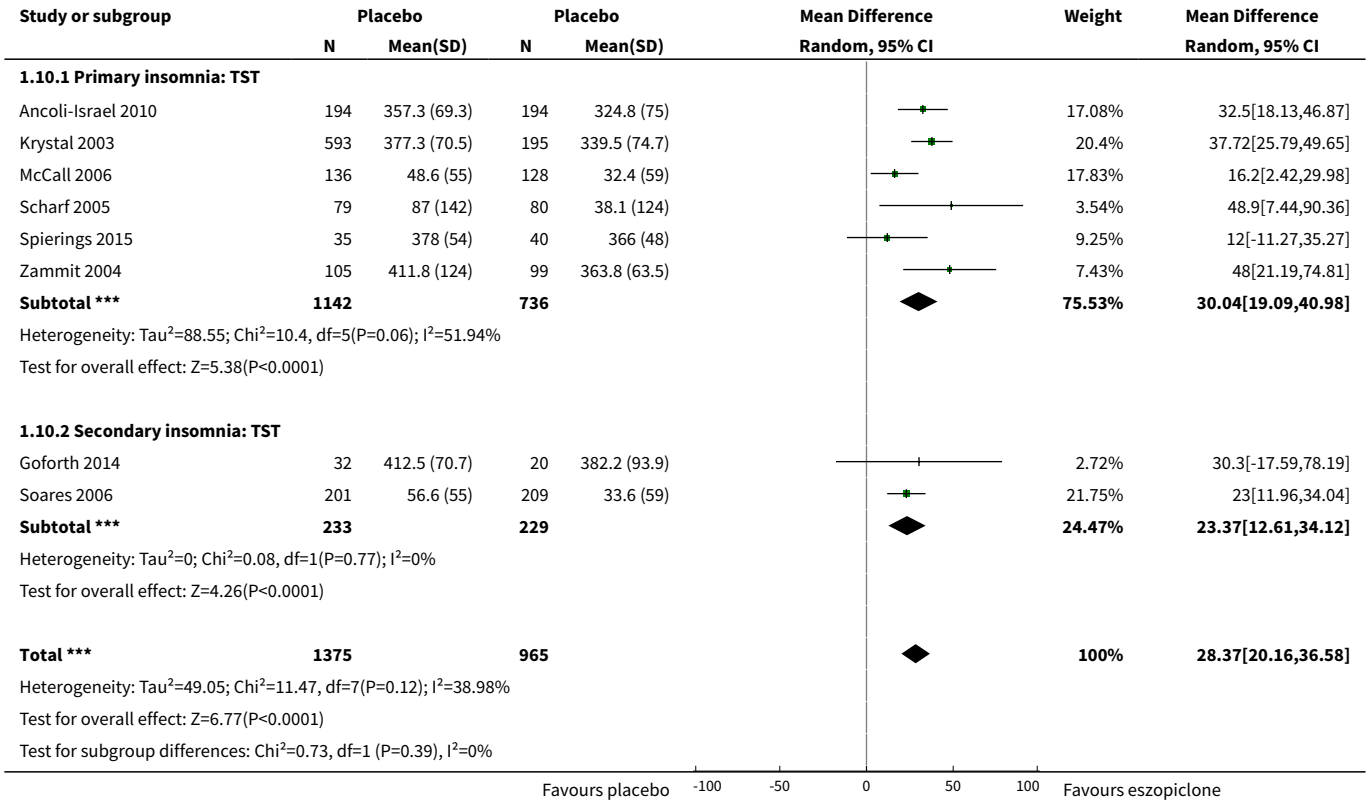
Analysis 1.9. Comparison 1 Eszopiclone versus placebo, Outcome 9 Subgroups: insomnia type - WASO.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Primary insomnia: WASO							
Ancoli-Israel 2010	194	57.8 (55)	194	76.8 (55)		17.82%	-19[-29.95,-8.05]
Krystal 2003	593	43.8 (68.4)	195	55.9 (71.2)		17.35%	-12.1[-23.51,-0.69]
McCall 2006	136	-31.3 (45.7)	128	-24.5 (48.3)		17.4%	-6.8[-18.16,4.56]
Scharf 2005	79	-39.9 (79)	80	8.3 (65)		8.81%	-48.2[-70.7,-25.7]
Zammit 2004	105	41.2 (39)	99	49.1 (36.1)		18.49%	-7.9[-18.21,2.41]

Favours eszopiclone | Favours placebo

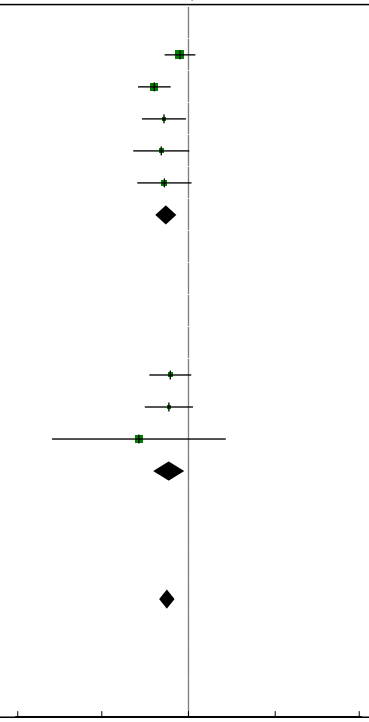


Analysis 1.10. Comparison 1 Eszopiclone versus placebo, Outcome 10 Subgroups: insomnia type - TST.



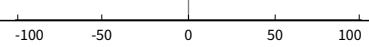
Analysis 1.11. Comparison 1 Eszopiclone versus placebo, Outcome 11 Subgrups: age groups - SOL.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 Younger age - SOL							
Goforth 2014	32	18.4 (14)	20	23.3 (16.9)		25.17%	-4.9[-13.75,3.95]
Krystal 2003	593	46 (47.4)	195	65.7 (61.3)		22.28%	-19.7[-29.11,-10.29]
Pollack 2008	294	-41.8 (69.8)	301	-27.6 (86.8)		12.35%	-14.15[-26.79,-1.51]
Soares 2006	201	-25.8 (109)	209	-10.1 (42.9)		7.56%	-15.7[-31.85,0.45]
Zammit 2004	105	44.5 (68.8)	99	58.4 (42.9)		8.07%	-13.9[-29.54,1.74]
Subtotal ***	**1225**		**824**			**75.43%**	**-13.08[-19.15,-7]**
Heterogeneity: Tau^2=11.84; Chi^2=5.31, df=4(P=0.26); I^2=24.67%							
Test for overall effect: Z=4.22(P<0.0001)							
1.11.2 Older age - SOL							
Ancoli-Israel 2010	194	52 (55)	194	62.5 (65.8)		13.55%	-10.5[-22.57,1.57]
McCall 2006	136	-40.8 (59.4)	128	-29.5 (55.7)		10.24%	-11.3[-25.18,2.58]
Scharf 2005	79	-70 (175)	80	-41.4 (146)		0.79%	-28.6[-78.73,21.53]
Subtotal ***	**409**		**402**			**24.57%**	**-11.41[-20.37,-2.45]**
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%							
Test for overall effect: Z=2.5(P=0.01)							
Total ***	**1634**		**1226**			**100%**	**-12.48[-16.92,-8.04]**
Heterogeneity: Tau^2=0; Chi^2=5.86, df=7(P=0.56); I^2=0%							
Test for overall effect: Z=5.51(P<0.0001)							
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.76), I^2=0%							



