Drug Class Review
on
Newer Drugs for Insomnia

Final Report

July 2006

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

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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, but estimates vary depending on the methods and definitions used to define insomnia.[1] About three-fourths of those who have trouble sleeping say that the problem is ''occasional,'' averaging about six nights per month. The other 25% 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 include waking up feeling unrefreshed and being awake often during the night. The symptoms of difficulty falling asleep and waking up too early are less common, but still experienced at least a few nights a week by about one-fourth of adults with insomnia.[1] The risk of sleep disorders increases with age, affecting approximately 20% to 40% of older adults at least a few nights per month.[2]

Consequences of insomnia can include an 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, socioeconomic status and poorer social relationships, memory, mood and cognitive function. [4] Insomnia can occur in an acute, transient setting, and can also be a more chronic problem when associated with underlying psychiatric or medical illness.

Treatment of insomnia involves behavioral changes such as minimizing daily habits that interfere with sleep (e.g., drinking coffee or engaging in stressful activities in the evening),[4] and pharmacotherapy using sedating antidepressants (e.g., trazodone), sedating antihistamines, anticholinergics, benzodiazepines, or non-benzodiazepine hypnotics. The benzodiazepines and the newer sedative hypnotics zolpidem, zaleplon, zopiclone, and eszopiclone work through the *Gamma-aminobutyric acid* (GABA) receptors. Ramelteon, a hypnotic approved by the FDA in July 2005, is a selective melatonin receptor (MT_1 and MT_2) agonist.

The newer drugs for insomnia differ from each other in their pharmacokinetics (see Table 1), which could be expected to affect different aspects of insomnia. For example, drugs with a shorter half-life might be effective for sleep latency but less effective for sleep duration.[5]

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

Newer non-benzodiazepine drugs have been sought for multiple reasons, including but not limited to the risk of tolerance, dependence and abuse associated with the benzodiazepine class.

Scope and Key Questions

The purpose of this review is to help policymakers 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 (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the

populations, drugs, and outcome measures of interest to both 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 adults and children with insomnia?
2. What is the comparative tolerability and safety of newer drugs when used to treat adults and children with insomnia?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one newer drug for insomnia is more effective or associated with fewer adverse events?

Included populations

We included studies in adults or children with insomnia of any duration. We did not exclude studies that did not specify a definition of insomnia as part of enrollment criteria, but most studies specified a DSM-IV diagnosis of primary insomnia. The DSM-IV criteria for the diagnosis of primary insomnia are "a complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep that lasts for at least one month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance in sleep does not occur exclusively during the course of another sleep disorder or mental disorder and is not due to the direct physiological effects of a substance or a general medical condition."[3]

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)
		Pediatrics	Adults	Older adults	
eszopiclone	Lunesta	NA	2 mg	1 mg	6
ramelteon	Rozerem	NA	8 mg	8 mg	1-2.6
zaleplon	Sonata	NA	10 mg	5 mg	1
zolpidem	Ambien	NA	10 mg	5 mg	2.5
zolpidem extended release	Ambien CR	NA	12.5 mg	6.25 mg	2.8
zopiclone (Canada)	Imovane	NA	5 to 7.5 mg	3.75 mg	5

Included outcomes

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

Sleep latency is the time period taken by a person to fall asleep. *Sleep duration* is the time period a person remains asleep. The *number of awakenings* during the night is also frequently 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 wake-up.

These outcomes can be measured subjectively (e.g., using patient sleep diaries), or objectively, using *polysomnography* (PSG), 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 analogue scale (e.g., 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) upon treatment discontinuation. This can be measured using any of the outcomes above.

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 (4th Quarter 2005), Cochrane Database of Systematic Reviews, DARE, MEDLINE (1996 to November Week 3 2005), PsycINFO (1985 to December Week 4 2005) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). To identify additional studies, 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 9.0).

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 comparator, 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 comparators 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 utilize inadequately rigorous

methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing 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, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to followup, method of outcome ascertainment, and results for each outcome. Data were abstracted by one reviewer and checked by a second. We recorded intention-to-treat results if available and the trial did not report high overall loss to followup.

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 US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[6, 7] We rated the internal validity of each trial based 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 followup; and the use of intention-to-treat analysis. We rated the quality of observational studies of adverse events based on non-biased selection of patients, low loss to followup, non-biased 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 which 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 are only *probably* valid. A "poor quality" study is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of studies was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be 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). Meta-analysis was performed when possible (i.e., when populations and interventions were similar and when significant heterogeneity did not exist among trials), also using RevMan. Statistical heterogeneity was assessed using the chi-squared test; a level of 0.10 was considered significant. A fixed effects model was used.

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and

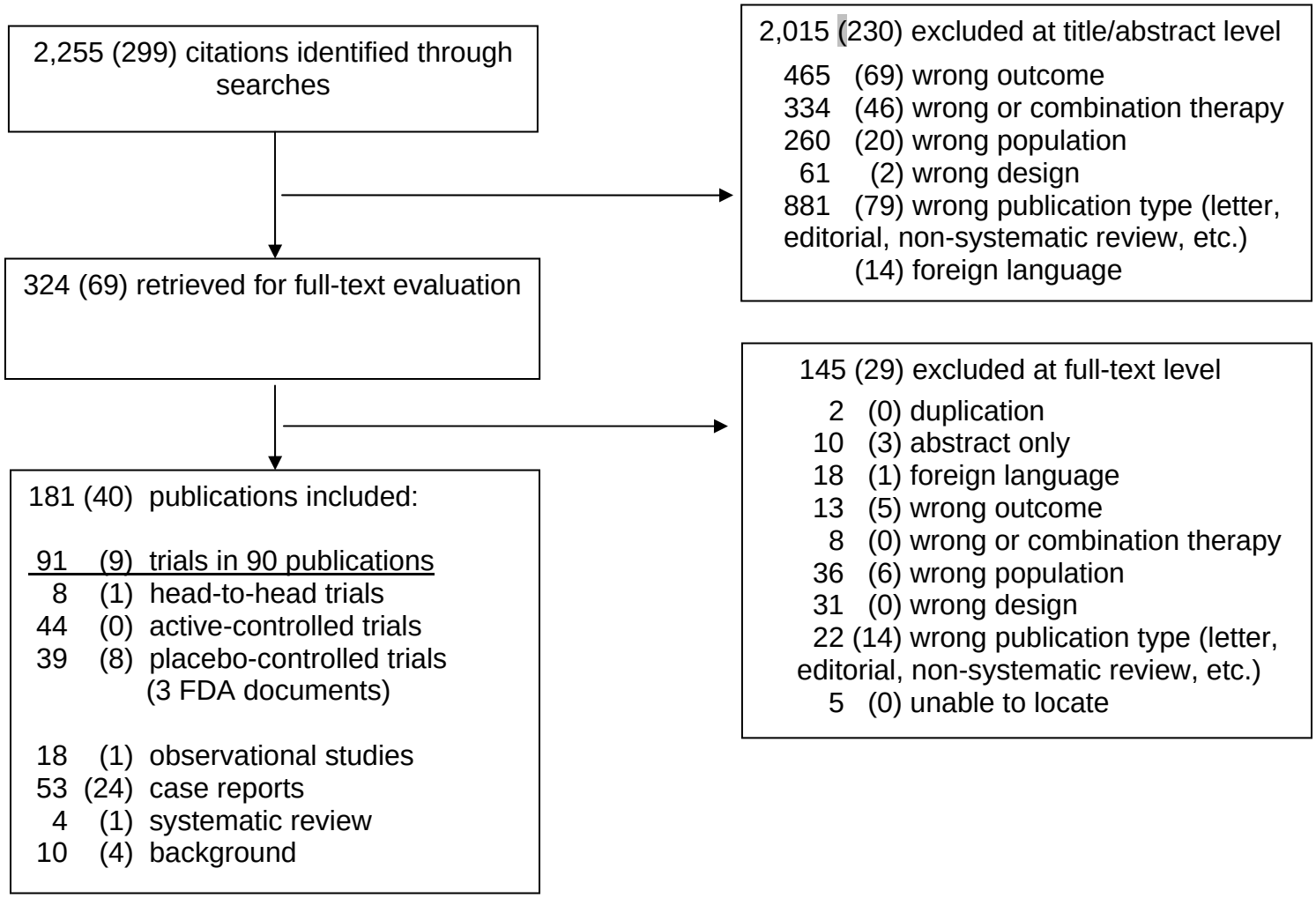
results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm. Poor-quality studies are not considered in the assessment of the overall body of evidence.

