Drug Class Review

Newer Drugs for Insomnia

Final Update 2 Report

October 2008

The Agency for Healthcare Research and
Quality has not yet seen or approved this report.

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The medical literature relating to the topic is scanned periodically (see http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report based on the information contained in the scan. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Insomnia is a serious health problem that affects millions of people. Population surveys have estimated the prevalence of insomnia to be about 30% to 50% of the general population. Variation in estimates depends on different methods of surveying and definitions of insomnia.[1] About three-fourths of people who have trouble sleeping say that the problem is "occasional," averaging about 6 nights per month. The other one-fourth have frequent or chronic insomnia, averaging about 16 nights per month.[2] Individuals with insomnia most often report a combination of difficulty falling asleep and intermittent wakefulness during sleep.[3] The most common symptoms of insomnia are waking up feeling unrefreshed and waking often during the night. The symptoms waking up too early and difficulty falling asleep are less common but still experienced at least a few nights a week by about 25% of adults with insomnia.[1] The risk of insomnia increases with age; affecting approximately 20% to 40% of older adults at least a few nights per month.[2]

Consequences of insomnia can include increased risk of depression, poor memory, reduced concentration, and poor work performance. Insomnia has been associated with poor general health, greater healthcare utilization, lower quality of life, lower socioeconomic status, and poorer social relationships, mood, and cognitive function.[4] Insomnia can be acute and transient. It also can be chronic, especially when associated with underlying psychiatric or medical illness.

Treatment of insomnia involves behavioral changes, such as minimizing habits that interfere with sleep (for example, drinking coffee or engaging in stressful activities in the evening),[4] and pharmacotherapy with sedating antidepressants (for example, trazodone), sedating antihistamines, anticholinergics, benzodiazepines, or nonbenzodiazepine hypnotics. The benzodiazepines and the newer sedative hypnotics zolpidem, zaleplon, zopiclone, and eszopiclone work through gamma-aminobutyric acid receptors. Ramelteon, a hypnotic approved by the United States Food and Drug Administration (FDA) in July 2005, is a selective melatonin receptor (MT_1 and MT_2) agonist. New nonbenzodiazepine drugs have been sought for multiple reasons, including reduction of the risk of tolerance, dependence, and abuse associated with benzodiazepines.

The newer drugs for insomnia differ from each other in their pharmacokinetics (see Table 1), and thus could be expected to affect different aspects of insomnia. For example, drugs with a shorter half-life might be effective for helping a person fall asleep faster but less effective for increasing the total time spent asleep during the night.[5]

In general, use of insomnia drugs is recommended to be short-term; however, it is recognized that some individuals may require longer-term treatment.[4]

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of newer drugs for insomnia. Our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety.

The Oregon Evidence-based Practice Center wrote preliminary Key Questions identifying the populations, interventions, and outcomes of interest and, based on these, the eligibility criteria for studies. These Key Questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the

Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. The participating organizations approved the following Key Questions to guide this review:

1. What is the comparative effectiveness of newer drugs for insomnia in treating patients with insomnia?

2. What are the comparative tolerability and safety of newer drugs for insomnia when used to treat patients with insomnia?

3. Are there subgroups of patients for which one newer drug for insomnia is more effective or associated with fewer adverse events based on
    a. demographics (age, racial groups, and gender)?
    b. other medications (for example, stimulants)?
    c. co-morbidities (including obstructive sleep apnea and other mental disorders)?
    d. pregnancy?
    e. history of substance abuse?

Included populations

Adults and children with insomnia of any duration, including the following DSM-IV-TR diagnoses:

- Primary insomnia
- Breathing-related sleep disorder (for example, obstructive sleep apnea)
- Insomnia related to another mental disorder
- Substance-induced sleep disorder, insomnia type
- Sleep disorder due to a general medical condition, insomnia type

Included interventions

Six nonbenzodiazepine drugs for insomnia have been introduced since 1992 (Table 1). Five are available in the US (eszopiclone, ramelteon, zaleplon, zolpidem, and zolpidem extended release) and two in Canada and other countries (zaleplon and zopiclone).

The recommended starting dose in older adults is half the recommended adult dose for all of these drugs except ramelteon because of the theoretical risk of increased adverse events such as somnolence. This is generally based on increased bioavailability observed in older adults.

Table 1. Newer drugs for insomnia

Active ingredient	Brand name	Initial dose (given at bedtime)			Half-life (hours)
		Adults	Older adults		
Eszopiclone	Lunesta	2-3 mg	1-2 mg	6 (9 in older adults)	
Ramelteon	Rozerem	8 mg	8 mg	1-2.6	
Zaleplon	Sonata, generic	10 mg	5 mg	1	
Zolpidem	Ambien, generic	10 mg	5 mg	2.5	
zolpidem extended-release	Ambien-CR		12.5 mg	6.25 mg	2.8
zopiclone (Canada)	Imovane		5 to 7.5 mg	3.75 mg	5

Included outcomes

Improvement in insomnia is measured in several ways. Effectiveness outcomes include sleep latency, sleep duration, number of awakenings, sleep quality, daytime alertness, rebound insomnia, and quality of life. Safety outcomes include tolerance, adverse effects, abuse potential, withdrawal symptoms, and dependency.

Sleep latency is the time taken by a person to fall asleep. *Sleep duration* is the time a person remains asleep. The *number of awakenings* during the night is often measured in insomnia trials. A measure used in some studies is *wake time after sleep onset (WASO)*. This is the total time that a person is awake between sleep onset and final waking.

These outcomes can be measured subjectively (for example, using patient sleep diaries), or objectively, using *polysomnography*, the testing of sleep cycles and stages through the use of continuous recordings of brain waves and other measures in a sleep laboratory. Most studies report subjective outcomes. While objective measures may give a more accurate indication of sleep duration and other outcomes, subjective outcomes may be more important to patients.

Sleep quality is usually measured by patient questionnaire using a Likert or visual analog scale (for example, 0=poor to 10=excellent). Similarly, *daytime alertness* and other *next-day effects* are usually measured by patient self-report.

Rebound insomnia is worsening of insomnia from baseline (prior to pharmacotherapy) when treatment is discontinued. Rebound insomnia can be determined through any of the outcomes listed earlier.

Quality of life includes influence upon physical, psychological, and social aspects of the patient.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2008), Cochrane Database of Systematic Reviews, DARE, MEDLINE (1996 to January week 3, 2008), PsycINFO (1985 to January week 3, 2008) using terms for included drugs, indications, and study designs. (See Appendix A for complete search strategy.) We also searched reference lists of included studies and reviews, FDA information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/), and dossiers submitted by pharmaceutical companies. All citations were imported into an electronic database (EndNote XI).

Study Selection

For assessment of efficacy and effectiveness we included English-language reports of randomized controlled trials of adults or children with insomnia. Interventions included one newer hypnotic compared with another newer hypnotic, another active agent, or placebo. Trials that evaluated one newer insomnia drug against another ("head-to-head" trials) provided direct evidence of comparative efficacy and adverse event rates. Trials with other comparisons provided indirect evidence. We included trials that were published in abstract or poster form only if they provided sufficient information to assess their validity.

For adverse effects, in addition to randomized controlled trials we included observational studies and case reports. Clinical trials are often not designed to assess adverse events and may select low-risk patients (in order to minimize dropout rates) or use inadequately rigorous methodology to assess adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer period, use higher quality methodological techniques to assess adverse events, or examine larger sample sizes.

Data Abstraction

We abstracted the following data from included studies: study design, setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. Data were abstracted by one reviewer and checked by a second. Intention-to-treat results were recorded if available and if the trial did not report high overall loss to follow-up.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[6, 7] We based our rating of the internal validity of each trial on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. We based our rating of the quality of observational studies of adverse events on unbiased selection of

patients, low loss to follow-up, unbiased and accurate ascertainment of events, and control for potential confounding factors.

Studies that had a fatal flaw in one or more categories were rated poor quality. Studies that met all criteria were rated good quality. The remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others only *might* be valid. A poor-quality study is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. External validity of studies was assessed based on whether the publication adequately described the study population, whether patients were sufficiently similar to the target population in which the intervention was applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source.

Data Synthesis

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. When possible, we calculated the weighted mean difference between treatments for continuous outcomes and displayed results in forest plots using RevMan (v4.2, Update Software).

To supplement information from head-to-head trials, we performed adjusted indirect comparisons of placebo-controlled trials using the method described by Bucher et al.[8] In theory, trials that compare two or more included drugs to a common intervention (usually placebo) can provide indirect evidence about comparative effectiveness while preserving some of the benefits of randomization.[8, 9] "Adjusted" indirect methods also incorporate the uncertainty that occurs when combining different sets of trials by adding together the variance from both sets of trials, resulting in less precise estimates of treatment effects compared to analyses based on the same number of similarly sized head-to-head trials.[8, 9] Although indirect comparisons usually agree with direct comparisons, large discrepancies have been reported in some cases.[10, 11] The validity of indirect analyses depends on how well the critical assumption of similarity of treatment effects across all studies is met. This assumption can be violated when there are methodological shortcomings in some or all of the trials or when there is clinical diversity in trial populations, interventions (for example, different durations of therapy or nonequivalent dosing), or assessment of outcomes. To assess stability of estimates and conclusions, we performed subgroup and sensitivity analyses based on populations (elderly compared with non-elderly adults), dose, and study quality.

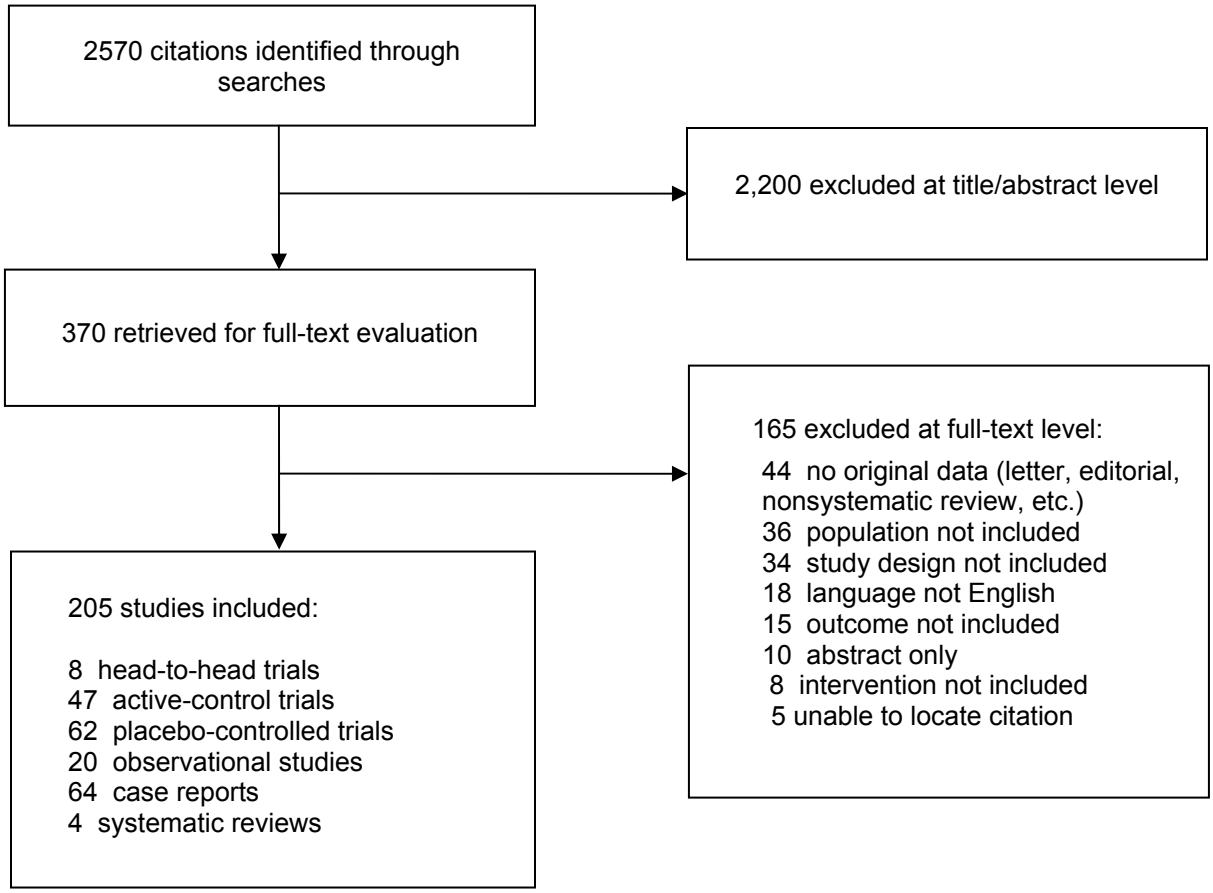
To assess the strength of evidence in a body of literature related to a particular key question, we examined consistency of study design, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

RESULTS

Overview of included studies

We identified 2570 citations from literature searches, reviews of reference lists, and citations from dossiers submitted by 2 pharmaceutical manufacturers, Sanofi-Aventis (zolpidem extended release) and Takeda (ramelteon). After applying the eligibility and exclusion criteria to titles and abstracts, we obtained the full text of 370 publications. After reapplying the criteria for inclusion, we included 205 studies. The flow of study inclusion and exclusion is detailed in Figure 1. A list of excluded trials is provided in Appendix C.

Figure 1. Newer drugs for insomnia: Results of literature search



We included eight head-to-head trials (Table 2).[12-19] One trial is published as a poster presentation only;[18] additional details were provided by the manufacturer and in the FDA review of eszopiclone.[20]

Table 2. Total numbers of head-to-head trials of newer drugs for insomnia

	Zaleplon	Zolpidem	Zolpidem extended release	Zopiclone	Eszopiclone	Ramelteon
Zaleplon	*********					
Zolpidem	4	**********				
Zolpidem extended release	0	0	**********			
Zopiclone	0	3	0	**********		
Eszopiclone	0	1	0	0	**********	
Ramelteon	0	0	0	0	0	**********

We included 44 trials in 45 publications comparing newer insomnia drugs compared with benzodiazepines.[21-65] Appendix D summarizes the efficacy, safety, and rebound insomnia results of these studies.

We identified two trials comparing trazodone compared with a sedative hypnotic; one (compared with zaleplon)[52] was rated poor quality and the other (compared with zolpidem)[61] was rated fair.