Analysis 1.12. Comparison 1 Eszopiclone versus placebo, Outcome 12 Subgroups: age groups - WASO.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 Younger age - WASO							
Goforth 2014	32	41.1 (27.9)	20	78.1 (68.8)		5.34%	-37[-68.66,-5.34]
Krystal 2003	593	43.8 (68.4)	195	55.9 (71.2)		17.35%	-12.1[-23.51,-0.69]
Soares 2006	201	-30.9 (79)	209	-16 (65)		14.8%	-14.9[-28.93,-0.87]
Zammit 2004	105	41.2 (39)	99	49.1 (36.1)		18.49%	-7.9[-18.21,2.41]
Subtotal ***	**931**		**523**			**55.97%**	**-12.2[-19.02,-5.37]**
Heterogeneity: Tau^2=2.77; Chi^2=3.17, df=3(P=0.37); I^2=5.26%							
Test for overall effect: Z=3.5(P=0)							
1.12.2 Older age - WASO							
Ancoli-Israel 2010	194	57.8 (55)	194	76.8 (55)		17.82%	-19[-29.95,-8.05]
McCall 2006	136	-31.3 (45.7)	128	-24.5 (48.3)		17.4%	-6.8[-18.16,4.56]
Scharf 2005	79	-39.9 (79)	80	8.3 (65)		8.81%	-48.2[-70.7,-25.7]
Subtotal ***	**409**		**402**			**44.03%**	**-22.16[-40.7,-3.63]**
Heterogeneity: Tau^2=209.93; Chi^2=10.61, df=2(P=0); I^2=81.15%							
Test for overall effect: Z=2.34(P=0.02)							
Total ***	**1340**		**925**			**100%**	**-16.55[-24.76,-8.35]**
Heterogeneity: Tau^2=67.1; Chi^2=14.71, df=6(P=0.02); I^2=59.2%							
Test for overall effect: Z=3.96(P<0.0001)							



Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=0.98, df=1 (P=0.32), I²=0%							

Favours eszopiclone -100 -50 0 50 100 Favours placebo

Analysis 1.13. Comparison 1 Eszopiclone versus placebo, Outcome 13 Subgroups: age groups - TST.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.13.1 Younger age - TST							
Goforth 2014	32	412.5 (70.7)	20	382.2 (93.9)		1.88%	30.3[-17.59,78.19]
Krystal 2003	593	377.3 (70.5)	195	339.5 (74.7)		17.55%	37.72[25.79,49.65]
Pollack 2008	294	71.4 (66.2)	301	41.3 (79.5)		17.84%	30.02[18.27,41.77]
Soares 2006	201	56.6 (55)	209	33.6 (59)		19.06%	23[11.96,34.04]
Spierings 2015	35	378 (54)	40	366 (48)		6.9%	12[-11.27,35.27]
Zammit 2004	105	411.8 (124)	99	363.8 (63.5)		5.43%	48[21.19,74.81]
Subtotal ***	**1260**		**864**			**68.66%**	**29.66[21.6,37.72]**
Heterogeneity: Tau²=28.96; Chi²=7.17, df=5(P=0.21); I²=30.24%							
Test for overall effect: Z=7.21(P<0.0001)							
1.13.2 Older age - TST							
Ancoli-Israel 2010	194	357.3 (69.3)	194	324.8 (75)		14.06%	32.5[18.13,46.87]
McCall 2006	136	48.6 (55)	128	32.4 (59)		14.82%	16.2[2.42,29.98]
Scharf 2005	79	87 (142)	80	38.1 (124)		2.47%	48.9[7.44,90.36]
Subtotal ***	**409**		**402**			**31.34%**	**27.01[11.83,42.18]**
Heterogeneity: Tau²=83.54; Chi²=3.88, df=2(P=0.14); I²=48.51%							
Test for overall effect: Z=3.49(P=0)							
Total ***	**1669**		**1266**			**100%**	**28.54[21.81,35.27]**
Heterogeneity: Tau²=30.24; Chi²=11.57, df=8(P=0.17); I²=30.84%							
Test for overall effect: Z=8.31(P<0.0001)							
Test for subgroup differences: Chi²=0.09, df=1 (P=0.76), I²=0%							

Favours placebo -100 -50 0 50 100 Favours eszopiclone

Analysis 1.14. Comparison 1 Eszopiclone versus placebo, Outcome 14 Subgroups: age groups - alertness.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.14.1 Younger age: next-day alertness							
Krystal 2003	593	6.4 (1.7)	195	5.7 (1.7)		21.44%	0.7[0.43,0.97]
Roth 2009	77	7 (1.6)	76	6.4 (1.6)		9.8%	0.6[0.09,1.11]
Spierings 2015	35	6.9 (1.3)	40	6.6 (1.2)		8.19%	0.3[-0.27,0.87]
Zammit 2004	105	7 (1.4)	99	6.7 (1.5)		13.79%	0.35[-0.05,0.75]
Subtotal ***	**810**		**410**			**53.22%**	**0.56[0.37,0.75]**
Heterogeneity: Tau²=0; Chi²=2.92, df=3(P=0.4); I²=0%							
Test for overall effect: Z=5.68(P<0.0001)							
1.14.2 Older age: next-day alertness							
Ancoli-Israel 2010	194	1 (1.3)	194	0.5 (1.3)		22.32%	0.5[0.24,0.76]

Favours eszopiclone -100 -50 0 50 100 Favours placebo

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
McCall 2006	136	7.3 (1.6)	128	7.3 (1.6)		14.38%	0[-0.39,0.39]
Scharf 2005	79	7.3 (1.6)	80	6.8 (1.6)		10.09%	0.5[0,1]
Subtotal * **	**409**		**402**			**46.78%**	**0.34[0.01,0.67]**
Heterogeneity: Tau²=0.05; Chi²=4.76, df=2(P=0.09); I²=57.97%							
Test for overall effect: Z=2.01(P=0.04)							
Total * **	**1219**		**812**			**100%**	**0.44[0.26,0.63]**
Heterogeneity: Tau²=0.02; Chi²=9.48, df=6(P=0.15); I²=36.7%							
Test for overall effect: Z=4.77(P<0.0001)							
Test for subgroup differences: Chi²=1.27, df=1 (P=0.26), I²=21.06%							

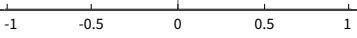
Favours eszopiclone -100 -50 0 50 100 Favours placebo

Analysis 1.15. Comparison 1 Eszopiclone versus placebo, Outcome 15 Subgroups: older participants - adverse events.