RESULTS

Overview of included studies

We identified 2,246 citations from literature searches, reviews of reference lists, and citations from dossiers submitted by three pharmaceutical manufacturers: Sanofi-Aventis (zolpidem and zolpidem extended release), Sepracor (eszopiclone), and Takeda (ramelteon). After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained the full text of 315 publications. After re-applying the criteria for inclusion, we included 175 publications. The flow of study inclusion and exclusion is detailed in Figure 1.

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



Numbers in parentheses indicate new studies added in Update 1

We excluded studies for the following reasons: study contained no original data, outcome measure not included, study design not included, drug not included or combined drug therapy where the effect of the hypnotics could not be distinguished, patient population not included, and language other than English. A list of excluded trials is reported in Appendix C.

We included eight head-to-head trials (Table 2).[8-15] One trial is published as a poster presentation only;[14] additional details were provided by the manufacturer and in the FDA review of eszopiclone.[16] Details of these trials are presented in Evidence Table 1 (efficacy), Evidence Table 2 (rebound insomnia), and Evidence Table 3 (adverse events).

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	**********

To supplement information from head-to-head trials, we attempted to make indirect comparisons of newer insomnia drugs from active- and placebo-controlled trials.

We included 44 trials in 45 publications of newer insomnia drugs versus benzodiazepines.[17-61] Most of the active-controlled studies included a placebo arm and reported efficacy and safety outcomes by comparing to placebo instead of comparing the two active drugs. Appendix D summarizes the efficacy, safety, and rebound insomnia results of these studies. Details of the populations, interventions, and outcomes are provided in Evidence Tables 4 through 12. Details of the quality assessment of all trials are provided in Evidence Table 16.

We identified two trials of a sedative hypnotic compared with trazodone; one (versus zaleplon)[48] was rated poor quality and the other (versus zolpidem)[57] was rated fair.

Thirty-four placebo-controlled trials in 35 publications were also included.[62-96]

Four good-quality systematic reviews (see Appendix B for quality criteria) of newer sedative hypnotics were included.[1, 97-99] The most relevant review to this report is a comparative review conducted by the National Institute for Clinical Excellence (NICE).[97] The others were not designed specifically 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.[99]

We included 18 observational studies (Evidence Table 17)[100-117] and 53 case reports (Evidence Table 18)[118-148149-170] of adverse events associated with newer drugs for insomnia.

Key Questions 1 and 2. What is the comparative effectiveness, safety, and tolerability of newer drugs in treating adults and children with insomnia?

Summary of the Evidence

Short-term Effectiveness and Safety

- We identified no effectiveness studies; trials assessed efficacy only.
- There are no randomized controlled trials of newer insomnia drugs in children.

Zolpidem vs zaleplon

- There is evidence from four head-to-head trials that zaleplon is more efficacious than zolpidem for sleep latency, but zolpidem is more efficacious than zaleplon for sleep duration and sleep quality.
- The drugs were similar for number of awakenings and daytime alertness.
- Zolpidem caused more rebound insomnia on the first night after discontinuation.
- Short-term adverse events and withdrawals due to adverse events were similar.

Zolpidem vs zopiclone

- One fair-quality head-to-head trial found that zolpidem and zopiclone were similar in efficacy on patient-rated sleep outcomes and investigator's global assessment of improvement. Zopiclone caused more rebound sleep latency insomnia than zolpidem.Overall adverse events and effects of withdrawal were similar in another study designed to measure withdrawal effects.There is limited indirect evidence that zopiclone was more effective for sleep latency at one week.

Zolpidem vs eszopiclone

- In one head-to-head trial, zolpidem and eszopiclone had similar objective sleep latency and Wake Time After Sleep Onset as measured by polysomnography after two nights of treatment.
- 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.
- Indirect comparisons based on placebo-controlled trials provide evidence that the drugs were similar for sleep latency and number of awakenings, but eszopiclone was more effective for increasing sleep duration. Comparisons were limited due to differences in populations across placebo-controlled studies.

Zolpidem extended release vs other newer drugs for insomnia

- There are no trials of zolpidem extended release compared to other newer insomnia drugs, benzodiazepines, or trazodone.
- No placebo-controlled trial has been fully published.
- Two placebo-controlled trials of 3 weeks' duration, one in adults and one in older adults, are available as poster presentations. An FDA review is not yet available.
    - According to data in these posters, zolpidem extended release was more effective than placebo on objective and subjective sleep outcomes, and caused rebound insomnia on the first night after discontinuation.

- It is not possible to make indirect comparisons from these trials because of limitations in reporting of the data.

Eszopiclone vs zaleplon

- There are no head-to-head trials.
- Limited indirect comparisons suggest the drugs are similar for sleep latency at one week. Indirect comparisons for other sleep outcomes are not possible.

Zaleplon vs zopiclone

- There are no head-to-head trials
- Limited indirect comparisons suggest the drugs are similar for sleep latency at one week. Indirect comparisons for other sleep outcomes are not possible.

Ramelteon vs newer sedative hypnotics

- There are no trials of ramelteon compared to newer sedative hypnotics, benzodiazepines, or trazodone in adults or children with insomnia.
- One placebo-controlled crossover trial of 2 nights of treatment in adults has been fully published. Its similar design, outcome measure, and population to a trial of zolpidem vs eszopiclone vs placebo allows an indirect comparison of objective sleep latency.
  - Objective sleep latency was 4 to 8 minutes longer with ramelteon compared with zolpidem and eszopiclone.
  - Confidence intervals for the differences from placebo for the 3 drugs overlapped, however.
  - There was no difference between ramelteon 8 mg and placebo on any subjective sleep measure. Sleep latency at the 16 mg dose was shorter than placebo (-13.1 minutes; 95% CI –24.3, –1.9).
- A five-week, placebo-controlled study in older adults found ramelteon 4 mg and 8 mg improved subjective sleep latency and total sleep time at some time points. There was no difference from placebo on other subjective sleep outcomes, including number of awakenings, ease of falling back to sleep after awakening, and sleep quality. There was no rebound insomnia on days 1 through 7 after discontinuation of ramelteon.
- Abstracts of additional placebo-controlled trials of ramelteon do not provide sufficient information to assess internal validity and are not included.