Sixty-one placebo-controlled trials were included. (Some publications described more than one trial).[5, 20, 66-9293-123]

Four good-quality systematic reviews of newer sedative hypnotics were included.[1, 124-126] The review most relevant to this report is a comparative review conducted by the National Institute for Clinical Excellence.[124] The others were not designed to compare the sedative hypnotics head-to-head. One meta-analysis examined the risks and benefits of sleep agents, including newer sedative hypnotics, in older people with insomnia.[126]

We included 20 observational studies of adverse events associated with newer drugs for insomnia.[127-146]

Key Question 1. What is the comparative effectiveness of newer drugs in treating adults and children with insomnia?

Summary of the Evidence

There is no evidence in children.

Direct evidence

- Direct evidence is from 8 short-term head-to-head trials (7 fair quality, 1 poor; 1 measured withdrawal effects only)
- Eszopiclone compared with zolpidem (1 trial)
  - There was no significant difference between eszopiclone 2 mg or 3 mg and zolpidem 10 mg on polysomnography-measured sleep latency, WASO, or number of awakenings.
  - Both active treatments were more effective than placebo for polysomnography-measured sleep latency
  - Eszopiclone 2.5 mg and 3 mg were significantly better than placebo for polysomnography-measured WASO
  - Eszopiclone 1mg or 2 mg (lower doses) and zolpidem 10 mg were no different from placebo on polysomnography-measured WASO
- Zaleplon compared with zolpidem (4 trials)
  - Zaleplon and zolpidem were similarly effective for subjective sleep latency in elderly patients and in patients under age 65
  - There is evidence from 2 head-to-head trials that zaleplon is less likely than zolpidem to cause rebound insomnia in adults under age 65
- Zolpidem compared with zopiclone (2 efficacy trials, 1 poor quality)
  - In a fair-quality trial, zolpidem and zopiclone were similarly effective in investigator and patient global assessments of improvement
  - Subjective sleep outcomes (latency, frequency of awakening, sleep duration) were improved from placebo to a similar extent in both treatment groups
  - A trial of simulated driving performance was rated poor quality

Indirect evidence

- Adjusted indirect analysis of 22 placebo-controlled trials found few differences between drugs on subjective sleep outcomes
- Sleep latency was shorter with eszopiclone than ramelteon (mean difference -11 minutes; 95% CI -21 to -1.3 minutes)
- Sleep duration was an average of 37 minutes longer with eszopiclone compared with ramelteon (95% CI 17 to 56 minutes)
- Comparing only manufacturers' recommended initial doses, there were no differences between drugs on any outcome, with the exception of longer sleep duration with eszopiclone compared to ramelteon (mean difference 28.9 minutes; 95% CI 6.2 to 51.7 minutes)
- Excluding poor-quality studies, eszopiclone significantly increased sleep duration compared with zolpidem (mean difference 37.1 minutes; 95% CI 23.9 to 50.4 minutes)
- In a subgroup analysis of elderly patients, eszopiclone significantly increased sleep duration compared with zolpidem (mean difference 32.8 minutes; 95% CI 1.2 to 64.4 minutes)

Zolpidem extended-release

- There are no head-to-head trials comparing zolpidem extended-release with other newer insomnia drugs
- Evidence of efficacy comes from 3 fair-quality placebo-controlled trials. We were unable to include data from these trials in the adjusted indirect analysis.
- In adults under age 65, polysomnography- measured WASO was significantly shorter than placebo on nights 1 and 2 of treatment but not on nights 15 and 16. A post hoc analysis found that WASO was significantly better than placebo through hour 6, although not at hours 7 and 8
- Results for subjective sleep outcomes were mixed, with zolpidem extended-release showing superiority to placebo at some, but not all, assessment points
- In patients over age 65, polysomnography-measured WASO was shorter than placebo through the first 6 hours of the night
- In a 6-month study of intermittent treatment (3 to 7 nights per week), 90% of patients taking zolpidem extended-release said the treatment helped them sleep, compared with 51% of the placebo group

Detailed Assessment

Direct evidence

Patient and study design characteristics of included head-to-head trials are shown in Table 3. No new head-to-head trials were identified for Update #2.

Table 3. Head-to-head trials of newer insomnia drugs: Study design and patient characteristics

Study, year (Quality)	Study arms	Design	Population	Treatment duration	Primary outcome
Erman (poster and FDA 190-045)[147] (FAIR)	Eszopiclone 1 mg Eszopiclone 2 mg Eszopiclone 2.5 mg Eszopiclone 3 mg Zolpidem 10 mg Placebo	Cross-over	N=65 Mean age 40.6 74% female	2 nights	polysomnography-measured sleep latency
Allain 2003 (FAIR)	Zaleplon 10 mg Zolpidem 10 mg	Cross-over	N=53 Mean age 52 51% female	Single dose	Patient preference
Ancoli-Israel 1999 (FAIR)	Zaleplon 5 mg Zaleplon 10 mg Zolpidem 5 mg Placebo	Parallel	N=549 Over age 65 (mean age 72) 57.9% female	2 weeks	Not specified; primary analysis compared zaleplon with placebo
Elie 1999 (FAIR)	Zaleplon 5 mg Zaleplon 10 mg Zaleplon 20 mg Zolpidem 10 mg Placebo	Parallel	N=615 Mean age 43 65.5% female	4 weeks	Subjective sleep latency; primary analysis compared zaleplon with placebo
Fry 2000 (FAIR)	Zaleplon 5 mg Zaleplon 10 mg Zaleplon 20 mg Zolpidem 10 mg Placebo	Parallel	N=595 Mean age 42 58.4% female	4 weeks	Subjective sleep latency; primary analysis compared zaleplon compared
Lemoine 1995 (FAIR)	Zolpidem 10 mg Zopiclone 7.5 mg	Parallel	N=394 Demographics not reported	3 weeks	Withdrawal effects only
Staner 2005 (POOR)	Zolpidem 10 mg Zopiclone 7.5 mg Placebo Lorazepam	Cross-over	N=23 Mean age 38.8 61% female	1 week	Next-day effects (driving simulation)
Tsutsui 2001 (FAIR)	Zolpidem 10 mg Zopiclone 7.5 mg	Parallel	N=479 Mean age 42.2 65% female	2 weeks	Investigators' assessment of global improvement

Eszopiclone compared with zolpidem

One head-to-head trial compares eszopiclone compared with zolpidem.[20, 147] According to the study funder, the objective of the study was to evaluate the polysomnographic efficacy and safety of eszopiclone relative to placebo. Zolpidem 10 mg was included as an active control to allow qualitative comparisons to eszopiclone. The primary efficacy outcome was latency to persistent sleep as measured by polysomnography. The study compared 4 doses of eszopiclone (1 mg, 2 mg, 2.5 mg, and 3 mg) to placebo and zolpidem 10 mg in a crossover design over 2 nights of treatment.

Both drugs were more effective than placebo for the primary outcome of polysomnography-measured sleep latency. Eszopiclone 2.5 mg and 3 mg were more effective than placebo for polysomnography-measured WASO, but there was no difference from placebo for eszopiclone at lower doses or for zolpidem 10 mg. There was also no difference between zolpidem and eszopiclone on subjective measures of next-day effects, including morning sleepiness, daytime alertness, and daytime ability to function.[20]

The main analysis in this study compared eszopiclone with placebo; no analysis comparing eszopiclone with zolpidem was presented. To make a direct comparison between the two drugs, we calculated the weighted mean difference between eszopiclone and zolpidem for polysomnography-measured sleep outcomes using data provided in the FDA review of eszopiclone. Results of these analyses are shown in Table 4.[20] There were no significant differences between eszopiclone and zolpidem on polysomnography-measured sleep latency, WASO, or number of awakenings.

Subjective measures were also reported, but standard deviations were not provided, so we could not calculate a mean difference.

Table 4. Head-to-head comparison of eszopiclone compared with zolpidem on polysomnography-measured outcomes[147]

Outcome	Mean (SD) at endpoint (*P* value compared with placebo) 1. Eszopiclone 2 mg 2. Eszopiclone 3 mg 3. Zolpidem 10 mg 4. Placebo	Eszopiclone 2 mg compared with zolpidem 10 mg, mean difference (95% CI)	Eszopiclone 3 mg compared with zolpidem 10 mg, mean difference (95% CI)
Sleep latency	1. 20.1 (17.6) min (*P*<0.0001) 2. 18.3 (19.6) min (*P*<0.0001) 3. 16.6 (14.4) min (*P*<0.0001) 4. 37.8 (31.1) min	1.70 min (-4.26 to 7.66)	3.5 min (-2.10 to 6.74)
WASO	1. 36.0 (25.0) min (*P*=0.1104) 2. 35.9 (31.7) min (*P*=0.0122) 3. 39.3 (28.5) min (*P*=0.3287) 4. 43.1 (32.5) min	-3.40 min (-13.84 to 7.04)	-3.30 min (-12.62 to 6.02)
Number of awakenings	1. 7.6 (4.5) times; (*P*=0.5983) 2. 6.5 (4.4) times; (*P*=0.0031) 3. 7.2 (4.3) times; (*P*=0.1838) 4. 7.7 (4.1) times	0.40 times (-1.13 to 1.93)	-0.70 times (-1.23 to 0.92)

Abbreviations: SD, standard deviation; min, minutes; WASO, wake time after sleep onset.

Zaleplon compared with zolpidem

Four fair-quality head-to-head studies compared zolpidem with zaleplon and placebo.[12, 14, 15, 17] Two of these were conducted in adults under age 65 and had identical designs.[14, 15] Another was conducted in older adults.[12] The fourth head-to-head study[17] was a small, single-dose crossover trial that measured patient preference as a primary outcome.

In the 3 studies with sleep outcomes, comparisons between zaleplon and placebo were the primary comparisons. Published reports do not provide a head-to-head analysis comparing

zaleplon with zolpidem, and it was not possible to conduct an analysis of zaleplon compared with zolpidem from data provided.

Sleep latency. Sleep latency was the primary outcome in two studies in adults.[14, 15] Both compared zaleplon at three fixed doses (5 mg, 10 mg, or 20 mg) with zolpidem 10 mg for 4 weeks. A placebo arm was also included, and analyses are presented for the comparison to placebo. Neither publication provided a head-to-head analysis of zolpidem compared with zaleplon, but a head-to-head analysis is provided in the FDA statistical review of zaleplon[5] for one trial.[15] At weeks 1 through 4,[15] there was no difference between zaleplon 5 mg or 10 mg and zolpidem 10 mg on the median number of minutes to sleep onset. The only significant difference between the drugs on this outcome was a shorter latency with zaleplon 20 mg compared with zolpidem 10 mg. There was no difference in the comparison of recommended starting doses zaleplon 10 mg and zolpidem 10 mg. These results are not from intention-to-treat analyses.

For the second trial,[14] intention-to-treat results using the last observation carried forward method are presented in the FDA review of zaleplon.[5] Analyses compared zaleplon with placebo. Results were mixed. Zaleplon at all three doses had a shorter latency than placebo at all time points, with the exception of 5 mg at week 4. For zolpidem 10 mg, at weeks 2 and 3 latency was significantly shorter than for placebo but was not significantly different at week 4. At week 1, there was a trend for shorter latency, but this was not significant (-10 minutes; P=0.07).

In a 2-week head-to-head trial of zaleplon 5 mg or 10 mg compared with zolpidem 5 mg conducted in 549 older adults (65 years or older),[12] results were similar to those of the trials in younger patients. There was no difference in sleep latency for zaleplon 5 mg and zolpidem 5 mg, but zaleplon at a higher dose (10 mg) was associated with a shorter latency than zolpidem 5 mg. Zolpidem, but not zaleplon, was associated with rebound sleep latency on the first night of discontinuation.

Sleep duration. Duration of sleep was a secondary outcome in three head-to-head trials of zaleplon compared with zolpidem.[12, 14, 15] Zolpidem 5 mg and 10 mg increased sleep duration more than placebo in all three studies. In two studies in adults, zaleplon 5 mg and 10 mg were no different from placebo on this outcome at any time period. Zaleplon 20 mg was more effective than placebo at weeks 1 and 3, but not weeks 2 and 4.

Number of awakenings. The difference from placebo in the median number of awakenings during the night was another secondary outcome in head-to-head trials. In one trial,[14] there was no difference from placebo for any dose of either zaleplon or zolpidem at any time point. The other trial in adults[15] had mixed results. Zaleplon 5 mg and 10 mg was no different from placebo, zaleplon 20 mg was more effective than placebo at weeks 2, 3, and 4, and zolpidem 10 mg was better than placebo at weeks 1, 2, and 3. In older adults, only zolpidem 5 mg was more effective than placebo.[12]

Sleep quality. In a pooled analysis of three trials of zaleplon compared with zolpidem,[12, 14, 15] the National Institute for Clinical Excellence review[124] found that patients on zaleplon were less likely to experience improvement in sleep quality at the end of treatment than patients taking zolpidem (odds ratio 0.66; 95% CI 0.51 to 0.87).

Rebound insomnia. Two head-to-head trials found zolpidem 10 mg to be associated with more rebound insomnia than zaleplon as measured by an increase in median sleep latency on the first night after discontinuation.[14, 15] Zolpidem 10 mg was associated with a 20- to 22-minute increase in sleep latency compared with placebo on the first night of discontinuation. Rebound sleep latency was not seen with zaleplon at any dose. Zaleplon at all doses (5 mg, 10 mg, and 20 mg) was less likely to cause rebound sleep latency than zolpidem 10 mg. The mean difference between zolpidem 10 mg and zaleplon 10 mg was 34 minutes (95% CI 10.5 to 57.5 minutes). Head-to-head studies also found zolpidem to be associated with rebound decrease in sleep duration on the first night of discontinuation. Zaleplon was not associated with rebound on this outcome, except at the 10 mg dose in older adults. In two studies in adults[14, 15] zolpidem, but not zaleplon, was associated with an increase in awakenings compared to placebo on the first night after withdrawal. In older adults, neither drug was associated with rebound insomnia on this measure.[12]

Other outcomes. A small (N=53) single-dose crossover study comparing zolpidem 10 mg with zaleplon 10 mg was designed to measure patient preference for a drug as the primary outcome.[17] This was measured by a questionnaire filled in by the patient the evening following administration of the drug. More patients preferred zolpidem, but the difference was not statistically significant (62% compared with 32%; P=0.81). Secondary outcomes were mean scores on the Leeds sleep evaluation questionnaire, and "day quality," a visual analog scale (0-100, higher is better) measuring 7 factors on the day following the administration of the drug. Zolpidem patients improved more on two of four factors on the Leeds sleep evaluation questionnaire (Getting to Sleep and Quality of Sleep); there was no difference between drugs on the other two factors (Ease of Waking Up and Behavior Following Wakefulness). Only one of 7 factors of the day-quality measure was significantly different between drugs. Zolpidem patients reported better quality of sleep (mean score 68.8 compared with 50.2, P<0.0001), but there were no differences on other factors.