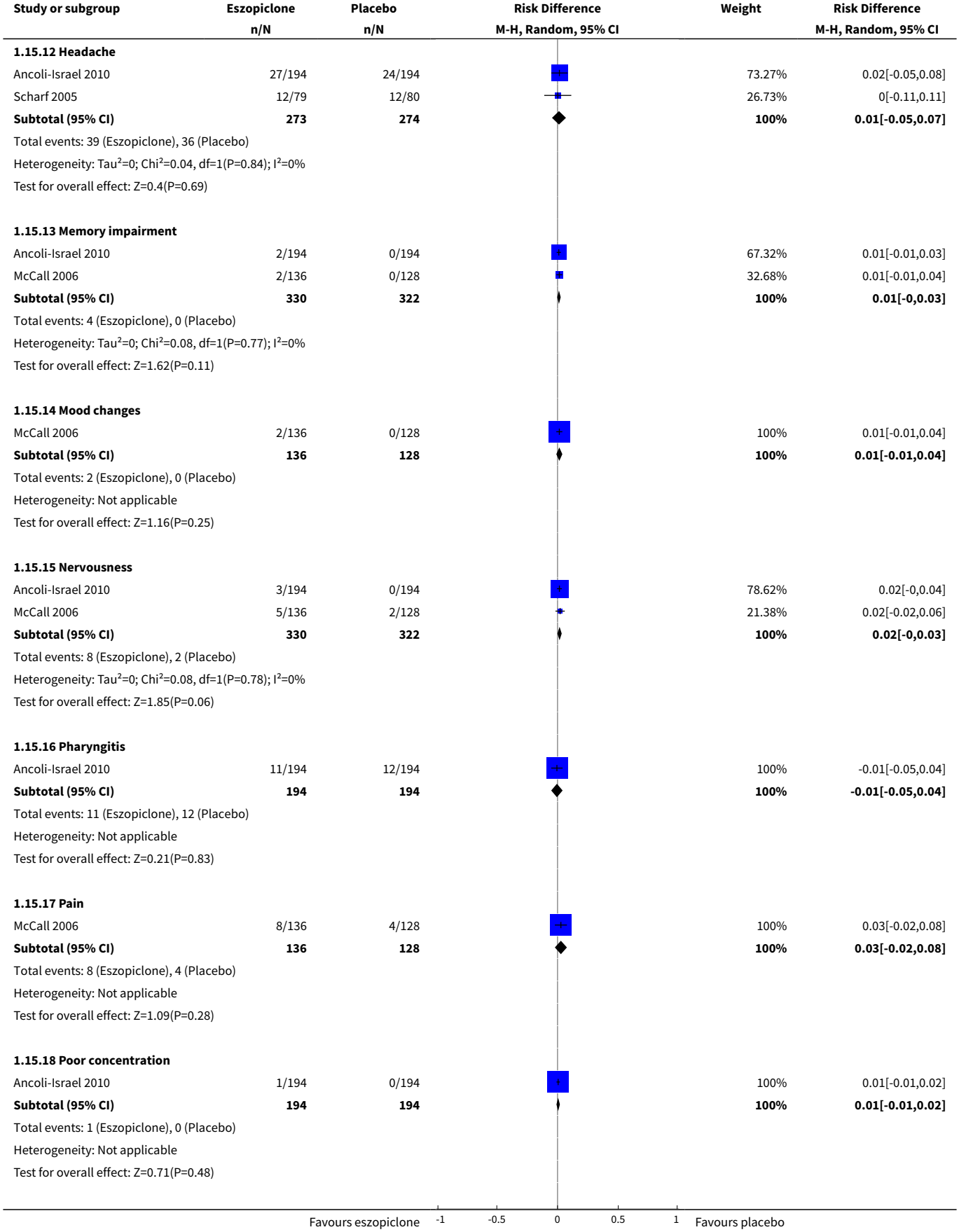
Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.15.1 Serious adverse events					
Ancoli-Israel 2010	4/194	2/194		42.6%	0.01[-0.01,0.03]
McCall 2006	1/136	2/128		38.4%	-0.01[-0.03,0.02]
Scharf 2005	1/72	0/80		18.99%	0.01[-0.02,0.05]
Subtotal (95% CI)	**402**	**402**		**100%**	**0[-0.01,0.02]**
Total events: 6 (Eszopiclone), 4 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.41, df=2(P=0.49); I²=0%					
Test for overall effect: Z=0.47(P=0.64)					
1.15.2 Dropout					
Ancoli-Israel 2010	14/194	9/194		31.46%	0.03[-0.02,0.07]
McCall 2006	2/136	3/128		48.59%	-0.01[-0.04,0.02]
Scharf 2005	2/79	5/80		19.94%	-0.04[-0.1,0.03]
Subtotal (95% CI)	**409**	**402**		**100%**	**-0[-0.03,0.03]**
Total events: 18 (Eszopiclone), 17 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.87, df=2(P=0.24); I²=30.39%					
Test for overall effect: Z=0.22(P=0.82)					
1.15.3 Accidental injury					
Ancoli-Israel 2010	2/194	1/194		80.68%	0.01[-0.01,0.02]
McCall 2006	4/136	2/128		19.32%	0.01[-0.02,0.05]
Subtotal (95% CI)	**330**	**322**		**100%**	**0.01[-0.01,0.02]**
Total events: 6 (Eszopiclone), 3 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.23, df=1(P=0.63); I²=0%					
Test for overall effect: Z=0.85(P=0.39)					
1.15.4 Anxiety					
Ancoli-Israel 2010	4/194	0/194		62.18%	0.02[-0,0.04]
McCall 2006	3/136	0/128		37.82%	0.02[-0.01,0.05]
Subtotal (95% CI)	**330**	**322**		**100%**	**0.02[0,0.04]**
Total events: 7 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%					

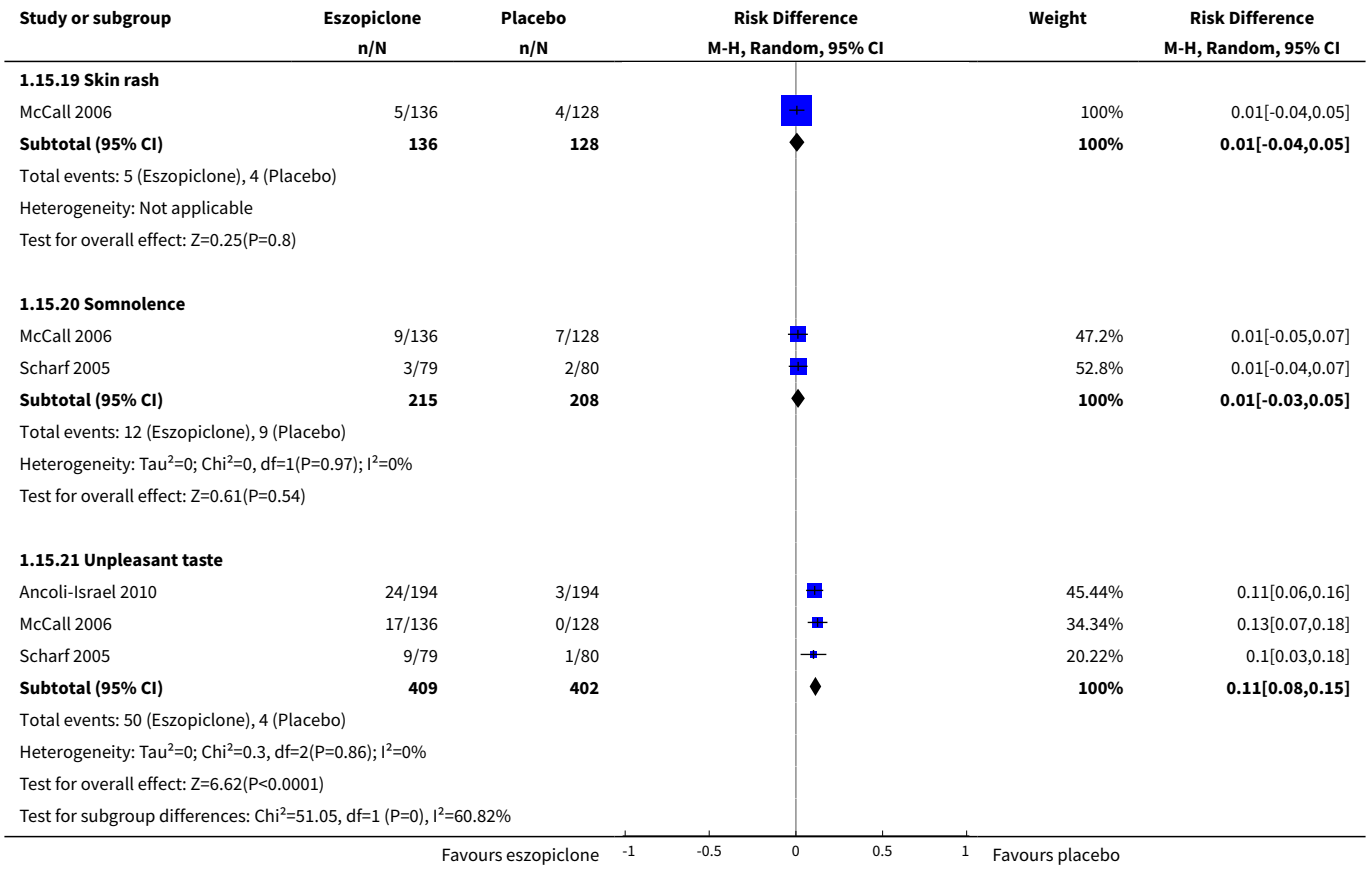
Favours eszopiclone -1 -0.5 0 0.5 1 Favours placebo