Long-term efficacy and safety

- Evidence about long-term safety is limited; there is no comparative evidence.
- Two placebo-controlled trials provide evidence that eszopiclone 3 mg is efficacious for up to 6 months. One of these is currently available only as a poster presentation.
  - Withdrawal symptoms were not observed after discontinuation.
  - There was no evidence of rebound insomnia in one trial; rebound insomnia was not assessed in the other.
  - These trials do not add any information about the *comparative* long-term efficacy and safety of eszopiclone versus other newer drugs for insomnia.
- In a 6-month open-label extension of one 6-month placebo-controlled trial of eszopiclone 3 mg, improvements in sleep outcomes were sustained; 3.8% of patients discontinued due to adverse events. Withdrawal effects and rebound insomnia were not assessed.

- A one-year open-label extension study of zaleplon 5 mg in older adults found most adverse events were mild. Sleep outcomes worsened after discontinuation, indicating rebound insomnia, but did not approach baseline levels. 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 disturbances (2%).
- There are case reports of dependence with zolpidem and zopiclone.

Newer insomnia drugs vs benzodiazepines

- There are no studies of eszopiclone or ramelteon versus benzodiazepines
- Most comparisons found the newer sedative hypnotics to be similar to benzodiazepines in efficacy and short-term adverse events
- Some studies found less rebound insomnia with newer sedative hypnotics.

Newer insomnia drugs vs trazodone

- We identified one fair-quality, short-term trial of zolpidem versus trazodone.
- Sleep latency was shorter with zolpidem after 1 week of treatment, but the difference was not significant at week 2.
- Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2.
- More patients reported daytime somnolence with trazodone. Withdrawals due to adverse events and overall adverse events were similar between the drugs.
-

Detailed Assessment

Zolpidem vs Zaleplon

Direct comparisons

Four fair-quality head-to-head studies compared zolpidem to zaleplon and placebo.[8, 10, 11, 13] Two of these were conducted in adults under age 65 and had identical designs.[10, 11] Another was conducted in older adults.[8] The fourth head-to-head study[13] was a small, single-dose crossover trial that measured patient preference as a primary outcome. All were funded by the manufacturer of zaleplon. Comparisons between zaleplon and placebo were the primary comparisons; published reports do not provide a head-to-head analysis of the two active drugs. More complete reporting and head-to-head analyses would facilitate direct comparisons from these studies.

Sleep latency. Sleep latency (time to sleep onset) was the primary outcome in two studies in adults (Table 3).[10, 11] Both compared zaleplon at three fixed doses (5 mg, 10 mg, or 20 mg) to 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 versus zaleplon, but a head-to-head analysis is provided in the FDA statistical review of zaleplon[5] for one trial.[11]

At weeks 1 through 4,[11] 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 to zolpidem 10 mg. There was no zolpidem 20 mg arm in this trial. There was no difference in the comparison of recommended starting doses zaleplon 10 mg and zolpidem 10 mg. These results are not intention-to-treat.

For the second trial,[10] intention-to-treat results using the last observation carried forward method (LOCF) are presented in the FDA review of zaleplon.[5] Analyses were conducted versus placebo. Results in this study 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, latency at weeks 2 and 3 was significantly shorter than 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).

Table 3. Median sleep latency (time to sleep onset) in studies of zolpidem vs zaleplon (difference from placebo, minutes)

Study	Week 1	Week 2	Week 3	Week 4	Withdrawal day +1 (rebound)
Fry (not ITT)[5]	Zaleplon (p vs zolpidem) 5 mg: -12 (0.764) 10 mg: -17 (0.490) 20 mg: -22 (0.003) Zolpidem 10 mg: -12	Zaleplon (p vs zolpidem) 5 mg: -6 (0.959) 10 mg: -13 (0.183) 20 mg: -18 (<0.001) Zolpidem 10 mg: -3	Zaleplon (p vs zolpidem) 5 mg: -4 (0.323) 10 mg: -9 (0.110) 20 mg: -15 (<0.001) Zolpidem 10 mg: -0.7	Zaleplon (p vs zolpidem) 5 mg: -2 (0.124) 10 mg: -12 (0.988) 20 mg: -17 (<0.037) Zolpidem 10 mg: -13	Zaleplon (p vs zolpidem) 5 mg: 0 (0.012) 10 mg: -2 (0.008) 20 mg: -11 (<0.001) Zolpidem 10 mg: +20
Elie (LOCF analysis)[5]	Zaleplon (p vs placebo) 5 mg: -8 (0.02) 10 mg: -14 (0.001) 20 mg: -17 (<0.001) Zolpidem (p vs placebo) 10 mg: -5 (0.07)	Zaleplon (p vs placebo) 5 mg: -12 (0.01) 10 mg: -16 (0.008) 20 mg: -17 (<0.001) Zolpidem (p vs placebo) 10 mg: -11 (0.05)	Zaleplon (p vs placebo) 5 mg: -9 (0.04) 10 mg: -11 (0.02) 20 mg: -13 (<0.001) Zolpidem (p vs placebo) 10 mg: -5 (0.04)	Zaleplon (p vs placebo) 5 mg: -6 (0.37) 10 mg: -9 (0.04) 20 mg: -10 (0.004) Zolpidem (p vs placebo) 10 mg: -3 (0.55)	Zaleplon (p vs placebo) 5 mg: +9 (0.37) 10 mg: +9 (0.14) 20 mg: +2 (0.99) Zolpidem (p vs placebo) 10 mg: +22 (0.003)
Ancoli-Israel 1999*[8]	Zaleplon (p vs zolpidem) 5 mg: +4** (NS) 10 mg: -17** (0.001) Zolpidem (p vs placebo) 5 mg: -7 **	Zaleplon (p vs zolpidem) 5 mg: -18** (NS) 10 mg: -26** (0.001) Zolpidem (p vs placebo) 5 mg: -16**	--	--	Zaleplon (p vs placebo) 5 mg: -14 (NS) 10 mg: +1 (NS) Zolpidem (p vs placebo) 5 mg: +16 (<0.01)

*patients > age 65
**estimated from graphL
OCF=Last observation carried forward analysis; ITT=intention-to-treat analysis

Table 3 also shows results of a 2-week head-to-head trial of zaleplon 5 mg or 10 mg versus zolpidem 5 mg conducted in 549 older adults (65 years or older).[8] Results were similar to those of the trials in younger patients: there was no difference in sleep latency for zaleplon 5 mg versus 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 versus zolpidem.[8, 10, 11] Table 4 shows outcomes for weeks 1 through 4 and rebound on the first day after the end of treatment. 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.