Zopiclone compared with zolpidem

Two fair-quality[13, 16] and one poor-quality study[19] compared zolpidem with zopiclone. One was designed to assess the effect of withdrawal in patients already taking the drugs for insomnia and did not report efficacy outcomes; it is discussed under Key Question 2.[13]

A two-week, double-blind trial in 479 patients at multiple centers in Japan[16] is the only head-to-head trial of zolpidem compared with zopiclone in which efficacy is the primary outcome. The primary outcome was the investigator's global assessment of improvement, based on patient sleep diaries and reported as the proportion of patients who were "moderately improved" or "markedly improved." At the end of treatment, there were no significant differences between treatment groups in the number of patients "markedly improved" (18.7% zolpidem compared with 16.4% zopiclone) or "moderately improved" (49.3% zolpidem compared with 45.2% zopiclone). Patients' ratings of treatment efficacy were similar and did not differ between treatment groups. Sleep outcomes (sleep onset latency, frequency of awakening, sleep duration, daytime mood, and daytime physical condition) were improved from placebo to a similar extent in both treatment groups, but data were not reported. Rebound insomnia was reported as the percentage of patients with an aggravation of sleep onset latency by one grade or more after 2 weeks of treatment.[16] More patients who took zopiclone had rebound insomnia by this definition than those who took zolpidem (15.4% compared with 4.5%, P<0.005).

Another head-to-head study comparing zolpidem with zopiclone measured next-day simulated driving performance as the primary outcome and reported subjective sleep parameters as secondary outcomes.[19] This study was rated poor quality because no baseline demographic or clinical data were reported, and so it cannot be determined if groups were comparable at baseline, and there is no information about withdrawals, so it is impossible to determine if an intention-to-treat analysis was conducted.

Indirect evidence: Meta-analysis of placebo-controlled trials

Because of the limited amount of direct evidence available to compare efficacy across drugs, we conducted a meta-analysis of placebo-controlled trials reporting subjective sleep outcomes. Studies were included in the meta-analysis if they reported endpoint mean scores and standard deviations (or the data to calculate these) for subjective sleep latency, sleep duration, number of awakenings, or WASO in patients with chronic insomnia. Studies were excluded if they reported only objective outcomes, if they used an intermittent dosing strategy (for example, treatment as needed), or if they were conducted in patients with acute insomnia or co-morbid conditions such as depression or sleep apnea.

Twenty-two trials contributed data to the meta-analysis; their characteristics are shown in Table 5.[5, 15, 29, 32, 40, 61, 71, 72, 80, 84, 90, 96, 106, 110, 111, 118, 119, 122, 123, 148] We included 4 trials of eszopiclone, 4 of ramelteon, 4 of zaleplon, 7 of zolpidem, and 4 of zopiclone (one trial included both zaleplon and zolpidem[15]). Five trials were conducted in older adults[40, 80, 106, 110, 118] and the rest in adults under age 65. Sample sizes ranged from 14 to 848, and treatment durations ranged from 2 nights to 6 months. Three studies were rated poor quality[71, 84, 118] and the rest were fair; no study met all quality criteria.

Table 5. Placebo-controlled trials included in meta-analysis of subjective sleep outcomes

Study, year (Quality)	Interventions	Sample size	Population (Elderly=age 65 or older)	Treatment duration/ Design
Scharf 2005[110] (FAIR)	Eszopiclone 2 mg	231	Elderly	2 weeks/ Parallel
Zammit 2004[123] (FAIR)	Eszopiclone 2 mg Eszopiclone 3 mg	308	Adults	6 weeks/ Parallel
Krystal 2003[90] (FAIR)	Eszopiclone 3 mg	788	Adults	6 months/ Parallel
Walsh 2007[119] (FAIR)	Eszopiclone 3 mg	830	Adults	6 months/ Parallel
Ramelteon FDA Study #020[80] (FAIR)	Ramelteon 8 mg Ramelteon 16 mg	848	Adults	5 weeks/ Parallel
Roth 2006[105]	Ramelteon 4 mg Ramelteon 8 mg	829	Elderly	5 weeks/ Parallel

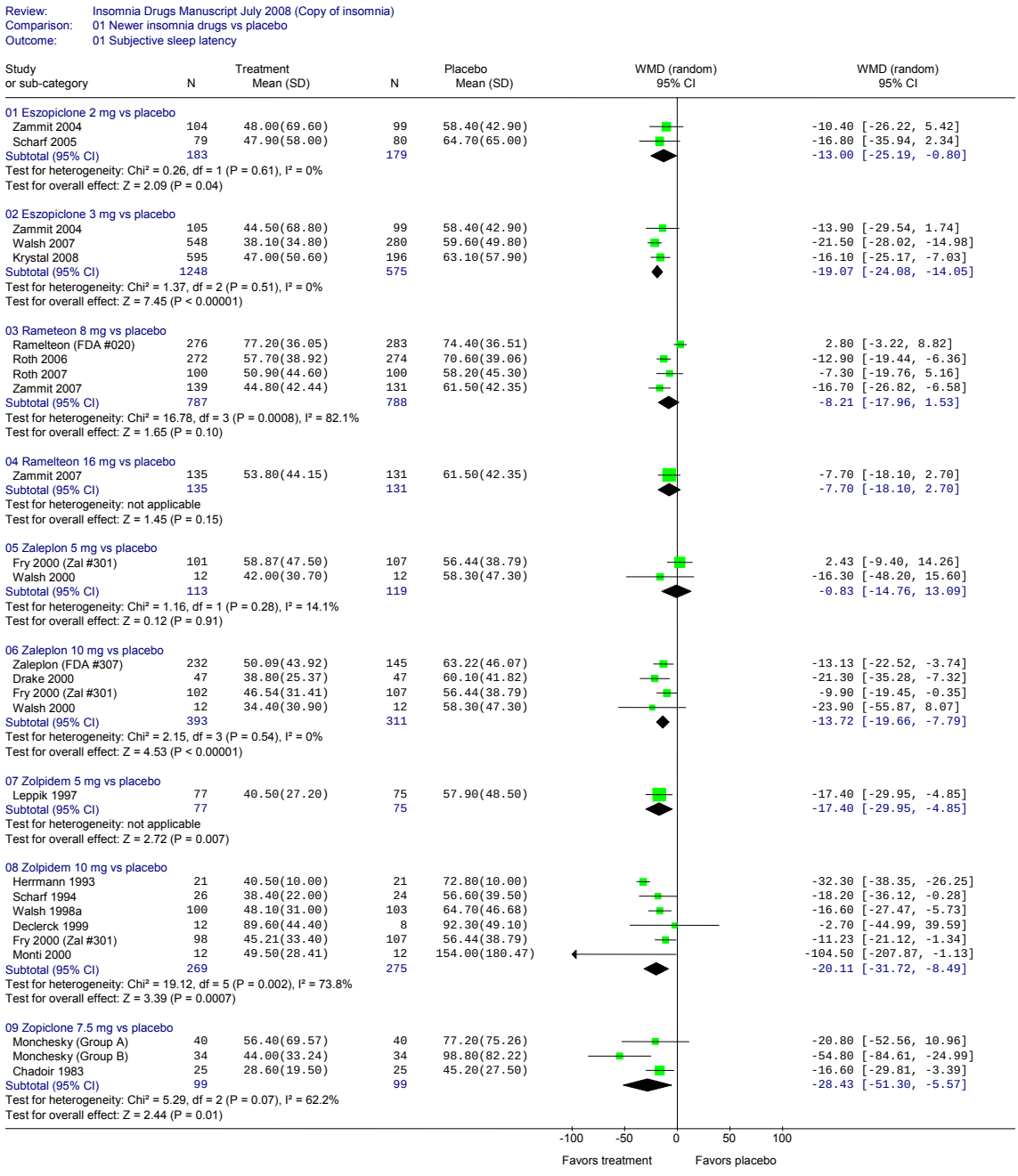
Study, year (Quality)	Interventions	Sample size	Population (Elderly=age 65 or older)	Treatment duration/ Design
(FAIR)				
Roth 2007[106] (FAIR)	Ramelteon 4 mg Ramelteon 8 mg	100	Elderly	2 nights/ Crossover
Zammit 2007[122] (FAIR)	Ramelteon 8 mg Ramelteon 16 mg	405	Adults	5 weeks/ Parallel
Drake 2000[29] (FAIR)	Zaleplon 10 mg	47	Adults	2 nights/ Crossover
Zaleplon FDA Study #307[5]	Zaleplon 10 mg	367	Adults	2 weeks/ Parallel
Fry 2000[15] (FAIR)	Zaleplon 5 mg Zaleplon 10 mg Zolpidem 10 mg	595	Adults	4 weeks/ Parallel
Walsh 2000a[118] (POOR)	Zaleplon 5 mg Zaleplon 10 mg	48	Elderly	2 nights Parallel
Declerck 1999[72] (FAIR)	Zolpidem 10 mg	22	Adults; regular users of benzodia-zepines	1 week/ Parallel
Fleming 1995[32] (FAIR)	Zolpidem 10 mg	141	Adults	3 nights/ Parallel
Herrmann 1993[84] (POOR)	Zolpidem 10 mg	21	Adults	2 weeks/ Parallel
Scharf 1994[111] (FAIR)	Zolpidem 10 mg	75	Adults	4 weeks/ Parallel
Walsh 1998a[61] (FAIR)	Zolpidem 10 mg	306	Adults	2 weeks/ Parallel
Leppik 1997[40] (FAIR)	Zolpidem 5 mg	335	Elderly	4 weeks/ Parallel
Chaudoir 1983[71] (POOR)	Zopiclone 7.5 mg	25	Adults	1 week Crossover
Monchesky (Group A)[96] (FAIR)	Zopiclone 7.5 mg	26	Adults	1 week/ Crossover
Monchesky (Group B)[96] (FAIR)	Zopiclone 7.5 mg	14	Adults	1 week/ Crossover

Study, year (Quality)	Interventions	Sample size	Population (Elderly=age 65 or older)	Treatment duration/ Design
Sivertsen 2006[148] (FAIR)	Zopiclone 7.5 mg	28	Adults	6 weeks/ Parallel

Subjective sleep latency

Figure 2 shows the pooled estimates of subjective sleep latency from 22 placebo-controlled trials of individual insomnia drugs. Ramelteon, whether at the 8 mg or the 16 mg dose, and zaleplon 5 mg, were not statistically significantly better than placebo. In the remaining studies, the active drug decreased the time to fall asleep by about 13 to 20 minutes compared with placebo. There was significant heterogeneity among the ramelteon 8 mg, zolpidem 10 mg, and zopiclone 7.5 mg trials (P>0.10).

Figure 2. Subjective sleep latency in placebo-controlled trials of newer insomnia drugs

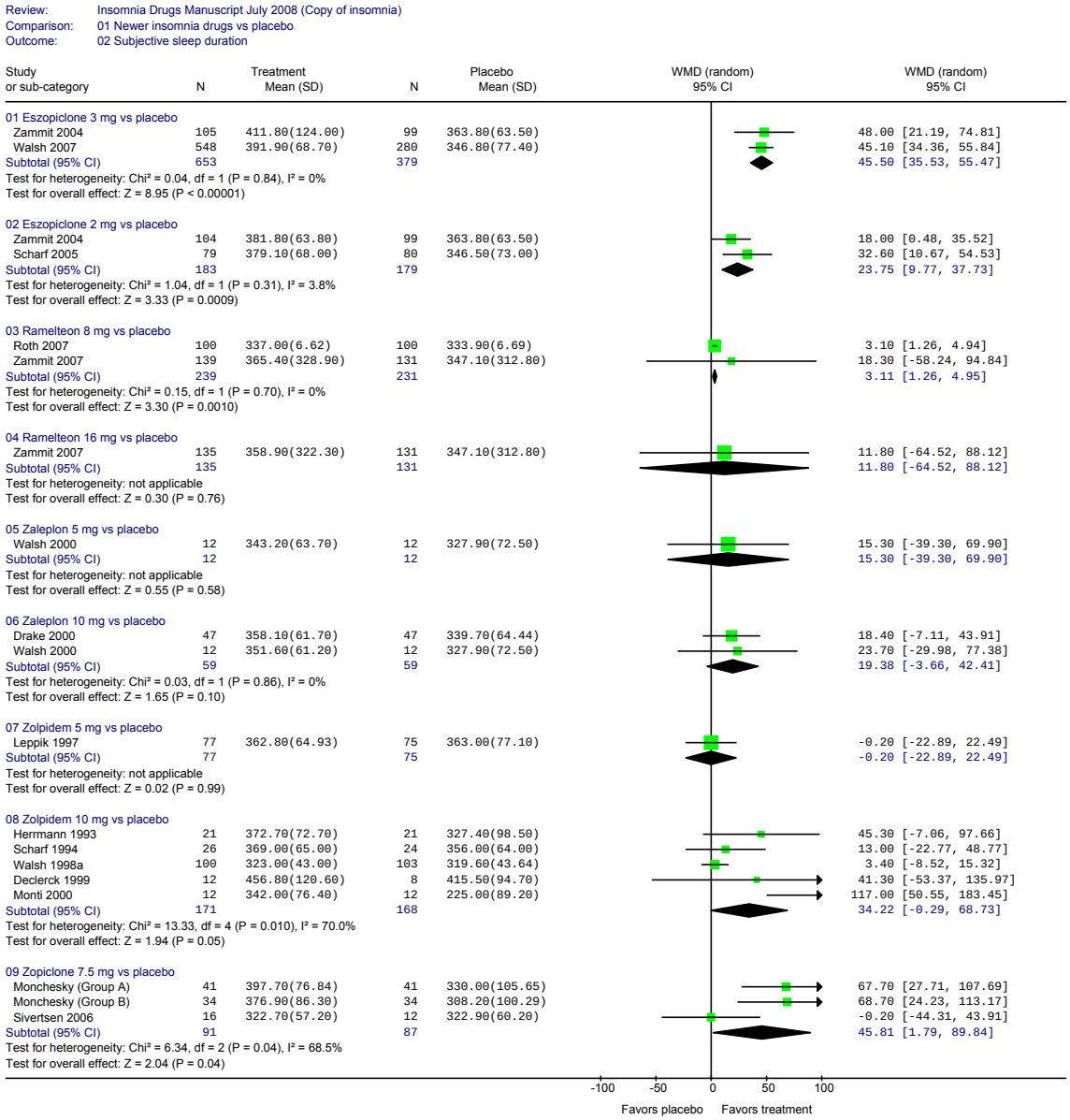


Sleep duration

Figure 3 shows the pooled estimates for subjective sleep duration in 16 placebo-controlled trials reporting this outcome. Eszopiclone was significantly better than placebo for increasing total sleep time. At the 3 mg dose, the difference from placebo was an increase of 46 minutes (95% CI 36 to 56 minutes). Eszopiclone 2 mg increased the total time slept by 24 minutes over placebo (95% CI 10 to 38 minutes). Ramelteon 8 mg and zopiclone 7.5 mg were also significantly better than placebo. For ramelteon, the difference from placebo was only 3 minutes, however. There

was significant heterogeneity among the zopiclone studies (*P*=0.04), and the estimate was imprecise, with a very wide confidence interval (1.79 to 89.84 minutes).