Study or subgroup	Eszopiclone n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Test for overall effect: Z=2.37(P=0.02)					
1.15.5 Arthralgia					
McCall 2006	3/136	1/128		100%	0.01[-0.01,0.04]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.01[-0.01,0.04]**
Total events: 3 (Eszopiclone), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
1.15.6 Backpain					
McCall 2006	3/136	0/128		100%	0.02[-0.01,0.05]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.02[-0.01,0.05]**
Total events: 3 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
1.15.7 Dry mouth					
McCall 2006	12/136	2/128		100%	0.07[0.02,0.12]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.07[0.02,0.12]**
Total events: 12 (Eszopiclone), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.72(P=0.01)					
1.15.8 Dizziness					
Ancoli-Israel 2010	8/194	3/194		67.06%	0.03[-0.01,0.06]
McCall 2006	9/136	2/128		32.94%	0.05[0,0.1]
Subtotal (95% CI)	**330**	**322**		**100%**	**0.03[0.01,0.06]**
Total events: 17 (Eszopiclone), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=2.47(P=0.01)					
1.15.9 Dyspepsia					
Scharf 2005	1/79	2/80		100%	-0.01[-0.05,0.03]
Subtotal (95% CI)	**79**	**80**		**100%**	**-0.01[-0.05,0.03]**
Total events: 1 (Eszopiclone), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
1.15.10 Edema					
McCall 2006	3/136	0/128		100%	0.02[-0.01,0.05]
Subtotal (95% CI)	**136**	**128**		**100%**	**0.02[-0.01,0.05]**
Total events: 3 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
1.15.11 Hallucinations					
Ancoli-Israel 2010	1/194	0/194		100%	0.01[-0.01,0.02]
Subtotal (95% CI)	**194**	**194**		**100%**	**0.01[-0.01,0.02]**
Total events: 1 (Eszopiclone), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					

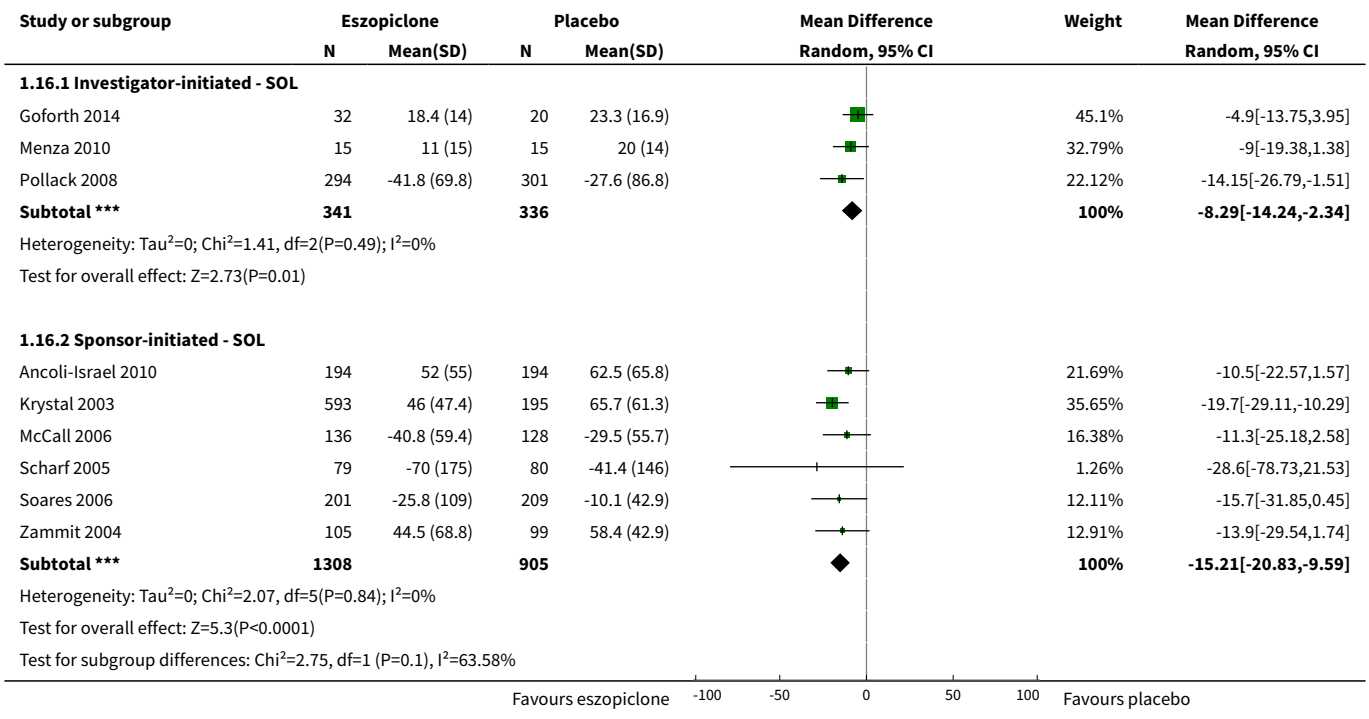


Favours eszopiclone Favours placebo





Analysis 1.16. Comparison 1 Eszopiclone versus placebo, Outcome 16 Subgroups: study initiation - SOL.



Analysis 1.17. Comparison 1 Eszopiclone versus placebo, Outcome 17 Subgroups: study initiation - WASO.