Table 4. Median sleep duration in trials of zaleplon versus zolpidem (difference from placebo, minutes)

Study	Week 1	Week 2	Week 3	Week 4	Withdrawal day +1 (rebound)
Fry (not ITT)[5]	Zaleplon (p vs placebo) **5 mg: +13** (NS) 10 mg: +14 (NS) 20 mg: +22 **(<0.05)** Zolpidem (p vs placebo) 10 mg: +30 **(<0.001)**	Zaleplon (p vs placebo) **5 mg: +6** (NS) 10 mg: +4 (NS) 20 mg: +9 **(NS)** Zolpidem (p vs placebo) **10 mg: +24** **(<0.05)**	Zaleplon (p vs placebo) **5 mg: -5** (NS) 10 mg: +11 (NS) 20 mg: +20 (<0.05) Zolpidem (p vs placebo) **10 mg: +26** **(<0.01)**	Zaleplon (p vs placebo) **5 mg: -4** (NS) 10 mg: +12 (NS) 20 mg: +13 **(NS)** Zolpidem (p vs placebo) **10 mg: +29** **(<0.05)**	Zaleplon (p vs placebo) **5 mg: 0** **(NS)** 10 mg: 0 (NS) 20 mg: 0 **(NS)** Zolpidem (p vs placebo) **10 mg: -30** **(P<0.05)**
Elie (LOCF analysis)[5]	Zaleplon (p vs placebo) **5 mg: 0** **(0.92)** **10 mg: +19** **(0.11)** 20 mg: +19 (0.04) Zolpidem (p vs placebo) 10 mg: +28 **(<0.001)**	Zaleplon (p vs placebo) **5 mg: 0** **(0.28)** **10 mg: +8** **(0.24)** 20 mg: +13 **(0.01)** Zolpidem (p vs placebo) **10 mg: +29** (<0.001)	Zaleplon (p vs placebo) **5 mg: +10** **(0.26)** **10 mg: +10** **(0.43)** 20 mg: +9 (0.07) Zolpidem (p vs placebo) **10 mg: +21** (<0.001)	Zaleplon (p vs placebo) **5 mg: +13** **(0.47)** **10 mg:+15** **(0.10)** 20 mg: +23 **(0.02)** Zolpidem (p vs placebo) **10 mg: +39** (<0.001)	Zaleplon (p vs placebo) **5 mg: 0** **(NS)** **10 mg: 0** **(NS)** 20 mg: 0 (NS) Zolpidem (p vs placebo) **10 mg: 0** (<0.05 using F test)
Ancoli-Israel 1999*[10 1]	Zaleplon (p vs placebo) **5 mg: NR** **(NS)** **10 mg: +27** (0.05) Zolpidem (p vs placebo) **5 mg: +42** **(<0.001)**	Zaleplon (p vs placebo) **5 mg: NR** **(NS)** **10 mg: NR** **(NS)** Zolpidem (p vs placebo) **5 mg: +34** (<0.01)	--	--	Zaleplon (p vs placebo) **5 mg: +12.5** **(NS)** **10 mg: -2.5** (<0.05) Zolpidem (p vs placebo) **5 mg: -17.5** (<0.001)

ITT= intention-to-treat analysis; LOCF=last observation carried forward analysis

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 (Table 5). In

one trial,[10] there was no difference from placebo for any dose of either zaleplon or zolpidem at any time period. The other trial in adults,[11] had mixed results. Zaleplon 5 mg and 10 mg was no different from placebo, zaleplon 20mg 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.[8]

Table 5. Median number of awakenings in studies of zaleplon vs zolpidem

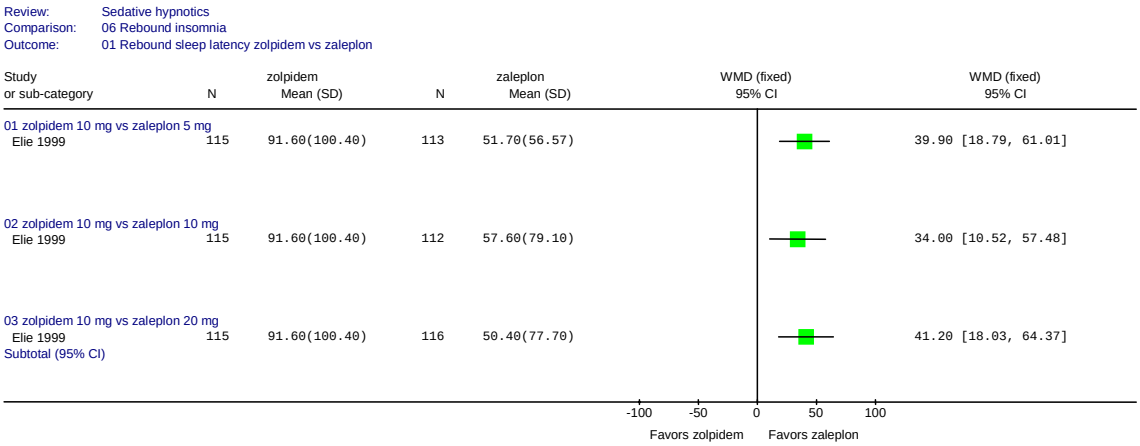
Study	Week 1	Week 2	Week 3	Week 4	Withdrawal day +1 (rebound)
Fry (not ITT)[11]	Zaleplon (p vs placebo) **placebo: 1.71** **5 mg: 1.93** (NS) 10 mg: 1.69 (NS) 20 mg: 1.75 (NS) Zolpidem (p vs placebo) 10 mg: 1.59 **(<0.01)**	Zaleplon (p vs placebo) **placebo: 2.00** **5 mg: +6** (NS) 10 mg: +4 (NS) 20 mg: +9 (<0.001) Zolpidem (p vs placebo) **10 mg: +24** **(<0.001)**	Zaleplon (p vs placebo) **placebo: 2.00** **5 mg: 1.67** (NS) 10 mg: 1.69 (NS) 20 mg: 1.50 (<0.001) Zolpidem (p vs placebo) **10 mg: 1.50** **(N<0.001)**	Zaleplon (p vs placebo) **placebo: 1.86** **5 mg: 1.71** (NS) 10 mg: 1.71 (NS) 20 mg: 1.43 (<0.05) Zolpidem (p vs placebo) **10 mg: 1.71** (NS)	Zaleplon (p vs placebo) **placebo: 2.00** **5 mg: 2.00** **(NS)** 10 mg: 2.00 (NS) 20 mg: 2.00 **(NS)** Zolpidem (p vs placebo) **10 mg: 2.00** **(<0.05 by F test)**
Elie (not ITT)[10]	Zaleplon (p vs placebo) placebo: 2 **5 mg: 2** **(NS)** **10 mg: 2** **(NS)** 20 mg: 2 (NS) Zolpidem (p vs placebo) 10 mg: 2 (NS) **Placebo: 2.0**	Zaleplon (p vs placebo) placebo: 2 **5 mg: 2** **(NS)** **10 mg: 2** **(NS)** 20 mg: 2 (NS) Zolpidem (p vs placebo) **10 mg: 2** **(NS)** **Placebo: 1.9**	Zaleplon (p vs placebo) placebo: 2 **5 mg: 2** **(NS)** **10 mg: 2** **(NS)** 20 mg: 1 (NS) Zolpidem (p vs placebo) **10 mg: 2** **(NS)**	Zaleplon (p vs placebo) placebo: 2 **5 mg: 2** **(NS)** **10 mg: 2** **(NS)** 20 mg: 1 (NS) Zolpidem (p vs placebo) **10 mg: 2** **(NS)**	Zaleplon (p vs placebo) placebo:1 **5 mg: 2** **(NS)** **10 mg: 2** **(NS)** 20 mg: 1 (NS) Zolpidem (p vs placebo) **10 mg: 2** (<0.01) **Placebo: 2**
Ancoli-Israel[8]	Zaleplon (p vs placebo) 5 mg: 1.8 (NS) 10 mg: 1.8 (NS) Zolpidem (p vs placebo) 5 mg: 1.7 **(p<0.01)**	Zaleplon (p vs placebo) 5 mg: 1.9 (NS) 10 mg: 1.7 (NS) Zolpidem **5 mg: 1.6** **(p<0.05)**	**--**	**--**	Zaleplon (p vs placebo) 5 mg: 2 (NS) 10 mg: 2 (NS) Zolpidem **5 mg: 2** **(NS)**