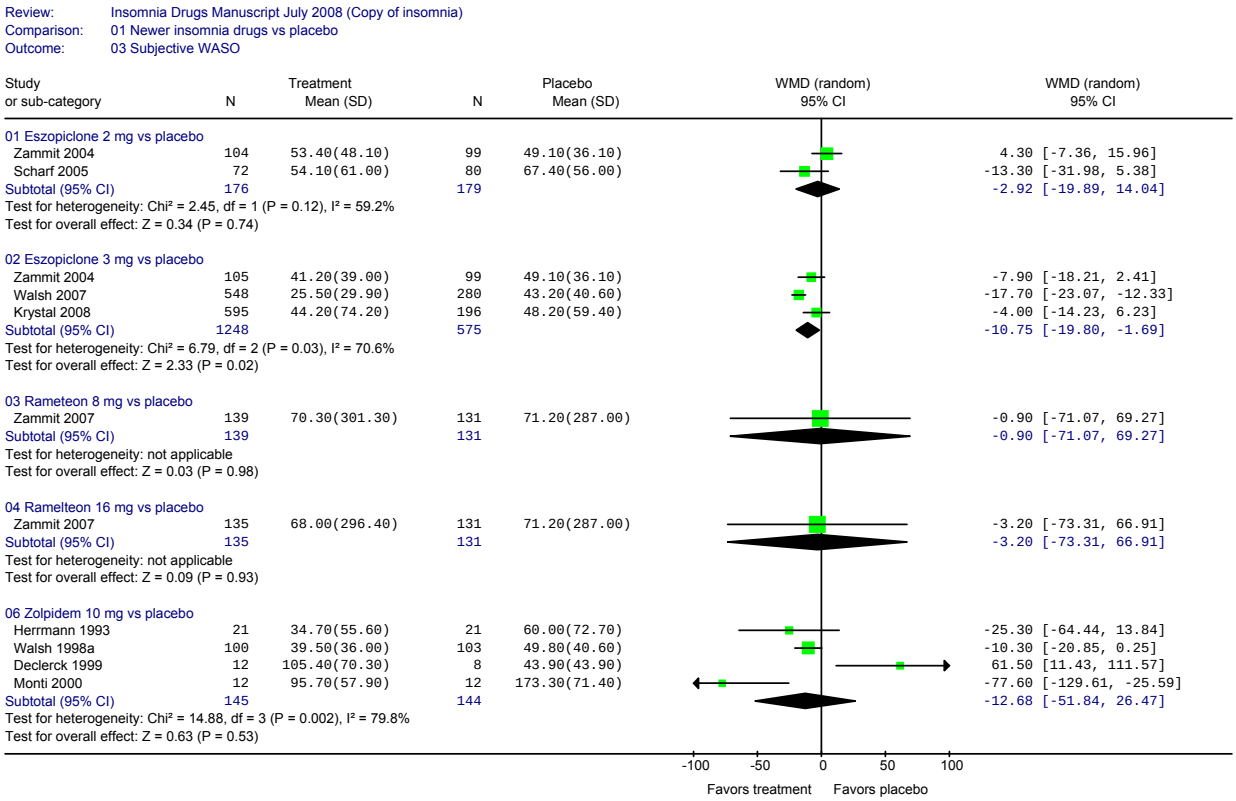
Figure 3. Subjective sleep duration in placebo-controlled trials of newer insomnia drugs



Subjective wake time after sleep onset

Subjective WASO was reported in 9 trials (Figure 4). Only eszopiclone 3 mg was significantly better than placebo on this outcome. Eszopiclone 3 mg shortened the time spent awake after sleep onset by 11 minutes compared with placebo (95% CI -20 to -2 minutes).

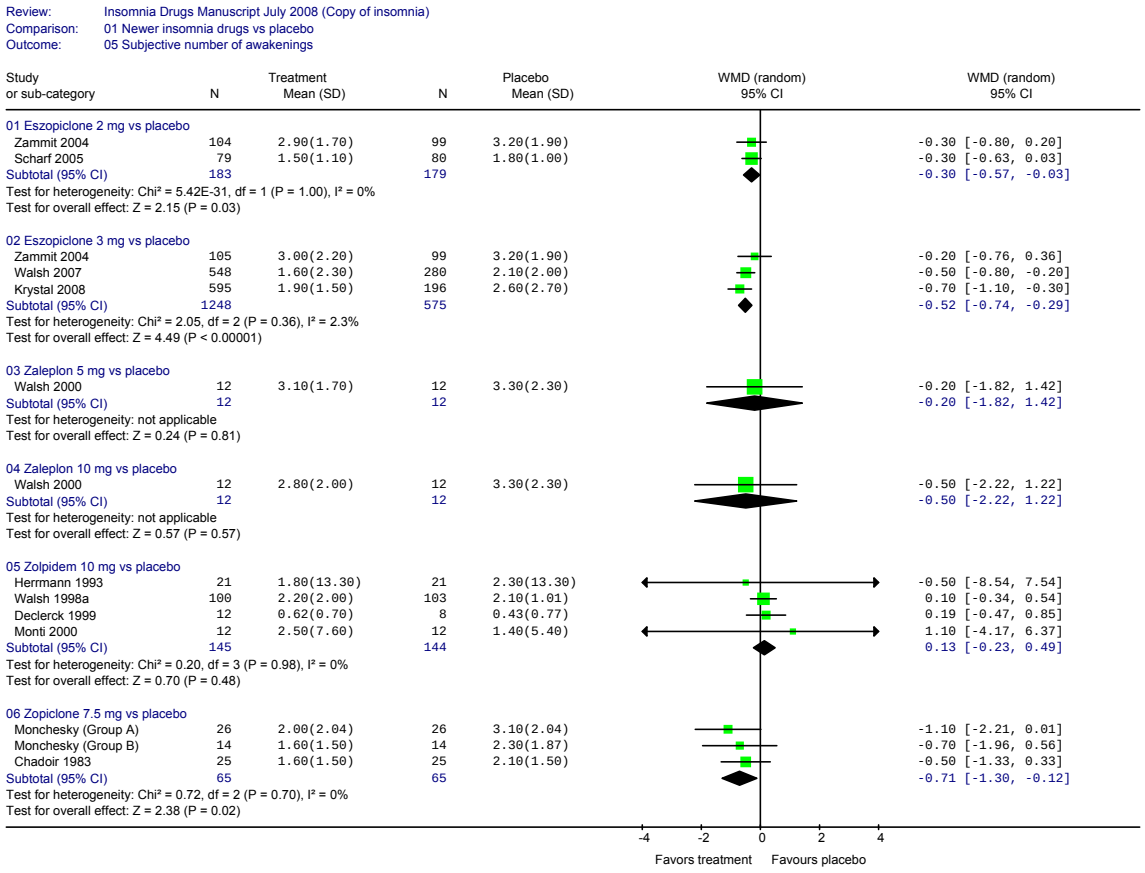
Figure 4. Subjective wake time after sleep onset in placebo-controlled trials of newer insomnia drugs



Subjective number of awakenings

Figure 5 shows results from 12 placebo-controlled trials reporting subjective number of awakenings. Only eszopiclone was significantly better than placebo for this outcome. The difference was less than one awakening per night (mean difference -0.52; 95% CI -0.57 to -0.03).

Figure 5. Subjective number of awakenings in placebo-controlled trials of newer insomnia drugs



Results of adjusted indirect meta-analysis

Results of the adjusted indirect meta-analysis are shown in Table 6. Data from varying doses of the same drug were combined for this indirect comparison. There were very few significant differences between the drugs on any outcomes. The exceptions were significantly shorter sleep latency and longer sleep duration with eszopiclone compared to ramelteon. On average, sleep latency was 11 minutes shorter with eszopiclone than ramelteon (95% CI -21 to -1.3 minutes). Sleep duration was an average of 37 minutes longer with eszopiclone than ramelteon (95% CI 17 to 56 minutes). Patients taking eszopiclone had significantly fewer awakenings than those taking zolpidem, but the difference was less than one time per night (mean difference 0.6 times per night; 95% CI -1.0 to -0.2).

Table 6. Adjusted indirect meta-analysis: Summary of results

	Mean difference (95% confidence interval)			
	Sleep latency in minutes	**Sleep duration in minutes**	**Number of awakenings**	**WASO in minutes**
Eszopiclone compared with ramelteon	**-11.2[a] (-21.2 to -1.3)**	**36.6 (17.0 to 56.3)**	--	-7.2 (-22.1 to 7.6)
Eszopiclone compared with zaleplon	-6.3 (-15.8 to 3.2)	22.0 (-2.1 to 46.0)	-0.1 (-1.6 to 1.4)	--
Eszopiclone compared with zolpidem	1.3 (-9.5 to 12.0)	19.0 (-5.9 to 43.9)	**-0.6 (-1.0 to -0.2)**	3.4 (-36.9 to 43.7)
Ramelteon compared with zaleplon	4.9 (-7.1 to 16.9)	-14.7 (-43.4 to 14.0)	--	--
Ramelteon compared with zolpidem	12.5 (-0.6 to 25.5)	-17.7 (-47.0 to 11.7)	--	10.7 (-30.2 to 51.5)
Ramelteon compared with zopiclone	21.2 (-3.3 to 45.7)	-41.8 (-89.3 to 5.6)	0.3 (-0.3 to 0.9)	--
Zaleplon compared with zolpidem	7.6 (-5.1 to 20.3)	-3.0 (-35.5 to 29.5)	-0.5 (-2.0 to 1.1)	--
Zaleplon compared with zopiclone	16.3 (-8.0 to 40.6)	-27.2 (-76.6 to 22.3)	0.4 (-1.2 to 2.0)	--
Zolpidem compared with zopiclone	8.7 (-16.1 to 33.6)	-24.2 (-74.0 to 25.7)	**0.8 (0.2 to 1.5)**	--

[a] Statistically significant results are in boldface type.

We performed several subgroup analyses to determine if meta-analysis results varied by population or study design characteristics. These analyses were planned a priori.

When studies conducted in adult and elderly patients were analyzed separately, adjusted indirect analysis showed no significant differences between any of the drugs in subjective sleep latency or WASO (Table 7). In elderly patients, sleep duration was significantly longer with eszopiclone than with ramelteon and zolpidem in elderly patients, but there was no difference between any of the drugs in adult patients under age 65.

Table 7. Subgroup analysis by elderly and non-elderly adult patients

		Mean difference (95% confidence interval)			
		Sleep latency in minutes	**Sleep duration in minutes**	**Number of awakenings**	**WASO in minutes**
Eszopiclone compared with ramelteon	Adults Elderly	-14.1 (-29.7 to 1.4) -5.1 (-25.1 to 14.9)	26.4 (-40.5 to 93.3) **29.5 (0.8 to 58.2)**[a]	--	-6.4 (-22.5 to 9.7) --
Eszopiclone compared with zaleplon	Adults Elderly	-6.8 (-17.4 to 3.8) 3.3 (-31.8 to 38.4)	23.1(-4.6 to 50.8) 13.1 (-39.7 to 65.9)	0.1 (-1.5 to 1.6) --	--
Eszopiclone compared with zolpidem	Adults Elderly	1.6 (-11.0 to 14.2) 0.6 (-22.3 to 23.5)	7.2 (-28.9 to 43.4) **32.8 (1.2 to 64.4)**	-0.6 (-1.1 to -0.2) --	4.3 (-36.5 to 45.0) --
Ramelteon compared with zaleplon	Adults Elderly	7.3 (-10.1 to 24.8) 8.4 (-21.6 to 38.4)	-3.3 (-74.1 to 67.5) -16.4 (-67.9 to 35.1)	--	--
Ramelteon compared with zolpidem	Adults Elderly	15.7 (-3.0 to 34.5) 5.7 (-8.1 to 19.5)	-19.1 (-93.6 to 55.4) 3.3 (-25.9 to 32.5)	--	10.7 (-30.2 to 51.5) --
Ramelteon compared with zopiclone	Adults Elderly	24.1 (-3.1 to 51.3) NA	-30.7 (-110.1 to 48.6) NA	--	--
Zaleplon compared with zolpidem	Adults Elderly	8.4 (-6.5 to 23.3) -2.7 (-34.7 to 29.3)	-15.8 (-58.7 to 27.1) 19.7 (-33.4 to 72.8)	--	--
Zaleplon compared with zopiclone	Adults Elderly	16.7 (-8.0 to 41.4) NA	-27.4 (-78.3 to 23.5) NA	--	--
Zolpidem compared with zopiclone	Adults Elderly	8.3 (-17.3 to 34.0) NA	-11.6 (-67.5 to 44.4) NA	0.8 (0.2 to 1.5) --	--

[a] Statistically significant results are in boldface type.

We also performed a subgroup analysis excluding studies that used doses other than the manufacturers' recommended initial dose. Recommended initial doses are eszopiclone 2 mg, ramelteon 8 mg, zaleplon 10 mg, zolpidem 10 mg, and zopiclone 7.5 mg. (Note: Although the eszopiclone product label states that eszopiclone can be started at 3 mg if clinically indicated, the 2 mg dose is recommended for 'most non-elderly adults.') In this subgroup analysis, there were

no differences between any drugs on any outcome, with the exception of longer sleep duration for eszopiclone than ramelteon (mean difference 28.9 minutes; 95% CI 6.2 to 51.7 minutes).

Exclusion of poor-quality studies[71, 84, 118] did not change results of the sleep latency, WASO, or number-of-awakenings analyses. In fair-quality studies, eszopiclone significantly increased sleep duration compared with zolpidem (mean difference 37.1 minutes; 95% CI 23.9 to 50.4 minutes).