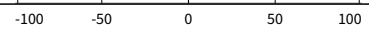
Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.17.1 Investigator-initiated WASO							
Goforth 2014	32	41.1 (27.9)	20	78.1 (68.8)		53.61%	-37[-68.66,-5.34]
Menza 2010	15	17 (50)	15	46 (45)		46.39%	-29[-63.04,5.04]
Subtotal ***	**47**		**35**			**100%**	**-33.29[-56.47,-10.1]**
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%							
Test for overall effect: Z=2.81(P=0)							
1.17.2 Sponsor-initiated WASO							
Ancoli-Israel 2010	194	57.8 (55)	194	76.8 (55)		18.92%	-19[-29.95,-8.05]
Krystal 2003	593	43.8 (68.4)	195	55.9 (71.2)		18.38%	-12.1[-23.51,-0.69]
McCall 2006	136	-31.3 (45.7)	128	-24.5 (48.3)		18.44%	-6.8[-18.16,4.56]
Scharf 2005	79	-39.9 (79)	80	8.3 (65)		9.05%	-48.2[-70.7,-25.7]
Soares 2006	201	-30.9 (79)	209	-16 (65)		15.54%	-14.9[-28.93,-0.87]
Zammit 2004	105	41.2 (39)	99	49.1 (36.1)		19.67%	-7.9[-18.21,2.41]
Subtotal ***	**1308**		**905**			**100%**	**-15.31[-23.5,-7.11]**
Heterogeneity: Tau^2=61.2; Chi^2=12.67, df=5(P=0.03); I^2=60.53%							
Test for overall effect: Z=3.66(P=0)							
Test for subgroup differences: Chi^2=2.05, df=1 (P=0.15), I^2=51.33%							

Analysis 1.18. Comparison 1 Eszopiclone versus placebo, Outcome 18 Subgroups: study initiation - TST.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.18.1 Investigator-initiated TST							
Goforth 2014	32	412.5 (70.7)	20	382.2 (93.9)		19.92%	30.3[-17.59,78.19]
Menza 2010	15	342 (69.6)	15	360 (69.6)		18.82%	-18[-67.81,31.81]
Pollack 2008	294	71.4 (66.2)	301	41.3 (79.5)		61.26%	30.02[18.27,41.77]
Subtotal ***	**341**		**336**			**100%**	**21.04[-4.19,46.27]**
Heterogeneity: Tau^2=234.61; Chi^2=3.39, df=2(P=0.18); I^2=41.08%							
Test for overall effect: Z=1.63(P=0.1)							
1.18.2 Sponsor-initiated TST							
Ancoli-Israel 2010	194	357.3 (69.3)	194	324.8 (75)		17.53%	32.5[18.13,46.87]
Krystal 2003	593	377.3 (70.5)	195	339.5 (74.7)		20.51%	37.72[25.79,49.65]
McCall 2006	136	48.6 (55)	128	32.4 (59)		18.21%	16.2[2.42,29.98]
Scharf 2005	79	87 (142)	80	38.1 (124)		3.96%	48.9[7.44,90.36]
Soares 2006	201	56.6 (55)	209	33.6 (59)		21.69%	23[11.96,34.04]
Spierings 2015	35	378 (54)	40	366 (48)		9.97%	12[-11.27,35.27]
Zammit 2004	105	411.8 (124)	99	363.8 (63.5)		8.12%	48[21.19,74.81]
Subtotal ***	**1343**		**945**			**100%**	**28.4[19.6,37.21]**
Heterogeneity: Tau^2=61.25; Chi^2=11.46, df=6(P=0.08); I^2=47.65%							
Test for overall effect: Z=6.33(P<0.0001)							
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.59), I^2=0%							

Analysis 1.19. Comparison 1 Eszopiclone versus placebo, Outcome 19 Sensitivity: sleep assessment.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.19.1 Sleep onset latency							
McCall 2006	136	-33.5 (30)	128	-17 (33)		19.85%	-16.5[-24.12,-8.88]
Zammit 2004	105	18 (15.7)	99	33 (22.6)		40%	-15[-20.37,-9.63]
Subtotal ***	**241**		**227**			**59.86%**	**-15.5[-19.89,-11.11]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%							
Test for overall effect: Z=6.92(P<0.0001)							
1.19.2 Wake time after sleep onset							
McCall 2006	136	-25.3 (40.3)	128	-12.5 (35.9)		13.64%	-12.8[-22,-3.6]
Zammit 2004	105	38 (26.7)	99	50 (34.5)		15.96%	-12[-20.5,-3.5]
Subtotal ***	**241**		**227**			**29.61%**	**-12.37[-18.61,-6.13]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%							
Test for overall effect: Z=3.88(P=0)							
1.19.3 Total sleep time							
McCall 2006	136	56.2 (43.3)	128	27.6 (43.4)		10.54%	28.6[18.14,39.06]
Subtotal ***	**136**		**128**			**10.54%**	**28.6[18.14,39.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.36(P<0.0001)							
Total ***	**618**		**582**			**100%**	**-9.92[-13.32,-6.53]**
Heterogeneity: Tau^2=0; Chi^2=58.97, df=4(P<0.0001); I^2=93.22%							
Test for overall effect: Z=5.73(P<0.0001)							
Test for subgroup differences: Chi^2=58.85, df=1 (P<0.0001), I^2=96.6%							



Analysis 1.20. Comparison 1 Eszopiclone versus placebo, Outcome 20 Sensitivity: withdrawal assessment.

Study or subgroup	Eszopiclone N	Eszopiclone Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Ancoli-Israel 2010	194	-0.3 (3.3)	194	0.2 (2.7)		0%	-0.18[-0.38,0.02]
Walsh 2007	550	3 (28.8)	280	2.3 (15.9)		0%	0.03[-0.12,0.17]

ADDITIONAL TABLES

Table 1. Overview of included studies

Author	N	Female (%)	Specific sample characteristics	Primary insomnia	Method	Duration (weeks)	Single-blind run-out (days)
Ancoli-Israel 2010	388	63	Elderly	X	Participant reports (diary)	12	14
Fava 2006	545	66.6	Comorbid depression	—	Participant reports (IVRS)	8	14
Goforth 2014	58	63	Comorbid back pain	—	Participant reports (diary)	4	—
Krystal 2003	788	63	—	X	Participant reports (IVRS)	24	— (follow-up)
McCall 2006	264	67.4	Elderly	X	Participant reports (IVRS), PSG	2	—
McCall 2010a	60	66.7	Comorbid depression	—	Participant reports (diary); actigraphy	8	— (follow-up)
Menza 2010	30	20	Comorbid Parkinsons disease	—	Participant reports (diary)	3	—
Pollack 2008	595	66	Comorbid anxiety disorder	—	Participant reports (diary)	8	14
Roth 2009	153	86.9	Comorbid rheumatoid arthritis	—	Participant reports (IVRS)	4	7
Scharf 2005	231	57.8	Elderly	X	Participant reports (IVRS)	2	—
Soares 2006	410	100	Menopause	—	Participant reports (IVRS)	4	7
Spierings 2015	75	82.5	Migraine	X	Participant reports (diary)	6	2 (open label)
Walsh 2007	830	61	—	X	Participant reports (IVRS)	24	14
Zammit 2004	305	65	—	X	Participant reports (IVRS), PSG	6	2