Sleep Quality. In a pooled analysis of three trials of zaleplon versus zolpidem[8, 10, 11], the NICE review[97] found that patients on zaleplon were less likely to experience improvement in sleep quality at the end of treatment than patients taking zolpidem (OR 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 median sleep latency on the first night after discontinuation.[10, 11] Zolpidem 10 mg was associated with a 20- to 22-minute increase in sleep latency versus placebo on the first night of discontinuation. Rebound sleep latency was not seen with zaleplon at any dose. Figure 2 shows the mean difference between zolpidem and zaleplon for rebound sleep latency, measured on the first day after withdrawal after 4 weeks of treatment in one of these studies.[10] 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 for zolpidem 10 mg versus zaleplon 10 mg was 34 minutes (95% CI, 10.5 to 57.5 minutes).

Figure 2. Rebound sleep latency: head-to-head comparison of zolpidem vs zaleplon



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,[10, 11] 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.[8]

Other Outcomes. A small (N=53) single-dose crossover study of zolpidem 10 mg versus zaleplon 10 mg was designed to measure patient preference for a drug as a primary outcome.[13] 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% vs 32%; p=0.81).

Secondary outcomes were mean scores on the Leeds sleep evaluation questionnaire (LSEQ), and "day quality," a visual analogue 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 LSEQ (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 on the "day quality" measure was significantly different between drugs. Zolpidem patients reported better quality of sleep (mean score 68.8 vs 50.2, p<0.0001), but there were no differences on other factors.

Short-term adverse events. Table 6 shows the total withdrawals and withdrawals due to adverse events reported in short-term head-to-head trials of zaleplon versus zolpidem. Rates of overall adverse events and withdrawals due to adverse events were similar for both drugs and increased with longer duration of the trials.

The most common treatment-emergent adverse events were headache and dizziness. In a 2-week trial in older adults,[8] 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,[11] dizziness was significantly more frequent in 10 mg and 20 mg treatment groups than placebo (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 the single-dose study conducted in 53 general practice patients,[13] 3 adverse events occurred in the zolpidem 10 mg group (sluggish tongue, impaired concentration, leg complaints), and 4 in the zaleplon 10 mg group (cephalgia requiring analgesic treatment, headache, abdominal fullness, vertigo).

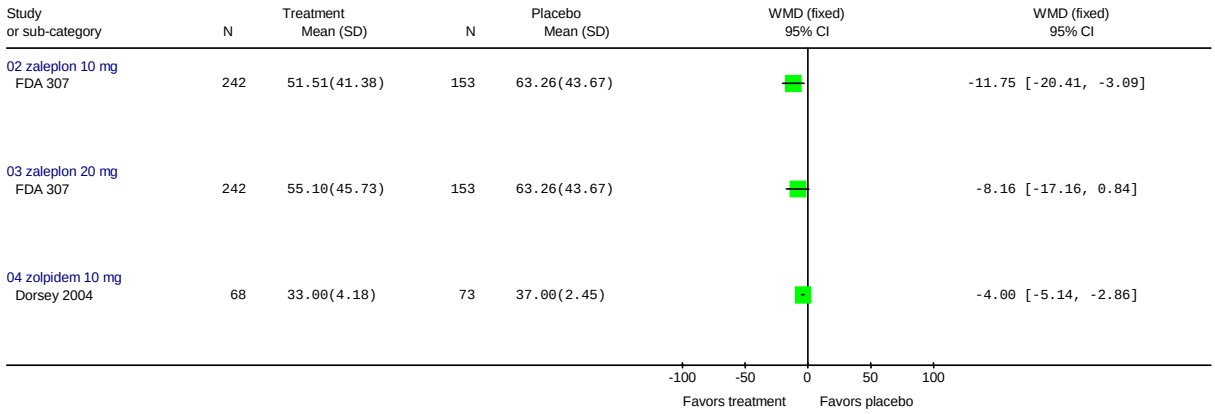
Table 6. Adverse events in head-to-head studies of zaleplon vs zolpidem

		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 vs zolpidem 10 mg[10, 11] (4 weeks)	476	67% vs 73%	-6% (-14% to 2%)	2% vs 6%	-4% (-7% to 0%)
Zaleplon 10 mg vs zolpidem 10 mg[10, 11] (4 weeks)	476	74% vs 73%	0% (-8% to 8%)	5% vs 6%	-1% (-5% to 3%)
Zaleplon 20 mg vs zolpidem 10 mg[10, 11] (4 weeks)	477	70% vs 73%	-3% (-11% to 5%)	5% vs 6%	-1% (-5 to 3%)
Zaleplon 5 mg vs zolpidem 5 mg[8] (2 weeks)	331	56% vs 63%	-7% (-18% to 4%)	Not reported	Not reported
Zaleplon 10 mg vs zolpidem 5 mg (2 weeks)	276	59% vs 63%	-4% (-16% to 7%)	Not reported	Not reported

Indirect comparisons

Figure 3 shows results of two placebo-controlled trials of zolpidem and zaleplon for the outcome of sleep latency at one week. At one week, only zaleplon 10 mg was significantly better than placebo for sleep latency (mean difference, -11.75 minutes; 95% CI –20.41 to –3.09 minutes). There was no difference between placebo and zolpidem 10 mg or zaleplon 20 mg. Indirect comparisons that can be made from these studies are limited. Placebo group sleep latency rates varied considerably in these studies (63 minutes for zaleplon vs 37 minutes for zolpidem), indicating that the populations may have had different baseline severity, which could account for differences in response rates.

Figure 3. Sleep latency at one week in placebo-controlled trials of zolpidem and zaleplon



Zolpidem vs Zopiclone

Direct comparisons

Two fair-quality studies compared zolpidem to zopiclone.[9, 12] One was designed to assess the effect of withdrawal in patients already taking the drugs for insomnia and did not report efficacy outcomes.[9]

A third head-to-head study measured next-day simulated driving performance as the primary outcome, and reported subjective sleep parameters as secondary outcomes.[15] This study was rated poor quality because no baseline demographic or clinical data are reported, 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.

A two-week, double-blind trial in 479 patients at multiple centers in Japan[12] is the only head-to-head trial of zolpidem versus zopiclone in which efficacy is the primary outcome. The funding source is not reported.

Global assessment of improvement. 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 vs 16.4% zopiclone) or "moderately improved" (49.3% zolpidem vs 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 are not reported.