PSG-measured outcomes in trials of ramelteon

PSG-measured sleep outcomes were reported in three placebo-controlled trials of ramelteon.[77, 106, 122]

PSG- measured sleep outcomes were measured at weeks 1, 3, and 5 in a trial of ramelteon 8 mg or 16 mg compared with placebo.[122] The primary outcome, sleep latency at week 1 was reduced for both the 8 mg (32 minutes) and 16 mg (29 minutes) groups compared to placebo (48 minutes, $P<0.001$); improvements were also shown at weeks 3 and 5. Total sleep time was improved with ramelteon compared with placebo at weeks 1 and 3 but not week 5. There were no differences in WASO or number of awakenings.

In a crossover study of 2 nights of treatment with ramelteon 4 mg, 8 mg, 16 mg, or 32 mg, all doses of ramelteon resulted in reductions in PSG-measured sleep latency ($P<0.001$) and increases in total sleep time ($P<0.05$).[77] There were no differences in WASO for any of the treated groups compared to placebo.

In a 2-night crossover study conducted in patients over age 65, there were significant improvements in PSG-measured sleep latency with ramelteon 4 mg (28.7 minutes, $P<0.001$) and 8 mg (30.8 minutes, $P=0.005$) compared with placebo (38.4 minutes).[106] PSG-measured total sleep time was also improved with ramelteon (359 minutes for 4 mg and 362 minutes for 8 mg compared with 350 minutes for placebo; $P=0.018$). There was no difference in objective WASO with either dose of ramelteon compared to placebo, and there was an increase in number of awakenings with ramelteon 4 mg (but not with the 8 mg dose).

Zolpidem extended-release

There are no head-to-head trials comparing zolpidem extended-release with other newer drugs for insomnia. Evidence for the efficacy of zolpidem extended-release comes from three fair-quality placebo-controlled trials.[89, 115, 121] Additional information is provided in the FDA statistical review of zolpidem extended-release[79] Table 8 summarizes the results of these trials. Because they did not report means for subjective sleep outcomes at endpoint, we were not able to include their data in our meta-analysis.

Table 8. Placebo-controlled trials of zolpidem extended-release

Author, year (Quality)	Population	Dose, duration	Main efficacy results
Roth 2006;[107] FDA Study EFC4529 (FAIR)	Adults N=212	12.5 mg 3 weeks	**Primary outcome**: Polysomnography-recorded WASO during first 8 hours of the night, mean difference from placebo (95% CI): Nights 1 and 2: -25 minutes (-34 to -16); *P*<0.0001 Nights 15 and 16: -7 minutes (-18 to -3); *P*=0.1913 **Secondary outcomes:** Polysomnography-recorded sleep latency (mean change from baseline, zolpidem-XR compared with placebo): Nights 1 and 2: -23 compared with -13 minutes; *P*<0.0001 Nights 15 and 16: -21 compared with -13 minutes; *P*=0.0338 Polysomnography-recorded number of awakenings: Nights 1 and 2: -2.7 compared with -0.8; *P*<0.0001 Nights 15 and 16: -3.0 compared with -0.9; *P*<0.0001
Walsh 2008[121] (FDA Study 4530) (FAIR)	Elderly N=205	6.25 mg 3 weeks	**Primary outcome**: Polysomnography-recorded WASO during first 6 hours of the night, adjusted mean difference from placebo (95% CI): Nights 1 and 2: -25 minutes (-32 to -19); *P*<0.0001 Nights 15 and 16: -11 minutes (-19 to -3); *P*=0.0042
Krystal 2008[89] (FAIR)	Adults N=1018	12.5 mg, as needed, 3 to 7 nights per week 6 months	**Primary outcome:** Patient's Global Impression at week 12: 89.8% zolpidem-XR compared with 51.4% placebo group said treatment helped them sleep (*P*<0.0001). **Secondary outcomes:** Improvements in patient-reported sleep duration, WASO, sleep latency, quality of sleep, and number of awakenings in treatment group (data reported graphically)

A placebo-controlled trial of zolpidem extended-release 12.5 mg was conducted in 212 adults with primary insomnia.[107] This study included 2 nights of polysomnography recording, 12 nights of outpatient treatment, 2 more nights of polysomnography recording, 5 nights of outpatient treatment, and a 2-night placebo run-out to measure rebound. The primary outcome measure was polysomnography-recorded WASO in the first 8 hours of the night, measured on nights 1 and 2, and nights 15 and 16, with scores averaged over each 2-night period. WASO was significantly shorter with zolpidem-XR than placebo on nights 1 and 2, but not on nights 15 and 16. A post hoc analysis found that WASO was significantly better than placebo through hour 6, but not during hours 7 and 8 of the night, suggesting that the effects of zolpidem extended-release did not persist past 6 hours.[79] The publication of this trial reports only 6-hour results.[107] The 8-hour results are reported in the FDA review.[79]

Data for subjective sleep outcomes are reported graphically only. Results for subjective WASO, subjective number of awakenings, subjective sleep duration, and subjective sleep latency were mixed. Zolpidem extended-release was superior to placebo ($P<0.05$) at some, but not all, assessment points. Both groups had worse outcomes in the sleep laboratory than at home.

A second placebo-controlled trial, with an identical design was conducted in elderly patients.[121] In this trial, the primary outcome was polysomnography-measured WASO in the first 6 hours of the night. This was significantly better than placebo at both nights 1 and 2, and nights 15 and 16. WASO through 8 hours was not measured.

There was a rebound effect in both studies after discontinuation on the first night after discontinuation (night 22), but not on night 23.

A third placebo-controlled trial studied the effect of 6 months of treatment with zolpidem extended-release 12.5 mg in 1018 adults with chronic primary insomnia.[89] Patients were instructed to take the medication only as needed, but were required to take a minimum of 3 doses per week. By month 6, the mean number of doses patients took per month was 19.6 (SD 5.2; median 20.0). The primary outcome was the patients' assessment of the treatment's aid to sleep, measured by the Patient's Global Impression at week 12. At week 12, 89.8% of patients treated with zolpidem extended-release said the treatment helped them sleep, compared with 51.4% of the placebo group ($P<0.0001$).

Key Question 2. What are the comparative tolerability and safety of newer drugs for insomnia when used to treat patients with insomnia?

Summary of the Evidence

Direct evidence

- Eszopiclone compared with zolpidem
  - In one head-to-head trial, there was no difference between zolpidem and eszopiclone on subjective measures of next-day effects, including morning sleepiness, daytime alertness, and daytime ability to function
- Zaleplon compared with zolpidem
  - In head-to-head trials, total withdrawals and withdrawals due to adverse events were similar for zaleplon and zolpidem and increased with longer duration of trials
- Zolpidem compared with zopiclone
  - In a study that measured withdrawal effects over 2 weeks, the incidence of adverse events was higher in withdrawal groups than in continued treatment groups but was similar for zolpidem and zopiclone (38% and 41%, respectively)

Indirect evidence

- There was no increased risk of withdrawal due to adverse events in placebo-controlled trials of eszopiclone, ramelteon, zaleplon, zolpidem, or zopiclone
- In a pooled analysis of 3 placebo-controlled trials, the risk of withdrawal due to adverse events was higher with zolpidem extended-release than placebo (relative risk 1.93; 95% CI 1.17 to 3.21)
- Adjusted indirect analysis of placebo-controlled trials found no differences between the newer sedative hypnotics in rates of withdrawals due to adverse events
- There is no comparative evidence about long-term safety

Detailed Assessment

Direct evidence

Eszopiclone compared with zolpidem

In an unpublished head-to-head trial, there was no difference between zolpidem and eszopiclone on subjective measures of next-day effects, including morning sleepiness, daytime alertness, and daytime ability to function.[20] A comparison of eszopiclone and zolpidem on other adverse events in this trial is not available.

Zaleplon compared with zolpidem

Rates of overall adverse events and withdrawals due to adverse events were similar in short-term head-to-head trials of zaleplon compared with zolpidem and increased with longer duration of the trials (Table 9).

Table 9. Adverse events in head-to-head studies of zaleplon compared with zolpidem

		Incidence of adverse events		Withdrawals due to adverse events	
Comparison (duration)	N	Percent	Risk difference (95% CI)	Percent	Risk difference (95% CI)
Zaleplon 5 mg compared with zolpidem 10 mg[14, 15] (4 weeks)	476	67% compared with 73%	-6% (-14% to 2%)	2% compared with 6%	-4% (-7% to 0%)
Zaleplon 10 mg compared with zolpidem 10 mg[14, 15] (4 weeks)	476	74% compared with 73%	0% (-8% to 8%)	5% compared with 6%	-1% (-5% to 3%)
Zaleplon 20 mg compared with zolpidem 10 mg[14, 15] (4 weeks)	477	70% compared with 73%	-3% (-11% to 5%)	5% compared with 6%	-1% (-5 to 3%)
Zaleplon 5 mg compared with zolpidem 5 mg[12] (2 weeks)	331	56% compared with 63%	-7% (-18% to 4%)	Not reported	Not reported
Zaleplon 10 mg compared with zolpidem 5 mg (2 weeks)	276	59% compared with 63%	-4% (-16% to 7%)	Not reported	Not reported

The most common treatment-emergent adverse events were headache and dizziness. In a 2-week trial in older adults,[12] somnolence was significantly more common ($P<0.05$) with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%). In one of two 4-week trials in adults,[15] dizziness was significantly more frequent in 10 mg and 20 mg treatment groups than in the placebo group ($P<0.001$), occurring in 8% of patients in the placebo group, 3% in the zaleplon 5 mg group, 9% in the zaleplon 10 mg group, 14% in the zaleplon 20 mg group, and 14% in the zolpidem 10 mg group.

In a single-dose study conducted in 53 general practice patients,[17] 3 adverse events occurred in zolpidem 10 mg group (sluggish tongue, impaired concentration, leg complaints), and 4 in the zaleplon 10 mg group (2 headache, 1 abdominal fullness, 1 vertigo).

Zolpidem compared with zopiclone

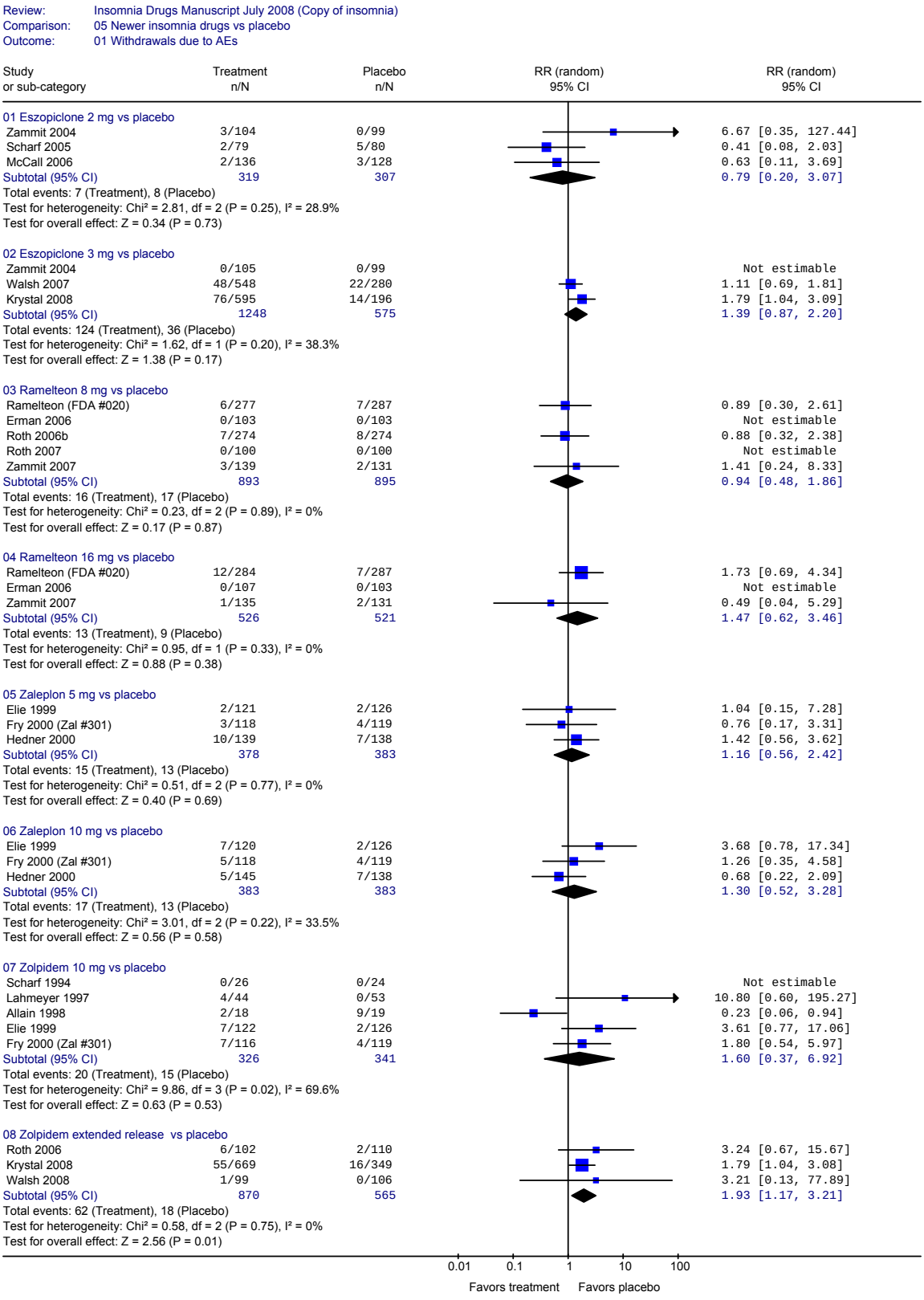
Zolpidem was compared with zopiclone in a study designed to measure withdrawal effects.[13] This was not a head-to-head trial, but 2 trials with the same design conducted simultaneously. The comparison in each trial was the effect of withdrawing treatment compared with continuing treatment. During the 2 weeks following withdrawal from treatment, the incidence of adverse events was higher in the withdrawal groups than the continued treatment groups, but was similar for zolpidem and zopiclone (38% and 41%, respectively). Most events were sleep-related.

In a two-week head-to-head study conducted in Japan, more patients in the zopiclone group than the zolpidem group had an adverse event "related," "probably related," or "possibly related" to treatment (31.3% compared with 45.3%; P=0.004).[16] There were no significant differences in the proportion of patients who withdrew due to any adverse event (8.5% zolpidem compared with 10.2% zopiclone) or due to a drug-related adverse event (6.6% compared with 8.9%). The frequency of specific adverse events was similar between groups, with the exception of bitter taste, which occurred in 3% of the zolpidem group and 31% of the zopiclone group.