IVRS: interactive voice response system

N: number

PSG: polysomnography

Table 2. Rates of unpleasant taste

Author	ESZ (%)	PBO (%)
Ancoli-Israel 2010	12.4	1.55
Fava 2006	22.7	6.93
Krystal 2003	26.1	5.64
McCall 2006	12.5	0.00
Pollack 2008	24.1	3.68
Roth 2009	27.3	0.00
Scharf 2005	11.4	1.25
Soares 2006	17.4	0.48
Walsh 2007	19.7	1.07
Zammit 2004	33.3	3.03

ESZ: eszopiclone
PBO: placebo

Table 3. Overview of outcome: means and medians

Author	Outcome statistic	Sleep efficacy			Rebound insomnia		
		SOL	WASO	TST	LPS	WASO	TST
		Sign.	Sign.	Sign.	—	—	—
Ancoli-Israel 2010	Means	P < 0.001	P < 0.001	P < 0.001	Ns	Ns	Ns
Fava 2006	Medians	P < 0.001	**P < 0.001**	**P = 0.004**	Ns	Ns	**Ns**
Goforth 2014	Medians, means	P = 0.026	P < 0.001	P = 0.017	—	—	—
Krystal 2003	Medians, means	P < 0.001	P = 0.032	P < 0.001	—	—	—
McCall 2006	Medians, means	P < 0.001	P = 0.022	P < 0.001	—	—	—
McCall 2010a	ß, SE	**P = 0.008**	**P = 0.16**	**P = 0.04**	—	—	—
Menza 2010	Means	Ns	P = 0.071.	Ns	—	—	—
Pollack 2008	Medians, means*	P < 0.001*	**P < 0.001**	P < 0.001*	Ns	Ns	Ns
Roth 2009	Medians	**P < 0.01**	**P < 0.01**	**P < 0.001**	Ns	Ns	**P = 0.01**
Scharf 2005	Medians, means	P = 0.003	P < 0.04	P < 0.001	—	—	—
Soares 2006	Medians, means	P < 0.001	P < 0.001	P < 0.01	Ns	Ns	Ns
Spierings 2015	Means	Nr	Nr	0.33	—	—	—
Walsh 2007	Medians	**P < 0.001**	**P < 0.001**	**P < 0.001**	Ns	Ns	Ns
Zammit 2004	Medians, means	P < 0.001	P = 0.02	P < 0.001	**Ns**	Ns	Ns

LPS: latency to persistent sleep
Nr: not reported
Ns: not statistically significant (no quantitative information provided)
P: P value
SOL: sleep onset latency
TST: total sleep time
WASO: wake time after sleep onset
bold: not included in the meta-analyses

APPENDICES

Appendix 1. Criteria for bias assessment

	Item	Judgement	Description
Sequence generation (selection bias)	Is the method used for randomisation adequate?	Yes	The method used for sequence generation constitutes a random process, in which every study participant has an equal chance to be assigned to each of the treatment conditions (e.g. allocation by random number table, computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice)
		No	The method used for sequence generation allows the prediction of assignments to treatment groups (e.g. allocation by date of birth, date of admission, hospital or clinic record number etc.)
		Unclear	Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'
Allocation concealment **(selection bias, detection bias)**	Was the treatment allocation concealed?	Yes	At least one of the following measures was undertaken to ensure allocation concealment: - randomisation or drug preparation were performed centralised and remote from the patient recruitment centres - sequentially numbered, opaque, sealed envelopes (SNOSE) were used for enclosing assignments - all of the drug containers were tamper-proof, equal in weight and similar in appearance
		No	Methods for allocation were used that allow unconcealment such as an open random allocation schedule, assignment envelopes without appropriate safeguards, alternation or rotation
		Unclear	Insufficient information about measures to ensure allocation concealment to permit judgement of 'Yes' or 'No'
Blinding (detection bias, expectation bias)	Was knowledge of the allocated interventions adequately prevented during the study?	Yes	At least one of the following measures were undertaken to ensure blinding: - participants and research staff were explicitly mentioned to be included in the blinding procedures AND active medication and placebo were of identical appearance, odour* and taste* OR - the influence of unpleasent tase perception on results or integrity of blinding was checked and confirmed at the end of the treatment. *Only required for drugs with a typical inherent taste or odour such as eszopiclone and valerian
		No	Evidence that indicates an unmasking of blinding by either participants, treatment providers or research staff such as significant group differences in the perception of appearance, odour

(Continued)

			or taste or significant group differences in guessing the affiliation to treatments as demonstrated by inquiries on blinding integrity
		Unclear	Insufficient information about blinding to permit judgement of 'Yes' or 'No'
Handling of incomplete outcome data (attrition bias)	Were incomplete outcome data adequately addressed?	Yes	At least one of the following procedures were undertaken to ensure adequate incomplete outcome data handling: All randomised participants (intention-to-treat analysis) or those who have received at least one dose of treatment (treatment-received analysis) were analysed in the group they had been allocated to by randomisation Dropouts were excluded from the analyses (available case analysis), but those who were excluded were shown not to differ from trial completers
		No	Dropouts were excluded from the analyses (available case analysis) and shown to differ from trial completers
		Unclear	Dropouts were excluded from the analyses (available case analysis) without testing if those who dropped out differ from trial completers OR Insufficient reporting of dropout rates or dropout handling to permit judgement of 'Yes' or 'No'
Selective reporting (Reporting Bias)	Are reports of the study free of suggestion of selective outcome reporting?	Yes	The reporting of outcomes in the trial publication fulfils both of the following criteria: - all outcomes listed in the methods section of the publication were adequately reported in the results section - the primary and secondary endpoints represent an adequate diversity of outcome criteria including at least one indicator of sleep induction, sleep maintenance, rebound insomnia* or withdrawal symptoms* *Only required in studies with treatment duration of 2 weeks or longer
		No	One or more outcomes listed in the study protocol or the methods section of the publication were not adequately reported in the results section OR The outcomes of the study are of limited diversity
		Unclear	Outcomes were not explicitly stated in the study protocol or the methods section of the trial publication
General susceptibility to bias effects: Blinding of outcome assessment (detection bias) - **sleep efficacy indicators**	Are sleep outcomes determined in a way that prevents bias effects?	Yes	The assessment of quantitative sleep outcomes fulfils one of the following conditions: (1) the quantitative sleep outcomes of the study are exclusively based on objective measures (e.g. PSG, electroencephalogram (EEG)) (2) the quantitative sleep outcomes of the study are based on patient self-reports and confirmed by objective measures,