Rebound insomnia. Rebound insomnia was defined as the percentage of patients with an aggravation of sleep onset latency by one grade or more after 2 weeks of treatment.[12] More patients who took zopiclone had rebound insomnia by this definition than those who took zolpidem (15.4% vs 4.5%, $p<0.005$).

Short-term adverse events. More patients in the zopiclone group than the zolpidem group had an adverse event "related", "probably related", or "possibly related" to treatment (31.3% vs 45.3%; $p=0.004$). There were no significant differences in the proportion of patients who withdrew due to any adverse event (8.5% zolpidem vs 10.2% zopiclone) or due to a drug-related

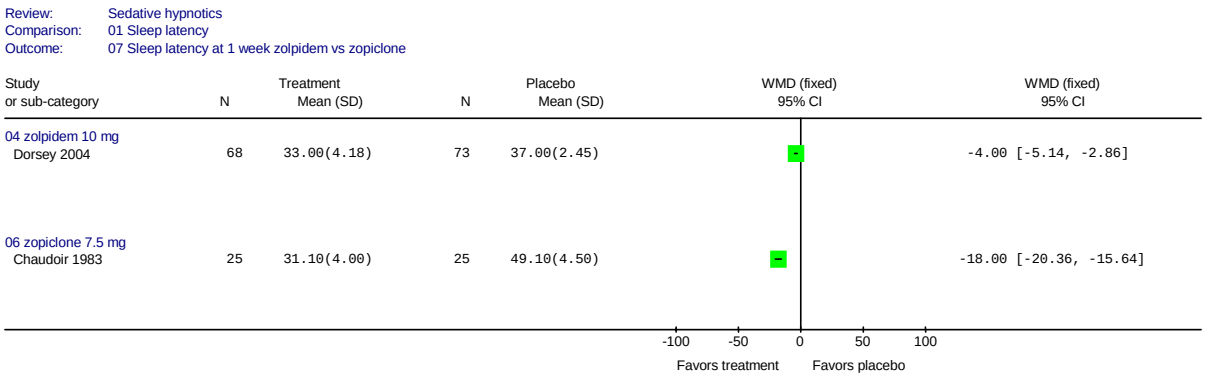
adverse event (6.6% vs 8.9%). The frequency of specific adverse events was similar between groups, with the exception of bitter taste, which occurred in 3% of patients in the zolpidem group, and 31% of those in the zopiclone group.

Effects of withdrawal. The study designed to assess the effect of withdrawing from zolpidem or zopiclone was not a head-to-head trial, but 2 trials with the same design conducted simultaneously.[9] The comparison in each trial was the effect of withdrawal of treatment versus continuing treatment. During the 2 weeks following withdrawal from treatment, the incidence of adverse events was higher in the withdrawal groups compared to continued treatment groups, but was similar for zolpidem and zopiclone (38% vs 41%, respectively). Most events were sleep-related.

Indirect comparisons

In placebo-controlled trials, sleep latency was significantly shorter with zopiclone 7.5 mg than with placebo (mean difference –18.00 minutes; 95% CI –20.36 to –15.64 minutes), but there was no difference between zolpidem 10 mg and placebo (-4.00 minutes; -5.14 to –2.86 minutes) (Figure 4). No head-to-head trial reported data on sleep latency, so it is not possible to compare these results to direct evidence.

Figure 4. Sleep latency at one week in placebo-controlled trials of zolpidem vs zopiclone



Trials comparing zolpidem and zopiclone to benzodiazepines do not add additional comparative information regarding zolpidem versus zopiclone. Outcomes were reported differently, so it is not possible to make indirect comparisons.

Zolpidem vs Eszopiclone

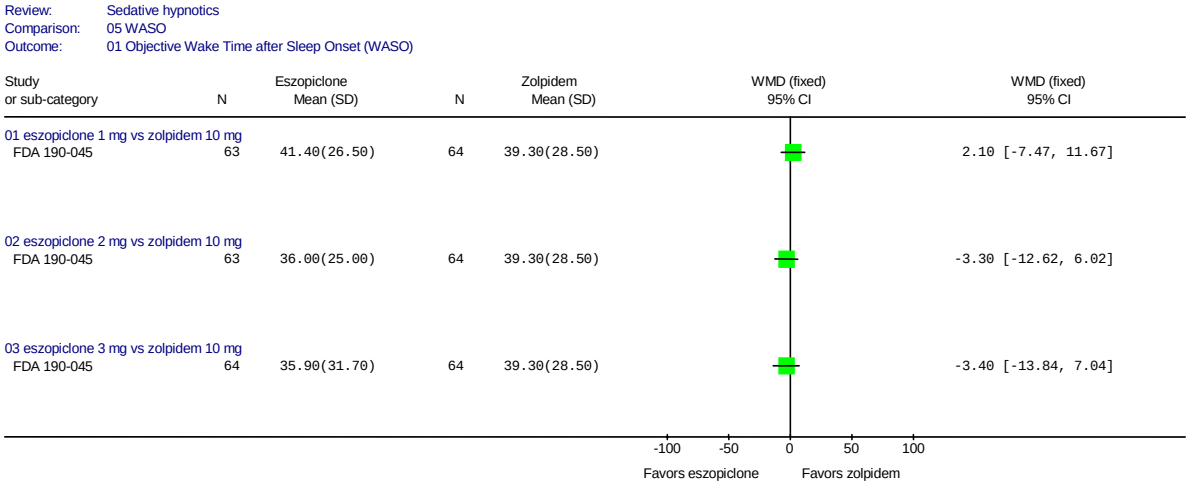
Direct comparisons

There is one head-to-head trial of eszopiclone versus zolpidem. This study has not yet been fully published. It has been reported in a poster presentation,[14] and additional information is provided in the FDA statistical review of eszopiclone.[16] 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, 3 mg) to placebo and zolpidem 10 mg in a crossover design over 2 nights of treatment. Subjective sleep outcomes are not available for this study.

Both drugs were more effective than placebo for PSG-measured sleep latency and total sleep time. Eszopiclone 2.5 mg and 3 mg were more effective than placebo for objective WASO, but there was no difference from placebo for eszopiclone at other doses or for zolpidem 10 mg.

Objective sleep latency was slightly shorter for zolpidem 10 mg compared to eszopiclone 1 mg (mean difference 8.6 minutes; 95% CI 1.68 to 15.52 minutes), but there was no difference between zolpidem 10 mg and eszopiclone 2 mg or 3 mg. There was no difference between zolpidem 10 mg and any dose of eszopiclone on objective WASO (figure 5).