Indirect evidence

Figure 6 shows withdrawals due to adverse events reported in placebo-controlled trials. There was no difference between active drugs and placebo with the exception of zolpidem extended-release. Using a pooled analysis of 3 trials of zolpidem extended-release, we found that risk of withdrawal due to adverse events was higher with zolpidem than placebo (relative risk 1.93; 95% CI 1.17 to 3.21).[89, 107, 121]

Figure 6. Withdrawals due to adverse events reported in placebo-controlled trials of newer drugs for insomnia



We conducted an adjusted indirect analysis of withdrawals due to adverse events and found no differences between any of the drugs (Table 10).

Table 10. Adjusted indirect analysis of placebo-controlled trials: Withdrawals due to adverse events

Comparison	Relative risk of withdrawal due to an adverse event (95% CI)
Eszopiclone compared with ramelteon	1.15 (0.55 to 2.41)
Eszopiclone compared with zaleplon	1.05 (0.49 to 2.25)
Eszopiclone compared with zolpidem	0.71 (0.30 to 1.64)
Eszopiclone compared with zolpidem extended-release	0.65 (0.33 to 1.25
Ramelteon compared with zaleplon	0.91 (0.38 to 2.20)
Ramelteon compared with zolpidem	0.62 (0.24 to 1.59)
Ramelteon compared with zolpidem extended-release	0.56 (0.25 to 1.24)
Zaleplon compared with zolpidem	0.68 (0.26 to 1.78)
Zaleplon compared with zolpidem extended release	0.62 (0.27 to 1.39)
Zolpidem compared with zolpidem extended release	0.83 (0.18, 3.89)

Newer insomnia drugs compared with benzodiazepines

No additional studies comparing newer insomnia drugs with benzodiazepines were identified for Update #2. Appendix D summarizes results of good- and fair-quality studies of newer drugs compared with benzodiazepines in the general population of adults and older adults with insomnia. We also included 6 active-control trials in subgroups of patients with comorbid conditions.

No trials compare eszopiclone, ramelteon, or zolpidem extended-release with benzodiazepines. Comparison of zaleplon with benzodiazepines is limited to 2 fair-quality trials comparing zaleplon with triazolam.[29, 62]

Zolpidem

Zolpidem was compared with flurazepam in 1 included study,[32] with temazepam in 2,[40, 60] and with triazolam in 4.[40, 44, 50, 53]

In the study comparing zolpidem 10 mg or 20 mg with flurazepam 30 mg, zolpidem was more effective for sleep outcomes.[32] Adverse events were similar for zolpidem 10 mg and flurazepam, but zolpidem 20 mg was associated with more adverse events.

The 2 studies comparing zolpidem with temazepam[40, 60] found the drugs similar in efficacy and rebound insomnia.

In 2 studies comparing zolpidem 10 mg with triazolam 0.25 mg,[50, 53] sleep outcomes were similar for the two drugs, but zolpidem caused less rebound insomnia. There was also less

rebound insomnia with zolpidem 5 mg than triazolam 0.25 mg[50] and with zolpidem 10 mg than triazolam 0.5 mg.[44]

A review by the National Institute for Clinical Excellence[124] presents an analysis of 2 studies comparing zolpidem with nitrazepam that were excluded from our review because they are not written in English.(Kazamatsuri, 1993 and Kudo, 1993) The 2 studies found no significant differences between drugs in sleep latency or duration. In one study more patients reported improved sleep quality with zolpidem than nitrazepam (66.7% compared with 37.5%, *P*=0.031) (Kudo, 1993). The other study found fewer awakenings with zolpidem (Kazamatsuri, 1993). Both studies found no differences in rates of adverse events (odds ratio 0.70; 95% CI 0.37 to 1.30) and no difference in daytime alertness or global impression of treatment.

Zaleplon

In 2 trials comparing zaleplon with triazolam, the drugs were similar in most sleep outcomes and short-term adverse events.[29, 62] In 1 study triazolam 0.25 mg was associated with more nausea than zaleplon 5 mg, a low dose.[62] The same study found no difference in nausea between triazolam 0.25 mg and zaleplon 10 mg, the manufacturer's suggested initial dose.[62]

Zopiclone

Zopiclone has been compared with four benzodiazepines (flurazepam, nitrazepam, temazepam, and triazolam). In 5 studies comparing zopiclone with flurazepam,[26, 31, 43, 45, 54] most comparisons found the two drugs to be similar in efficacy and adverse effects.

Zopiclone and triazolam were similar in efficacy and adverse events.[28, 37, 38] For rebound insomnia, results were mixed in 2 studies, with 1 finding that triazolam causes more rebound[33] and the other finding no difference.[36]

In studies comparing zopiclone with nitrazepam,[22, 39] efficacy and safety were similar, but nitrazepam was associated with more rebound insomnia.

The National Institute for Clinical Excellence review[124] presents an analysis of 4 studies comparing zopiclone with temazepam. No significant differences were found by the 2 studies that directly compared the drugs' sleep outcomes (sleep latency, sleep duration, number of awakenings, and sleep quality). Adverse events were similar in the study that directly compared them.

Newer insomnia drugs compared with trazodone

We identified 1 short-term, fair-quality study comparing zolpidem 10 mg with trazodone 50 mg.[61] Sleep latency was shorter with zolpidem after 1 week of treatment (48.2 compared with 57.7 minutes, *P*=0.037), but the difference was not significant at week 2 (48.1 compared with 54.5 minutes, *P* not reported). Sleep duration, number of awakenings, sleep quality, and patients' global impression of treatment were similar for the drugs at weeks 1 and 2. The number of total adverse events and withdrawals due to adverse events were similar for the drugs. However, more patients reported somnolence with trazodone (16% compared with 23%).

A trial of comparing trazodone with zaleplon in psychiatric inpatients was rated poor quality and does not provide additional comparative information about newer insomnia drugs compared with trazodone.[52]

Long-term safety

There is limited evidence about the long-term safety of newer drugs for insomnia and no direct evidence about their comparative long-term safety.

Eszopiclone

In a 6-month placebo-controlled trial of eszopiclone 3 mg,[90] the rate of serious adverse events was 2.9% for eszopiclone and 1.0% for placebo. The most common serious adverse events were gastrointestinal disorder (0.5% per group) and chest pain (0.5% per group). After discontinuation of the drug, similar overall rates of "new" events (defined as either not seen during the treatment period or worsening after the treatment period) were seen in placebo (10.7%) and eszopiclone (11.2%) groups. There were no reports of seizures, hallucinations, or perceptual-disturbance events. Anxiety was reported once in the eszopiclone group. Adverse events occurred in 81.1% of the eszopiclone group and 70.8% of the placebo group. The most common adverse event was unpleasant taste (26.1% eszopiclone compared with 5.6% placebo). Over 6 months, the rate of discontinuation due to adverse events was 12.8% in the eszopiclone group and 7.1% in the placebo group. The most common reasons for discontinuation were somnolence (2.2% eszopiclone compared with 1.5% placebo), depression (2.0% compared with 0.0%), unpleasant taste (1.7% compared with 0.5%), headache (0% compared with 2%), asthenia (1% compared with 1.5%), and insomnia (0.0% compared with 1.5%).

A 6-month, open-label extension study of this trial has also been conducted.[108] All patients who completed the double-blind phase were eligible to participate in the open-label extension. Of the 788 patients enrolled in the 6-month double-blind phase, 471 patients continued into the 6-month open-label extension study (59.8%), and 382 completed a full 12 months of treatment (48.5%). Improvements in sleep outcomes were sustained; rebound insomnia and withdrawal effects were not reported. During the extension study[108] 3.8% of patients discontinued due to adverse events. The most common treatment-related adverse events were unpleasant taste (6.8%), headache (4.7%), somnolence (3.8%), abnormal dreams (3.0%), and dizziness (2.5%).

A more recently published 6-month study of nightly treatment with eszopiclone 3 mg was conducted in 828 patients with chronic insomnia.[119] Rates of withdrawals due to adverse events were similar in the eszopiclone (9%) and placebo (8%) groups. By the end of the study, 37% of eszopiclone and 52% of placebo patients withdrew. There were more reports of somnolence, unpleasant taste, and myalgia in the eszopiclone group than the placebo group. Most events were mild or moderate. There was no evidence of withdrawal symptoms or rebound insomnia.

Zaleplon

A one-year open-label extension of a head-to-head trial[12] was conducted to assess the longer-term safety of zaleplon 5 mg in older patients.[128] In order to qualify for the extension phase, patients must have completed the trial and a 7-day placebo run-out without adverse effects. Thus this extension was limited to a sample of patients highly selected to be less likely to experience discontinuation effects. Sixty-four percent of patients who completed the 2-week trial enrolled in the extension study. Results of this open-label extension are reported in combination with those of an extension of a different, unpublished trial, also conducted in older people. The most frequent adverse events were headache (27%) and infection (13%). The most frequent adverse events resulting in discontinuation were pain (5%), somnolence or dizziness (4%), and gastrointestinal disturbance (2%). There was a significant increase in sleep latency, number of

awakenings, and reduced total time slept on the first night after discontinuation, but these did not approach original baseline levels.

Zolpidem

Two open-label studies in general practice patients in France assessed the safety of 6 months of treatment with zolpidem.[137, 142] One looked at zolpidem 10 mg or 20 mg[137] in 96 patients over age 40. All 96 patients were followed for 6 months; 49 of these patients continued treatment for an additional 6 months. Patients were evaluated every 30 days. About 70% of patients used the 10 mg dose. In the first 6 months, 7.3% of patients withdrew due to adverse events considered related to the drug, including a feeling of strangeness (1 patient), a feeling of drunkenness (1 patient), anterograde amnesia (2 patients), nausea (1 patient), a confusional episode (1 patient), malaise (1 patient), vertigo (4 patients), daytime drowsiness (2 patients), unpleasant awakening (1 patient), and diplopia (1 patient). Four of the 49 patients who continued treatment after 6 months withdrew (8%); two experienced nightmares, but these were not considered to be related to the study drug. No withdrawal or rebound phenomena were reported.

In the second study, 107 patients were enrolled, and 20 patients withdrew before 6 months (18.7%): two because of inefficacy, seven because of adverse events, two because of hospital admission for other reasons, and two because of resolution of sleeping disturbances.[142] Adverse events included malaise (5 events), vertigo (5 events), and anterograde amnesia (5 events). Patients experiencing vertigo and confusion were all over age 70. There was no evidence of tolerance over the 6-month course of the study, and no rebound insomnia.

Zolpidem extended-release

In a 6-month placebo-controlled trial of zolpidem extended-release 12.5 mg, administered for 3 to 7 nights per week, 8.5% of patients in the treatment group and 4.6% of patients in the placebo group withdrew due to adverse events.[89] The most common adverse events associated with zolpidem extended-release were headache (10.5%), anxiety (6.3%), somnolence (5.7%), dizziness (4.8%), fatigue (4.5%), disturbance in attention (4.3%), irritability (3.7%), nausea (3.4%), and sinusitis (3.3). Most events were mild or moderate in severity. There was no evidence of tolerance to treatment over the 6-month study period and no rebound insomnia on the first 3 nights after discontinuation of medication.

Zopiclone

We identified no prospective studies that assessed the long-term safety of zopiclone.

Abuse and dependence

Abuse and dependence have been associated with zolpidem and zopiclone.[149-166] A review of case reports and epidemiological data found most patients abusing or becoming dependent on zolpidem had a history of drug or alcohol abuse or other psychiatric conditions.[167] A study of French data on zolpidem collected by the Centers for Evaluation and Information on Pharmacodependence found that from 1993 to 2002, the period of the study, health professionals spontaneously reported an increasingly higher number of cases of abuse or dependence associated with zolpidem.[144] In 1993 <1% of abuse and dependence reports included zolpidem, and by 2002 almost 5.5% included zolpidem. An epidemiological survey of falsified or forged prescriptions shows that the popularity of zolpidem among forged prescriptions has increased: It was the 6th most common drug for which prescriptions were falsified in 1998 and had risen to #1

by 2004. The ratio of the number of forged zolpidem prescriptions to the number of legitimate zolpidem prescriptions indicates that zolpidem's falsification ratio is moderate, although higher than that of the leading benzodiazepine in France (specific data not reported). Finally, annual surveys of drug abusers show that the number of patients using zolpidem increased from <1% in 1998 to 4% in 2001. Nearly all patients abusing zolpidem were abusing more than one drug, 1 of 2 also using a benzodiazepine and 4 out of 10 using cannabis. Until 1998, 100% of patients obtained zolpidem through medical prescriptions; since 2001 nearly 15%–20% of users bought it through street deals.

A 2003 survey of 297 patients admitted to addiction treatment sites in the United Kingdom[136] found that while zopiclone was used by many more subjects than zolpidem (53.7% compared with 5.8%), the drugs were similar in their use to induce sleep (88% compared with 82%) or to get high (23% compared with 24%).

Eszopiclone, zaleplon, zolpidem extended-release, and ramelteon have been in use for a shorter period than zolpidem and zaleplon, so there is less information about their effects over the long term. The newer insomnia drugs, with the exception of ramelteon, are classified by the US Drug Enforcement Administration as controlled substances. Because of its different mechanism of action, ramelteon is not considered to have the potential for abuse and dependence of the other newer sedative hypnotics.

Case reports

We identified 64 case reports of adverse events: 1 with eszopiclone,[168] 3 with zaleplon,[169-171] 13 with zopiclone,[150, 152, 157, 160, 162, 166, 172-178] and 46 with zolpidem.[149, 151, 153-156, 158, 159, 161, 163-165, 179-213] Overall, the most commonly reported adverse event was hallucination, reported with eszopiclone (1 of 1 case), zaleplon (1 of 3 cases), and zolpidem (15 of 46 cases). The next most common adverse effect was dependence, with 7 cases reported for zolpidem and 6 for zopiclone. Somnambulism was also reported for zaleplon (1 of 3 cases) and zolpidem (6 of 46 cases). Finally, several cases of some form of amnesia were reported with zolpidem (4 of 46 cases).

Key Question 3. Are there subgroups of patients for which one newer drug for insomnia is more effective or associated with fewer adverse events?