(Continued)

			meaning that both types of measures come to consistent significance conclusions
		No	Objective measures and participant self-reports come to different significance conclusions
		Unclear	No objective measures were considered in the study Objective measures and participant self-reports were considered in the study, but it is unclear whether these come to consistent significance conclusions
General susceptibility to bias effects: Blinding of outcome assessment (detection bias): **next-day functioning**	Are next-day functioning outcomes determined in a way that prevents bias effects?	Yes	The assessment of next-day functioning fulfils one of the following conditions: (1) indicators of next-day functioning are exclusively based on objective measures (e.g. objective testes of psychomotor co-ordination, attention, vigilance, reaction time) (2) next-day functioning was assessed by subjective measures (visual analogue scale (VAS), Likert scale, etc.) and objective tests, both coming to consistent significance conclusions
		No	Objective measures and participant self-reports come to different significance conclusions
		Unclear	No objective measures were considered in the study Objective measures and participant self-reports were considered in the study, but it is unclear whether these come to consistent significance conclusions
Other bias: Baseline equivalence (selection bias)	Are groups equivalent at baseline?	Yes	The testing of baseline age, gender and sleep fulfils at least one of the following conditions: - baseline equivalence between groups was confirmed for age, gender AND at least one indicator of sleep induction and sleep maintenance - baseline differences between groups were demonstrated, but adequately controlled in the statistical analyses In RCTs on insomnia associated with a comorbid condition, baseline equivalence for comorbid symptoms were tested and confirmed OR controlled in the statistical analyses
		No	Differences between groups in one or more relevant baseline characteristics became evident, but were not controlled in the statistical analyses
		Unclear	Insufficient reporting of baseline equivalence or its testing to permit judgement of 'Yes' or 'No'
Other bias: **Equivalence of treatment utilisation (performance bias)**	Are groups equivalent in the utilisation of treatments?	Yes	Treatment utilisation fulfils at least one of the following conditions: - equivalence of medication compliance - equivalence of the use of further medications that might have a secondary effect on sleep - equivalence of daytime napping (*in elderly samples only)

(Continued)

		- differences in medication compliance* or the use of medications that might affect sleep were demonstrated, but adequately controlled in the statistical analyses
	No	Differences between groups in compliance or the use of medication became evident and were not controlled in the statistical analyses
	Unclear	Insufficient reporting of medication compliance or the concomitant use of medications to permit judgement of 'Yes' or 'No'

Appendix 2. Search strategies: CENTRAL, MEDLINE, EMBASE, PsycINFO

The Cochrane Central Register of Controlled Trials (CENTRAL) was searched (all years to Febraury 10 2016) using the following terms :

#1. (generation NEAR hypnotic*)
#2. (nonbenzodiazepin* or "non benzodiazepin*" or non-benzodiazepin*)
#3. (imidazopyridin* or cyclopyrrolon*)
#4. (eszopiclon* or zaleplon or zolpidem or zopiclon*)
#5. (z NEXT hypnotic*) or (z NEXT drug*)
#6. (#1 or #2 or #3 or #4 or #5)
#7. insomn*
#8. sleep*
#9. MeSH descriptor Sleep Initiation and Maintenance Disorders explode all trees
#10. MeSH descriptor Sleep Disorders, this term only
#11. MeSH descriptor Sleep, this term only
#12. MeSH descriptor Sleep Stages, this term only
#13. MeSH descriptor Wakefulness, this term only
#14. (#7 or #8 or #9 or #10 or #11 or #12 or #13)
#15 (#6 and #14)

OVID MEDLINE was searched (from 1950 to February 10 2016) using the following terms :

1. ((new generation or third generation) adj3 hypnotic*).tw.
2. (nonbenzodiazepin* or non benzodiazepin*).tw.
3. (imidazopyridin* or cyclopyrrolon*).tw.
4. (eszopiclon* or zaleplon or zolpidem or zopiclon*).mp.
5. (z hypnotic* or z drug*).tw.
6. or/1-5
7. insomnia*.tw.
8. insomn*.ot.
9. sleep*.tw.
10. exp Sleep Initiation and Maintenance Disorders/
11. Sleep Disorders/
12. Sleep/ or Sleep Stages/
13. Wakefulness/
14. or/7-13
15. randomised controlled trial.pt.
16. controlled clinical trial.pt.
17. randomi#ed.ti,ab.
18. randomly.ab.
19. placebo.ab.
20. drug therapy.fs.
21. trial.ab.
22. groups.ab

23.(control$ adj3 (trial or study)).ab,ti.
24.((singl$ or doubl$ or tripl$ or trebl$) adj3 (blind$ or mask$ or dummy$)).mp.
25.(animals not (humans and animals)).sh.
26.or/15-24
27.26 not 25
28.6 and 14 and 27

OVID EMBASE was searched (from 1980 to February 10 2016) using the following terms:

1. ((new generation or third generation) adj3 hypnotic*).tw.
2. (nonbenzodiazepin* or non benzodiazepin*).tw.
3. (imidazopyridin* or cyclopyrrolon*).tw.
4. (eszopiclon* or zaleplon or zolpidem or zopiclon*).mp.
5. Eszopiclone/ or Zaleplon/ or Zolpidem/ or Zopiclone/
6. (z hypnotic* or z drug*).tw.
7. or/1-6
8. insomnia*.tw.
9. insom*.ot.
10.exp Insomnia/
11.sleep*.tw.
12.Sleep/ or Sleep Induction/ or Sleep Pattern/ or Sleep Stage/ or Sleep Time/ or Sleep Waking Cycle/
13.Sleep Parameters/
14.Sleep Disorder/
15.Wakefulness/
16.or/8-15
17.randomised controlled trial.de.
18.randomisation.de.
19.placebo.de.
20.placebo.ti,ab.
21.randomi#ed.ti,ab.
22.randomly.ab.
23.((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
24.factorial$.ti,ab.
25.allocat$.ti,ab.
26.assign$.ti,ab.
27.volunteer$.ti,ab.
28.crossover procedure.de.
29.(crossover$ or cross over$).ti,ab.
30.(quasi adj (experimental or random$)).mp.
31.(control$ adj3 (trial$ or study or studies or group$)).ti,ab.
32.((animal or nonhuman) not (human and (animal or nonhuman))).de.
33.or/17-31
34.33 not 32
35.7 and 16 and 34

OVID PsycINFO was searched (all years to February 10 2016) using the following terms:

1. ((new generation or third generation) adj3 hypnotic*).tw.
2. (nonbenzodiazepin* or non benzodiazepin*).tw.
3. (imidazopyridin* or cyclopyrrolon*).tw.
4. (eszopiclon* or zaleplon or zolpidem or zopiclon*).mp.
5. (z hypnotic* or z drug*).tw.
6. or/1-6
7. insomnia*.tw.

8. insomn*.ot.
9. Insomnia/
10.sleep*.tw.
11.(insomnia or sleep).tm.
12.Sleep/ or Sleep Onset/ or Sleep Wake Cycle/
13.Sleepiness/
14.Sleep Disorders/
15.Wakefulness/
16.or/7-15
17.treatment effectiveness evaluation.sh.
18.clinical trials.sh.
19.mental health program evaluation.sh.
20.placebo.sh.
21.placebo.ti,ab.
22.randomly.ab.
23.randomi#ed.ti,ab.
24.trial.ti,ab.
25.((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$ or dummy)).mp.
26.(control$ adj3 (trial$ or study or studies or group$)).ti,ab.
27.factorial$.ti,ab.
28.allocat$.ti,ab.
29.assign$.ti,ab.
30.volunteer$.ti,ab.
31.(crossover$ or cross over$).ti,ab.
32.(quasi adj (experimental or random$)).mp.
33."2000".md.
34.or/17-33
35.(6 and 16 and 34)

Psyndex was searched for the initial Z-Drug search in 2011, using the following terms:

(*eszopiclon* or zaleplon or zolpidem or zopiclon**)

No unique studies were retrieved from this database, and as access was not always available, it was dropped from any further updates.