Figure 5. Objective WASO: head-to-head comparison of eszopiclone vs zolpidem



Next-day effects

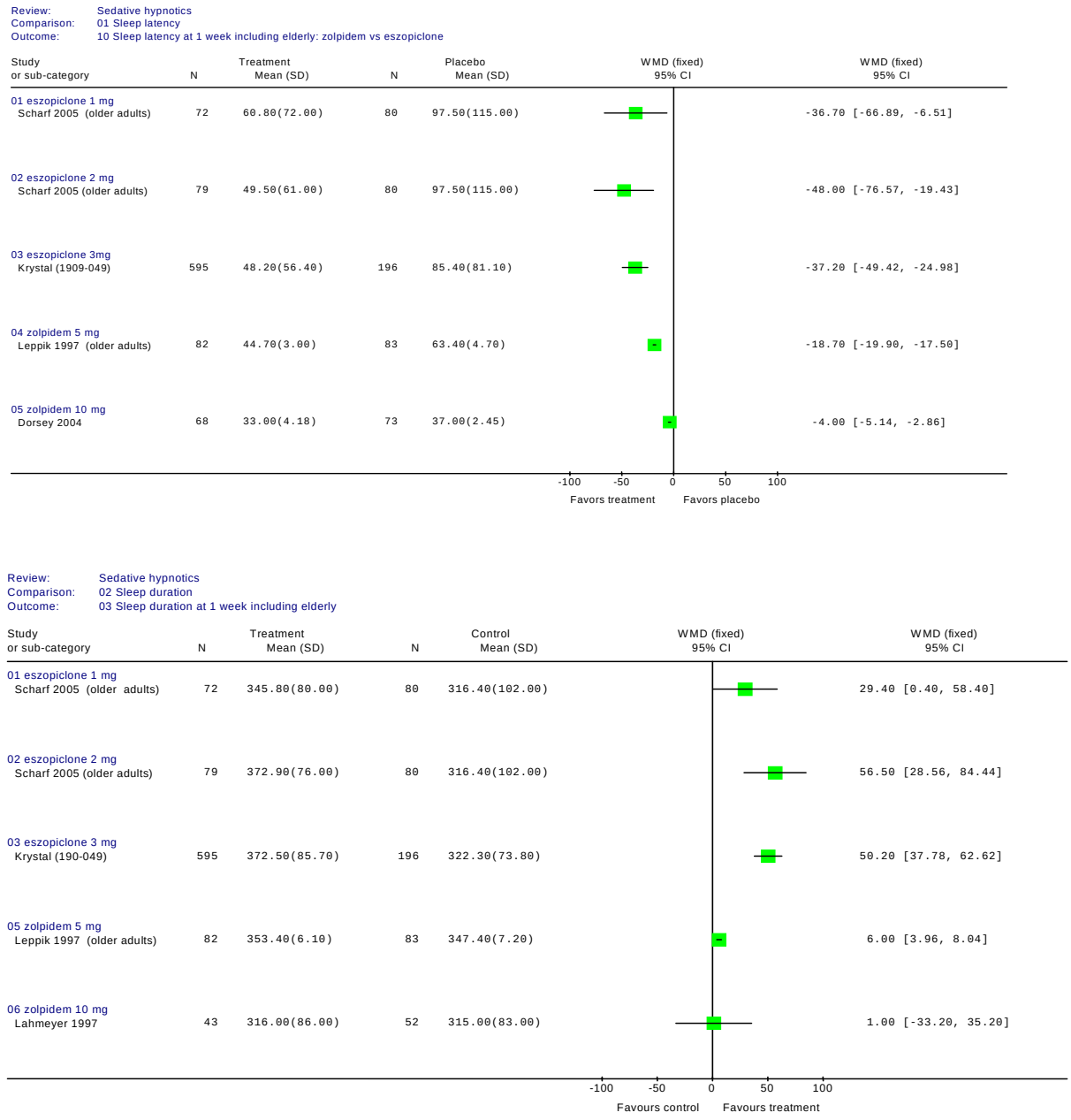
There was no difference between zolpidem and eszopiclone on subjective measures of next-day effects, including morning sleepiness, daytime alertness, and daytime ability to function.[16]

Indirect comparisons

Figure 6 shows outcomes at one week in placebo-controlled trials of eszopiclone and zolpidem. The studies are not directly comparable because the doses varied and populations differed in age and baseline severity of insomnia. In two studies in older adults, both zolpidem 5 mg and eszopiclone (1 mg and 2 mg) were more effective than placebo in reducing subjective sleep latency. In two studies in adults, eszopiclone 3 mg, but not zolpidem 10 mg, was more

effective than placebo. These studies varied considerably in their placebo response rates (37 minutes in the zolpidem 10 mg study vs 85 minutes in the eszopiclone 3 mg study), so they cannot be used to draw conclusions about comparative efficacy. Results for sleep duration were similar. On number of awakenings, zolpidem 10 mg and eszopiclone 3 mg were more effective than placebo, but eszopiclone 1 mg and 2 mg (in older adults) were not.

Figure 6. Sleep outcomes at one week in placebo-controlled trials of zolpidem and eszopiclone