Summary of the Evidence

- Older adults (age ≥65 years)
  - In a 2-week head-to-head trial comparing zolpidem with zaleplon in older adults, efficacy was similar to that in younger adults
  - Somnolence was more common ($P<0.05$) with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%), with no difference in overall adverse events or in withdrawals due to adverse effects
  - A case-control study in 6110 older women found that use of zolpidem was associated with an increased risk of hip fracture (adjusted odds ratio compared with nonuse 1.95; 95% CI 1.09-3.51). The risk was higher than with benzodiazepines (adjusted odds ratio compared with nonuse 1.46; 95% CI 1.21-1.76)
- Race and gender

  - We found no evidence that one newer insomnia drug is safer or more effective in any subgroup based on gender or race
- Pregnancy
  - In a prospective cohort study in 40 women with exposure to zopiclone in the first trimester of pregnancy, zopiclone use was associated with lower mean birth weight (3249 ± 676 grams compared with 3624 ± 536 grams; *P*=0.01) and gestational age (38.3 ± 2.7 weeks compared with 40.0 ± 1.6 weeks; *P*=0.002), but there were no differences in other pregnancy outcomes
  - A prescription event monitoring study in the United Kingdom found no congenital anomalies among 18 births in women who had taken either zolpidem or zopiclone during the first trimester of pregnancy
  - No evidence is available about use of other newer insomnia drugs during pregnancy
- Comorbid conditions
  - Active-control trials suggest that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol, patients with generalized anxiety disorder, and in patients with stroke living in a residential care facility
  - Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in patients with chronic obstructive pulmonary disease
  - Eszopiclone, ramelteon, and zolpidem, have been studied in short-term placebo-controlled trials of patients with obstructive sleep apnea or upper obstructive sleep apnea or upper airway resistance syndrome and symptoms of inadequate sleep. In mild to moderate sleep apnea, sleep laboratory outcomes were better with eszopiclone than placebo, but not with ramelteon compared with placebo. In severe sleep apnea, zolpidem was significantly better on 2 of 5 sleep laboratory outcomes.
  - In overweight patients with upper airway resistance syndrome, zopiclone was superior to placebo on 2 of 5 sleep laboratory measures

Detailed Assessment

Older adults

One head-to-head trial compared zaleplon with zolpidem in adults at least 65 years old.[12] In this 2-week trial,[12] somnolence was significantly more common (*P*<0.05) with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%). There was no difference in overall adverse events or in withdrawals due to adverse events. A one-year open-label extension of this trial was conducted to assess the longer-term safety of zaleplon in older patients.[128] Adverse events were mild. (See long-term-safety section for more details of this extension study).

In a subgroup analysis of our adjusted indirect meta-analysis, there was no difference between any of the newer insomnia drugs in sleep latency in older patients. (See Table 7.) Eszopiclone significantly increased sleep duration compared with ramelteon (mean difference 29.5 minutes; 95% CI 0.8-58.2) and zolpidem (mean difference 32.8 minutes; 95% CI 1.2-64.4) in older patients.

In a subgroup analysis of a study of ramelteon in older adults with severe sleep-onset insomnia (>60 minutes), there were significant reductions in subjective sleep latency with ramelteon 8 mg (-23.2 minutes) compared with placebo (-7.5 minutes; *P*=0.002) at week 1.[94] Improvement over placebo was also evident at weeks 3 and 5.

A case-control study (N=6110) of the relationship between use of zolpidem or other medications and occurrence of hip fracture in older women found an increased risk of fracture in patients using zolpidem (adjusted odds ratio 1.95; 95% CI 1.09-3.51).[145] This risk was higher than the risk with benzodiazepines (adjusted odds ratio 1.46; 95% CI 1.21-1.76). The study did not include other newer insomnia drugs, and so it provides no information for comparing the risk associated with zolpidem with the risk associated with other newer drugs for insomnia.

An observational study used data from a representative survey of Medicare beneficiaries to determine if the increased risk of hip fracture observed with sedative hypnotic use might be due to confounding factors that are not available from claims data.[143] Potential confounders were body mass index, current smoking status, activities-of-daily-living score, cognitive impairment, and Rosow-Breslau physical impairment scale. The authors found that the activities-of-daily-living score was the strongest confounder, causing an overestimation of 10% in comparisons of zolpidem users with benzodiazepine users. They conclude, however, that the magnitude of the effect of unmeasured confounders is unlikely to explain completely the greater incidence of hip fracture observed in older users of sedative hypnotic.

A good-quality systematic review and meta-analysis compared the risks and benefits of a variety of pharmacological treatments for insomnia in people at least 60 years old.[126] The review included studies of newer sedative hypnotics, benzodiazepines, and over-the-counter medications such as antihistamines. Only subjective sleep measures were included. Results were combined for all sleep agents for most outcomes, so this review cannot be used to make conclusions about the comparative efficacy and safety between newer sedative hypnotics or between newer sedative hypnotics and other sleep agents. Studies comparing zaleplon, zopiclone, and zolpidem (combined) with benzodiazepines found no significant difference in cognitive adverse events (odds ratio 1.12; 95% CI 0.16 to 7.76) or psychomotor-type adverse events (odds ratio 1.48; 95% CI 0.75 to 2.93).[126] For all sedative hypnotics (newer and older) compared with placebo, the number needed to harm for all adverse events was 6 (95% CI 4.7 to 7.1), and the number needed to treat for improved sleep quality was 13 (95% CI 6.7 to 62.9). On the basis of these results, the authors concluded that in older people the benefit of sleep agents may not outweigh their risks.

Pregnancy

A prospective cohort study in Canada evaluated pregnancy outcomes after first-trimester exposure to zopiclone in 40 women.[133] The sample consisted of women who had initiated contact with a program that provides counseling for pregnant women, thus it is not representative of the total population of women who were exposed to zopiclone during pregnancy.

Newborns in the zopiclone group had a significantly lower mean birth weight than newborns never exposed to the drug (3249 ± 676 grams compared with 3624 ± 536 grams; P=0.01). They also had a lower gestational age (38.3 ± 2.7 weeks compared with 40.0 ± 1.6 weeks; P=0.002). Once birth weight was adjusted for gestational age, the differences were no longer significant. There was no difference in outcome of pregnancy, delivery method, assisted deliveries, fetal distress, presence of meconium at birth, preterm deliveries, or neonatal intensive care admissions between zopiclone and control groups.

A 1998 report of prescription-event monitoring studies of newly marketed drugs, conducted in general practices in the UK, includes information on pregnancy outcome in 23 women exposed to zolpidem and 18 exposed to zopiclone during pregnancy.[146] In women who had taken zolpidem, there were 2 spontaneous and 6 legal abortions. In women who had taken

zopiclone, there were 3 spontaneous and 3 legal abortions, and in one the outcome is unknown. There were no congenital anomalies among the 18 live births in women exposed to either drug.

Comorbid conditions

Active-control trials show that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol,[23] patients with generalized anxiety disorder,[34] and in patients with stroke living in a residential care facility.[41]

Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in a trial in patients with chronic obstructive pulmonary disease.[55]

Zolpidem has been studied in placebo-controlled trials in patients with depression[68] and other psychiatric conditions,[113] in peri- and postmenopausal women,[74] and in patients with fibromyalgia.[95] Zaleplon has been studied in placebo-controlled trials in patients undergoing kidney dialysis.[109] Zopiclone has been compared with placebo in trials of patients with rheumatoid arthritis or[76] fibromyalgia[75, 82] and in patients who are shiftworkers.[97] Eszopiclone was more effective than placebo for insomnia in patients with rheumatoid arthritis,[112] in patients with depression who were also taking fluoxetine,[78] in patients with generalized anxiety disorder who were also taking escitalopram,[214] and in peri- and postmenopausal women.[114] In a single-dose study, ramelteon 16 mg improved polysomnographic sleep duration, total sleep time, and WASO in patients with mild to moderate chronic obstructive pulmonary disease; there was no difference between ramelteon and placebo on subjective sleep measures or on objective sleep latency.[215] While these studies provide evidence that these drugs are effective for some sleep outcomes in patients with particular comorbid conditions, they do not provide evidence about the comparative efficacy of newer insomnia drugs in these subgroups.

Three studies evaluated newer insomnia drugs in patients with obstructive sleep apnea and continuing symptoms of inadequate sleep: Eszopiclone[104] and ramelteon[86] were studied in patients with mild to moderate sleep apnea; zolpidem was studied in patients with severe sleep apnea;[69] and zopiclone was studied in patients with upper airway resistance syndrome.[92] These were all small (N = 8 to 26), short-term crossover studies conducted in sleep laboratories. We rated all of them fair quality. Patients enrolled were predominantly male and 45 to 55 years old. Three studies enrolled patients whose body mass index was in the obese or severely obese range (mean body mass indexes 30, 32, and 36),[69, 86, 104] and one study's patient population had a mean body mass index in the "overweight" category (26.3).[92] These studies were conducted with 1 to 7 nights of treatment.

In the studies of mild to moderate sleep apnea, sleep lab outcomes were better with eszopiclone than placebo, but ramelteon was no better than placebo. Latency to persistent sleep time and number of awakenings were similar for eszopiclone and placebo nights, but WASO, sleep efficiency, total sleep time, and wake time during sleep were statistically significantly better during the eszopiclone nights. Total sleep time was 15 minutes longer with eszopiclone.[104] No other measures were used. With ramelteon, sleep lab measures of latency to persistent sleep, number of awakenings, total sleep time, and WASO were similar during drug and placebo nights.[86] In addition, patient assessment of sleep (number of awakenings, total sleep time, sleep quality, sleep latency, level of alertness, awake time, and ability to concentrate) were also not different between the 2 sessions. However, the very small size of this study could have led to a type II error. For example, differences seen in total sleep time (14.6 minutes) and sleep latency (10.1 minutes) were similar to those seen in the eszopiclone study where statistical significance was found.

In 16 patients with severe obstructive sleep apnea, zolpidem was found to be significantly better on 2 of 5 sleep lab outcomes.[69] Sleep latency was 10.4 minutes shorter and sleep arousal was lower by 2.5 arousals per hour. Total sleep time was 17.2 minutes longer with zolpidem, but this difference did not reach statistical significance. Again, the small size of this study may have lead to type II error.

In upper airway resistance syndrome, a condition related to sleep apnea, patients who are habitual snorers but do not experience apnea have sleep disturbances as a response to airway obstruction.[92] Zopiclone was compared with placebo in 26 overweight patients in a 7-day crossover study. Zopiclone was superior to placebo in 2 of 5 measures taken in a sleep lab. In sleep efficiency and measures of daytime sleepiness, zopiclone was significantly better than placebo. Measures for which differences did not reach statistical significance were total sleep time (22 minutes longer with zopiclone) and sleep latency (23 minutes shorter with zopiclone).

SUMMARY

Table 11 summarizes the quality of the overall body of evidence for each key question.

Table 11. Summary of the evidence by key question

Key question	Quality of evidence	Conclusions
1. What is the comparative effectiveness of Newer Drugs for Insomnia in treating patients with insomnia?	Children: No evidence Adults: Good for the comparison of zaleplon to zolpidem (4 fair quality head-to-head trials) Fair for other comparisons	There was no significant difference between eszopiclone 2 mg or 3 mg and zolpidem 10 mg on polysomnography-measured sleep outcomes Zaleplon and zolpidem were similarly effective for subjective sleep latency in both elderly patients and those under age 65. Zolpidem and zopiclone were similarly effective in investigator and patient global assessments of improvement. Subjective sleep outcomes were improved from placebo to a similar extent in both treatment groups Indirect Evidence Adjusted indirect analysis of 22 placebo-controlled trials found few differences between drugs on subjective sleep outcomes Sleep latency was shorter with and sleep duration was longer with eszopiclone compared to ramelteon. In placebo-controlled trials of zolpidem extended-release, polysomnography- measured WASO was significantly shorter than placebo through hour 6. Results for subjective sleep outcomes were mixed, with zolpidem-XR showing superiority to placebo at some, but not all, assessment points.
2. What is the comparative tolerability and safety of Newer Drugs for Insomnia when used to treat patients with insomnia?	Fair	In one head-to-head trial, there was no difference between zolpidem and eszopiclone on subjective measures of next-day effects.

Key question	Quality of evidence	Conclusions
		In head-to-head trials, total withdrawals and withdrawals due to adverse events were similar for zaleplon and zolpidem. Zaleplon was less likely than zolpidem to cause rebound insomnia in adults under age 65. In one trial, the incidence of withdrawal effects was similar for zolpidem and zopiclone. There was no increased risk of withdrawal due to adverse events in placebo-controlled trials of eszopiclone, ramelteon, zaleplon, zolpidem, or zopiclone. In a pooled analysis of 3 placebo-controlled trials, there was an increased risk of withdrawal due to adverse events with zolpidem extended-release. Adjusted indirect analysis of placebo controlled trials found no differences between the newer sedative hypnotics in rates of withdrawals due to adverse events. There is no comparative evidence about long-term safety.
3. Are there subgroups of patients for which one Newer Drug for Insomnia is more effective or associated with fewer adverse events	Fair to poor	In a 2-week head-to-head trial of zolpidem compared with zaleplon in older adults, efficacy was similar to that in younger adults. Somnolence was more common with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%), but there was no difference in overall adverse events or in withdrawals due to adverse effects. In elderly patients, eszopiclone significantly increased sleep duration compared to zolpidem and ramelteon. Ramelteon 8 mg

Key question	Quality of evidence	Conclusions
		was more effective than placebo in older adults with severe sleep-onset insomnia (>60 minutes). There is no evidence that one newer insomnia drug is safer or more effective in any subgroup based on gender or race. In mild to moderate sleep apnea, sleep laboratory outcomes were better with eszopiclone compared to placebo, but not with ramelteon compared to placebo. Trials found mixed results on sleep laboratory outcomes for patients with severe sleep apnea (zolpidem) and upper airway resistance syndrome (zopiclone)

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Appendix A. Literature search strategies

Newer Drugs for Insomnia included interventions:

1. zaleplon (Sonata/Starnoc in Canada)
2. zolpidem (Ambien)**
3. zolpidem tartrate (Ambien CR)**
4. zopiclone (Imovane)*
5. eszopiclone (Lunesta)**
6. ramelteon (Rozerem)**

* available in Canada
** available in the US but not in Canada

Database: Medline 1966 -- November Week 3 2005
Embase 1985 -- 2005 (March)
Cochrane -- 4th Quarter 2005
PsycINFO --1985 to December Week 4 2005

Search Strategy:

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1 (zaleplon or zolpidem or zopiclone or eszopiclone).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 limit 1 to yr="2004 - 2006"
3 (sonata or ambien or Imovane or lunesta or estorra or stilnoct or zimovane or zileze).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 limit 3 to yr="2004 - 2006"
5 2 or 4
6 (zolpidem tartrate or ramelteon).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 (Starnoc or "Ambien CR" or Rozerem).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 5 or 6
10 from 8 keep 1-222

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center, based at Oregon Health & Science University, and subcontracting Evidence-based Practice Centers to produce drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document were adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001). It also incorporates material from the NHS Centre for Reviews and Dissemination's *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002.