Update search (February 2018) - Intervention only (results not yet incorporated)

1. CENTRAL via Cochrane Register of Studies (CRSO):
eszopiclone or lunesta AND 31/01/2016 TO 21/02/2018:DL (n=18)

2 Cochrane Common Mental Disorders Specialised Register (CCMD-CTR):
eszopiclone or lunesta AND 31/01/2016 TO 21/02/2018:DL (n=0)

3. Ovid Cross-Search
Databases: PsycINFO <1806 to February Week 2 2018>, Embase <1974 to 2018 Week 08>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to 21-02-2018> Limited 2016 to date
---
1 (eszopiclone or lunesta).af.
2 (2016* or 2017* or 2018*).yr,dc,dd,dp,dt,ed,ep.
3 (in-process or in data review or publisher).st.
4 1 and (2 or 3)
5 remove duplicates from 4 (244)

4. PubMed not MEDLINE
#1 (eszopiclone OR lunesta)
#2 pubmednotmedline[sb]
#3. (#1 and #2), n = 24

5 ClinicalTrials.gov, WHO ICTRP
eszopiclone OR lunesta | First posted from 01/01/2016 to 02/21/2018 (n = 3)

Total = 271
Deduplicated = 265
265 abstracts screened; 230 excluded; 35 records of potential interest identified at abstract screening stage (RCTs, Reviews, Guidelines); 3 new studies to assess.

Appendix 3. Abbreviations

IC Inclusion criteria

ALC Alcohol abuse

DRUG Drug abuse

BENZ Benzodiazepine use 14 days before treatment

DSM-4-TR Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision

DSST Digit-Symbol Substitution Test

HSAD History of substance abuse or dependence

ICD-10 International Classification of Mental and Behavioural Disorders

ICSD International Classification of Sleep Disorders, second edition

ITT Intention to treat

BZD benzodiazepine

FLX Fluoxetine

IVRS Interactive Voice Recording System

LS Likert Scale

MA meta-analysis

OSRD Other primary or secondary sleep disorders than insomnia such as sleep apnea, restless legs syndrome, periodic leg movement

OCAS Other medical or psychiatric condition that impacts or is likely to impact sleep

PRO participant-reported outcomes

PP Per Protocol

PSG polysomnography

PSY psychiatric disorders

SAD Sleep affecting disorder

SAM Sleep affecting medication

SAS

SDU standard drink unit

SE sleep efficiency

tmax time to maximum plasma concentration

TR Treatment-received

Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire

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Susanne Rösner:

- protocol elaboration
- study selection
- data extraction
- data management
- analysis of data (MAL)
- interpretation and discussion of results
- writing of the review
- securing funding

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DECLARATIONS OF INTEREST

Rösner S: no conflict of interest known

Englbrecht C: no conflict of interest known

Wehrle R: no conflict of interest known

Hajak G: received speaker/consultancy/advisory board honoraria from Actelion, Astra-Zeneca, Bristol-Meyers Squibb, Boehringer Ingelheim, Cephalon, EuMeCom, GlaxoSmithKline, Janssen-Cilag, Lilly, Lundbeck, Novartis, Organon, Pfizer, Sanofi-Aventis, Servier, Takeda, Wyeth. Advisory Boards: Actelion, Astra-Zeneca, Bristol-Meyers Squibb, Janssen-Cilag, Lilly, Lundbeck, Neurocrine, Organon, Pfizer, Sanofi-Aventis, Sepracor, Servier, Takeda, Wyeth.

Industrie-Drittmittel: Actelion, Affectis, Astra-Zeneca, Boehringer Ingelheim, GlaxoSmithKline, Lundbeck, Novartis, Organon, Sanofi-Aventis, Sepracor, Servier, Takeda.

Soyka M: received speaker/consultancy/advisory board honoraria from Lipha Pharmaceuticals, Forest Laboratories, Sanofi-Aventis, Essex Pharma, Eli Lilly, Prempharm, Lundbeck, and AstraZeneca.

SOURCES OF SUPPORT

Internal sources

- Ludwig Maximilian University of Munich, Germany.

  Provision of infrastructure and related services
- Forel Klinik, Switzerland.

  Provision of infrastructure, related services and salary

External sources

- Federal Ministry of Education and Research, Germany.

  Financial support/salary

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol limited 'type of participants' to patients with primary insomnia, which was based on the argument that therapeutic success in comorbid insomnia might depend on resolving the causative problem rather than on the efficacy of insomnia treatment. Neverthless, current developments in insomnia research, diagnosis, and treatment and a careful reappraisal of the current evidence, led us to include both primary and comorbid insomnia instead of limiting the review to primary insomnia only. To identify the impact that type of insomnia had on efficacy outcomes, we conducted subgroup analyses for participant groups with a) primary and b) comorbid insomnia. In detail, the following arguments were decisive for the change:

1. The utility of diagnostic distinctions between primary and secondary insomnia are questioned by DSM-5 criteria for sleep-wake disorders (American Psychiatric Association 2013), dropping the DSM-5's 'primary insomnia' diagnosis in favour of 'insomnia disorder' (Riemann 2014; Riemann 2015), reflecting a general move away from causal attributions and their relevance for insomnia treatment;
2. The high prevalence of comorbid insomnia within the insomniac population (Katz 1998; Krystal 2012b), but also in potentially eligible studies for the review, further underscored the clinical relevance of this participant subgroup. Accordingly, a limitation of the review to primary insomnia would have reduced the clinical relevance of its conclusions;
3. Definitions of primary and comorbid insomnia, based on different temporal relationships between insomnia and comorbid symptoms as applied in eligible studies for the review, further illustrated the difficulty of reliably distinguishing different types of insomnia from each other;
4. Even though larger benefits for eszopiclone are to be expected in participants with primary insomnia, treatment effects were also shown to reach statistical significance in samples with comorbid insomnia (Krystal 2012b; Wilson 2010).

In the protocol, not being aware of the problem, we missed specifying how of change from baseline scores and double-blind average scores would be handled. In order to provide clarity to the reader, we described the handling of different score types in the methods section (see Types of outcome measures). Furthermore, when writing the protocol we were not conscious of the fact that meta-analyses of adverse events would be based on number of events instead of participants. This has subsequently been added to Unit of analysis issues in the methods section. In addition, we added that 'temporary worsening' of sleep was evaluated as mean change from baseline for the primary efficacy outcomes (SOL, WASO) during the first three nights of the placebo run-out period (see Types of outcome measures).

Against our original planning in the protocol, we omitted sensitivity analyses for low and high heterogeneity outcomes due to methodological limitations, like the dependence between the mode of analyses and results. Furthermore, diverging from the protocol, we examined differences in results between investigator- and industry-initiated trials by subgroup analyses instead of sensitivity analyses as we became aware that sponsoring was not a result of methodological decision in the review process, but rather a criterion of the study itself.

We also think it should be briefly noted in the text of the review wherever a change has been made, and a link to the 'Differences' section provided.

INDEX TERMS

Medical Subject Headings (MeSH)

Eszopiclone [*therapeutic use]; Hypnotics and Sedatives [*therapeutic use]; Randomized Controlled Trials as Topic; Sleep Initiation and Maintenance Disorders [*drug therapy]; Time Factors; Treatment Outcome

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Middle Aged