All included studies and systematic reviews are assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality. Studies that meet all criteria are rated good quality. The remainder are rated fair quality. The "fair quality" category is broad, and studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others only might be valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

For Controlled Trials

Assessment of Internal Validity

1. Was assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, date of birth, or day of week
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially numbered, identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record number, date of birth, or day of week
        - Open random numbers lists

Serially numbered envelopes (Even sealed opaque envelopes can be subject to manipulation.)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed for one (that is, number of subjects assigned to each group, number of subjects who finished in each group, and the results for all subjects who finished)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Was there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the study population to the population to which the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

For Studies Reporting Complications, Adverse Effects, or Both

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded)?

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainer using validated ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using accepted statistical techniques?

7. Was the duration of follow-up reasonable with respect to timing of investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the study population to the population to which the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

For Systematic Reviews

1. Are there a clear review question and inclusion and exclusion criteria reported relating to the primary studies?

A good-quality review should focus on a well defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which primary studies are included or excluded. The criteria should relate to the 4 components of study design, indications (patient

populations), interventions (drugs), and outcomes of interest. In addition, the review should include details of the process of decision-making, that is how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, the search terms and the date and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale or one that they designed specifically for their review. Again, the process relating to the assessment should be explained (that is, how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the included studies are suitable to answer the question posed and that a judgement of the appropriateness of the authors' conclusions can be made. This criterion is usually fulfilled in papers that include a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, by sample size or by inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Excluded studies

290 trials were excluded with the exclusion code shown below (new trials from Update 2 are highlighted in gray-scale)

Codes:

1 = Foreign language
2 = Wrong outcome
3 = Wrong drug (including combination therapy)
4 = Wrong population
5 = Wrong publication type (letter, editorial, nonsystematic review, etc.)
6 = Wrong design (including dose-ranging study, pharmacokinetics, single-dose study, drug interaction)
7 = cannot find the study
8 = duplicated study
AO = abstract only
Poster= Poster only

Trials	Code
Abe K, Hikita T, Sakoda S. A hypnotic drug for sleep disturbances in patients with Parkinson's disease. *No to Shinkei - Brain & Nerve.* Apr 2005;57(4):301-305.	1
Allain H, Bentue-Ferrer D, Tarral A, Gandon JM. Effects on postural oscillation and memory functions of a single dose of zolpidem 5 mg, zopiclone 3.75 mg and lormetazepam 1 mg in elderly healthy subjects. A randomized, cross-over, double-blind study versus placebo. *European Journal of Clinical Pharmacology.* 2003;59(3):179-188.	4
Allain H, Le Breton S, Kleinermans D, Lavoisy J, Klausner J, Gandon JM. Assessment of patients preferences between two hypnotics, zolpidem (10 mg) vs. zaleplon (10 mg). *Sleep.* 2001;24(Abstr Suppl):A332.	5
Allain H, Patat A, Lieury A, et al. Comparative study of the effects of zopiclone (7.5 mg), zolpidem, flunitrazepam and a placebo on nocturnal cognitive performance in healthy subjects, in relation to pharmacokinetics. *European Psychiatry.* 1995;10(Suppl 3):129S-135S.	4
Allen D, Curran HV, Lader M. The effects of single doses of CL284,846, lorazepam, and placebo and psychomotor and memory function in normal male volunteers. *European Journal of Clinical Pharmacology.* 1993;45(4):313-320.	4
Amsterdam JD, Brunswick DJ, Hundert M. A single-site, double-blind, placebo-controlled, dose-ranging study of YKP10A - A putative, new antidepressant. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2002;26(7-8):1333-1338.	3
Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *Journal of Clinical Psychiatry.* 2003;64(2):208-214.	3
Ansseau M, Pitchot W, Hansenne M, Gonzalez Moreno A. Psychotic reactions to zolpidem. *Lancet.* 1992;339:809; 8796.	4

Trials	Code
Aranko K, Luurila H, Backman JT, Neuvonen PJ, Olkkola KT. The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *British Journal of Clinical Pharmacology.* 1994;38(4):363-367.	4
Arbus L, Lavoisy J, Belin J, Soubrane C. Efficacy and safety of zolpidem 10 mg administered pro re nata (P.R.N) during 4 weeks in patients with chronic insomnia. *Journal of the European College of Neuropsychopharmacology.* 1999;9(Suppl 5):S309.	6
Balkin TJ, O'Donnell VM, Wesensten N, McCann U, Belenky G. Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. *Psychopharmacology.* 1992;107(1):83-88.	4
Beaumont G, Holland RL. A multi-centre open study in general practice to evaluate the efficacy and acceptability of zopiclone 7.5 mg nocte in patients requiring the prescription of an hypnotic. *International Clinical Psychopharmacology.* 1990;5 Suppl 2:11-20.	6
Beaumont M, Batejat D, Coste O, et al. Effects of zolpidem and zaleplon on sleep, respiratory patterns and performance at a simulated altitude of 4,000 m. *Neuropsychobiology.* 2004;49(3):154-162.	6
Beaumont M, Goldenberg F, Lejeune D, Marotte H, Harf A, Lofaso F. Effect of zolpidem on sleep and ventilatory patterns at simulated altitude of 4,000 meters. *American Journal of Respiratory & Critical Care Medicine.* 1996;153(6 Pt 1):1864-1869.	4
Beaupre A, Soucy R, Phillips R, Bourgouin J. Respiratory center output following zopiclone or diazepam administration in patients with pulmonary disease. *Respiration.* 1988;54(4):235-240.	2
Bech P, Tanghoj P, Cialdella P, Andersen HF, Pedersen AG. Escitalopram dose-response revisited: an alternative psychometric approach to evaluate clinical effects of escitalopram compared to citalopram and placebo in patients with major depression. *International Journal of Neuropsychopharmacology.* Sep 2004;7(3):283-290.	3
Bechelli LP, Navas F, Pierangelo SA. Comparison of the reinforcing properties of zopiclone and triazolam in former alcoholics. *International Pharmacopsychiatry.* 1982;17 Suppl 2:235-241.	4
Beer B, Ieni JR, Wu W-H, et al. A placebo-controlled evaluation of single, escalating doses of CL 284,846, a non-benzodiazepine hypnotic. *Journal of Clinical Pharmacology.* 1994;34(4):335-344.	4
Benoit O, Bouard G, Payan C, Borderies P, Prado J. Effect of a single dose (10 mg) of zolpidem on visual and spectral analysis of sleep in young poor sleepers. *Psychopharmacology.* 1994;116(3):297-303.	2
Bensimon G, Foret J, Warot D, Lacomblez L, Thiercelin JF, Simon P. Daytime wakefulness following a bedtime oral dose of zolpidem 20 mg, flunitrazepam 2 mg and placebo. *British Journal of Clinical Pharmacology.* 1990;30(3):463-469.	4
Bergener M, Kranzhoff EU, Schwalb B, Fischer W. Sleep disorders in the elderly - Results of a multicenter study with zopiclone. *Pharmacopsychiatry.* 1995;28(165).	6
Berlin I, Warot D, Hergueta T, Molinier P, Bagot C, Puech AJ. Comparison of the effects of zolpidem and triazolam on memory functions, psychomotor performances, and postural sway in healthy subjects. *Journal of Clinical Psychopharmacology.* 1993;13(2):100-106.	4
Berthelon C, Bocca ML, Denise P, Pottier A. Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation? *Journal of Psychopharmacology.* 2003;17(3):324-331.	2
Bertschy G, Ragama-Pardos E, Muscionico M, et al. Trazodone addition for insomnia in venlafaxine-treated, depressed inpatients: A semi-naturalistic study. *Pharmacological Research.* 2005;51(1):79-84.	3

Trials	Code
Besset A, Tafti M, Villemin E, Borderies P, Billiard M. Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers. *Drugs under Experimental and Clinical Research.* 1995;21(4):161-169.	6
Billiard M, Besset A, de Lustrac C, Brissaud L. Dose-response effects of zopiclone on night sleep and on nighttime and daytime functioning. *Sleep.* 1987;10(1):27-34.	4
Biondi F, Casadei GL. Results of a multicenter trial with the hypnotic zolpidem in 1152 insomniac patients. *Current Therapeutic Research - Clinical and Experimental.* 1994;55(3):262-274.	6
Blin O, Micallef-Rolle J, Legangneux E, Zobouyan I. Zolpidem modified-release 12.5 mg has no residual effects on psychomotor performance and cognitive function in health adult subjects. *Sleep.* 2005;28(Suppl):A246.	(Poster)
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Blois R, Gaillard JM, Attali P, Coquelin JP. Effect of zolpidem on sleep in healthy subjects: a placebo-controlled trial with polysomnographic recordings. *Clinical Therapeutics.* 1993;15(5):797-809.	4
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Appendix D. Summary of results of trials comparing newer insomnia drugs compared with benzodiazepines

(No new trials were identified for Update #2)

Comparison	KQ outcome[a]	Hypnotic	Finding	Benzodiazepine	(No. of Studies) Citations[b]
Zaleplon compared with triazolam					
	Effectiveness outcomes	Zaleplon 5, 10 mg	=,=	Triazolam 0.25 mg	(2)[1, 2]
	Effectiveness outcomes	Zaleplon 20 mg	≤	Triazolam 0.25 mg	(1)[2]
	Effectiveness outcomes	Zaleplon 40-60 mg	Mixed	Triazolam 0.25 mg	(1)[2]
	Safety outcomes	Zaleplon 5, 10 mg	=	Triazolam 0.25 mg	(1)[1]
	Nausea	Zaleplon 5 mg	>	Triazolam 0.25 mg	(1)[1]
Zolpidem compared with flurazepam					
	Effectiveness outcomes	Zolpidem 10, 20 mg	>	Flurazepam 30 mg	(1)[3]
	Safety outcomes	Zolpidem 10 mg	=	Flurazepam 30 mg	(1)[3]
	Safety outcomes	Zolpidem 20 mg	<	Flurazepam 30 mg	(1)[3]
Zolpidem compared with temazepam					
	Effectiveness outcomes	Zolpidem 5 mg	=	Temazepam 15 mg	(1)[4]
	Effectiveness outcomes	Zolpidem 10 mg	=	Temazepam 20 mg	(1)[5]
	Less rebound	Zolpidem 10 mg	=	Temazepam 20 mg	(1)[5]
Zolpidem compared with trazodone					
	Effectiveness outcomes	Zolpidem 10 mg	=	Trazodone 50 mg	(1)[6]
Zolpidem compared with triazolam					
	Effectiveness outcomes	Zolpidem 5 mg	>	Triazolam 0.125 mg	(1)[4]
	Effectiveness outcomes	Zolpidem 10 mg	=,=	Triazolam 0.25 mg	(2)[7, 8]
	Effectiveness outcomes	Zolpidem 10 mg	>	Triazolam 0.5 mg	(1)[9]
	Less rebound	Zolpidem 5 mg	>	Triazolam 0.25 mg	(1)[7]
	Less rebound	Zolpidem 10 mg	≥,>	Triazolam 0.25 mg	(2)[7, 8]
	Less rebound	Zolpidem 10 mg	>	Triazolam 0.5 mg	(1)[9]
Zopiclone compared with flurazepam					
	Effectiveness outcomes	Zopiclone 3.75 mg	=	Flurazepam 30 mg	(1)[10]
	Effectiveness outcomes	Zopiclone 7.5 mg	=,≥,=	Flurazepam 30 mg	(3)[10-12]
	Effectiveness outcomes	Zopiclone 11.5 mg	=,≥	Flurazepam 30 mg	(2)[10, 11]
	Effectiveness outcomes	Zopiclone 15 mg	=	Flurazepam 30 mg	(1)[10]
	Safety outcomes	Zopiclone 7.5 mg	=,=	Flurazepam 30 mg	(1)[13, 14]

Comparison	KQ outcome[a]	Hypnotic	Finding	Benzodiazepine	(No. of Studies) Citations[b]
	Less rebound	Zopiclone 7.5 mg	≤	Flurazepam 30 mg	(1)[12]
Zopiclone compared with nitrazepam					
	Effectiveness outcomes	Zopiclone 7.5 mg	=,=	Nitrazepam 5 mg	(2)[15, 16]
	Daytime alertness	Zopiclone 7.5 mg	>,≥	Nitrazepam 5 mg	(2)[15, 16]
	Safety outcomes	Zopiclone 7.5 mg	=	Nitrazepam 5 mg	(1)[15]
Zopiclone compared with temazepam					
	Effectiveness outcomes	Zopiclone 7.5 mg	=,=,=	Temazepam 20, 30 mg	(3)[17-19]
	Safety outcomes	Zopiclone 7.5 mg	=	Temazepam 20 mg	(1)[17]
Zopiclone compared with triazolam					
	Effectiveness outcomes	Zopiclone 7.5 mg	=,=,=	Triazolam 0.25 mg	(3)[20-22]
	Safety outcomes	Zopiclone 7.5 mg	=	Triazolam 0.25 mg	(1)[20]
	Less rebound	Zopiclone 7.5 mg	>,≤	Triazolam 0.25 mg	(2)[21, 23]

≥, some outcomes showed a preference for the newer sedative hypnotic and others were equivalent;
≤, some outcomes showed a preference for the benzodiazepine and others were equivalent;
>, all outcomes (or the majority of outcomes) showed a preference for the newer sedative hypnotic;
<, all outcomes (or the majority of outcomes) showed a preference for the benzodiazepine;
=, all outcomes (or the majority of outcomes) showed no difference between the benzodiazepine and the newer sedative hypnotic;
Mixed, some outcomes showed a preference for the newer sedative hypnotic and others showed a preference for the benzodiazepine.

[a]*Efficacy outcomes* of individual studies were Sleep Duration, length of sleep, total sleep time; Sleep Quality, sleep efficiency, number of awakenings, Night awakenings, wake time after sleep onset, Daytime alertness, status of work, drowsiness, quality of morning awakening, morning state, feelings on awakenings, daytime well-being, Mental alertness on rising, morning sleepiness, morning alertness, Sleep latency, rapidity of sleep onset, sleep induction, sleep onset duration, Delay in falling sleep, latency to persistent sleep, *Safety outcomes* in individual studies were overall adverse events, side effects, and safety. *Rebound insomnia*: Rebound, withdrawal effects

[b]See Evidence Tables 4 through 9 for details of the population, interventions, and outcomes of these studies.

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