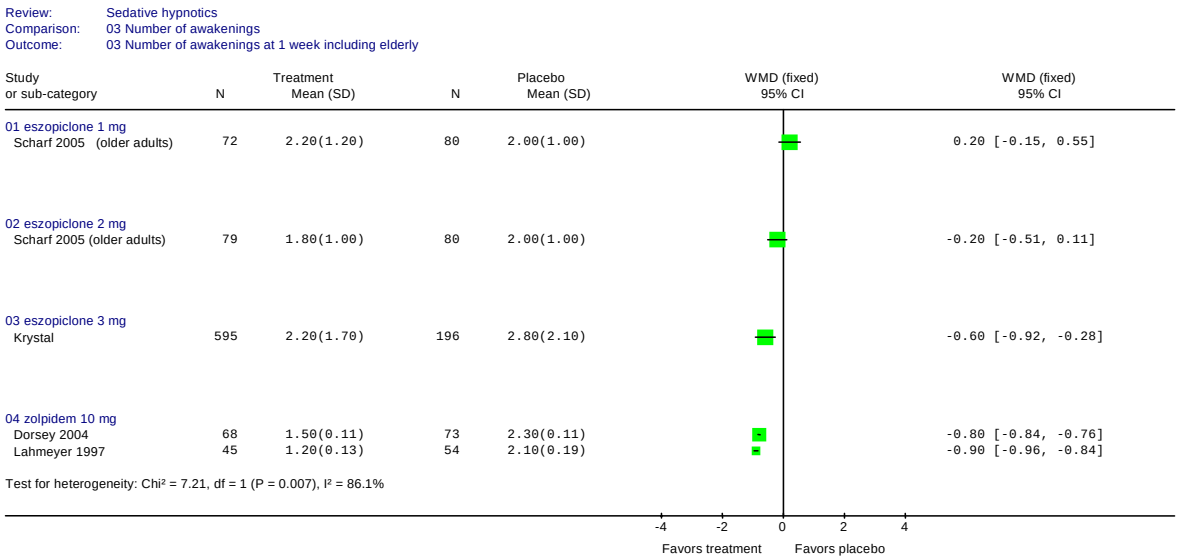
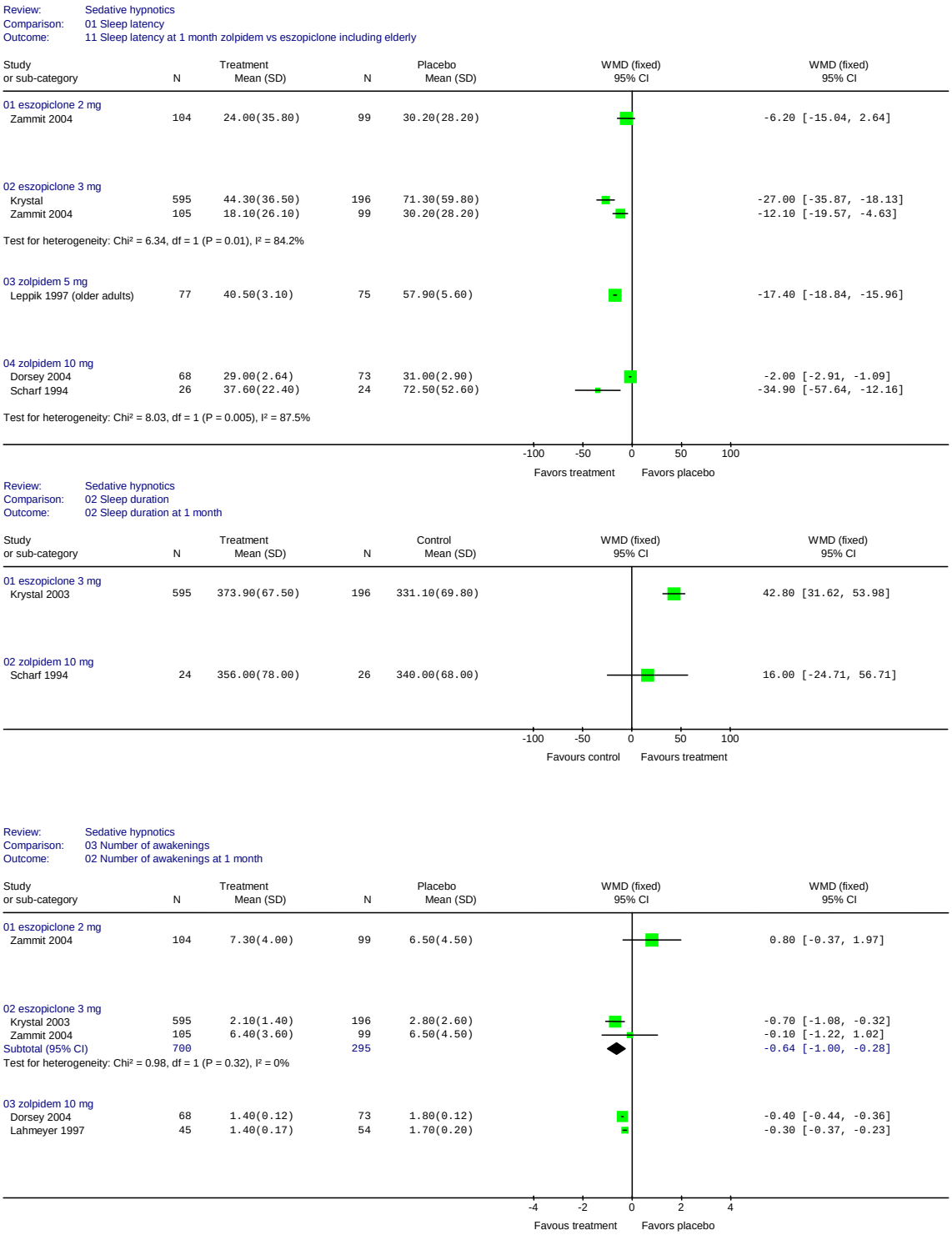


Figure 7 shows sleep outcomes at one month in placebo-controlled trials of zolpidem and eszopiclone. Sleep latency was reported in 5 trials. One trial of zolpidem 5 mg was conducted in older adults. Sleep latency was significantly shorter than placebo (mean difference –17.4 minutes; 95% CI –18.8 to –16.0 minutes). Eszopiclone 3 mg was significantly better than placebo but eszopiclone 2 mg was not. Zolpidem 10 mg had mixed results in two studies. There was no difference from placebo in one study in which placebo sleep latency was 31 minutes, but in another study with more severe patients (placebo sleep latency 72.5 minutes), zolpidem 10 mg was more effective than placebo (mean difference –34.9 minutes, 95% CI –57.6 to –12.2 minutes). This study was comparable to a study of eszopiclone 3 mg, where the placebo sleep latency was 71.3 minutes and mean difference versus placebo was –27 minutes (95% CI –35.9 to –18.1 minutes).

Two studies reported mean sleep duration and number of awakenings. Eszopiclone 3 mg increased sleep duration more than placebo, but zolpidem 10 mg did not. For number of awakenings, eszopiclone 3 mg and zolpidem 10 mg were more effective than placebo, but eszopiclone 2 mg was not.

Figure 7. Sleep outcomes at one month in placebo-controlled trials of zolpidem vs eszopiclone



Two placebo-controlled trials of eszopiclone also reported WASO, measured polysomnographically. Results at different time periods are shown in Table 7 below.

Table 7. Objective wake time after sleep onset (WASO) in placebo controlled trials of eszopiclone (mean difference; 95% CI)

Drug, dose	1 day	1 week
Eszopiclone 2 mg	**–14.7 minutes (–23.4 to –6.0)**	**--**
Eszopiclone 3 mg	**–15.4 minutes (–24.1 to –6.7)**	**–20.8 minutes (–39.6 to –2.0)**

Zolpidem extended release vs other newer drugs for insomnia

Direct comparisons

There are no head-to-head trials of zolpidem extended release compared to other newer drugs for insomnia.

Indirect comparisons

No trial of zolpidem extended release has been fully published. The FDA review of Ambien-CR is not yet publicly available. FDA approval was based on two placebo-controlled trials of 3 weeks' duration, one in adults[95] and one in older adults.[96]

Information about placebo-controlled trials is limited to poster presentations.[95, 96] Both trials were rated fair-quality based on the information provided in these posters. Intention-to-treat analyses were not conducted; analyses was performed on all patients who received at least one dose of double-blind study treatment with at least one post-baseline data point. In the study in adults, 9.4% of patients overall withdrew (8.8% of those taking zolpidem, 10% of those taking placebo); in the study in older adults, 3.4% of patients overall withdrew (5.0% of those taking zolpidem, 1.9% of those taking placebo). Neither poster reports the number analyzed, or at what point these patients withdrew. In the study in older adults,[96] there appear to be differences at baseline in sleep data for zolpidem versus placebo patients. For example, the number of awakenings in the placebo group was 4.1, compared with 6.2 in the zolpidem group. Baseline sleep outcomes are controlled for in the analysis, however.

A placebo-controlled trial of zolpidem extended release 12.5 mg was conducted in 212 adults with primary insomnia.[95] This study included 2 nights of PSG recording, 12 nights of outpatient treatment, 2 more nights of PSG recording, 5 nights of outpatients treatment, and a 2-night placebo run-out to measure rebound.

On objective measures (mean WASO, number of awakenings, sleep latency, and sleep duration, all baseline-adjusted) patients improved compared with placebo on both 2-night PSG assessment periods (nights 1-2 and nights 15-16).[95]

Subjective sleep outcomes are reported as the percentage of patients who reported improvements on day 2, night 15, and night 22. Significantly more zolpidem extended release-treated patients reported improvements on sleep latency, total time slept, sleep quality, and the statement, "treatment helped me sleep." Detailed data (e.g., difference from placebo in minutes) is not reported in the poster. There was a rebound effect shown on the first night after discontinuation (night 22) on sleep latency, sleep duration, and WASO; by night 23 the effect was not seen.

Results of a placebo-controlled trial of zolpidem extended release 6.25 mg in 205 older adults are available in a poster presentation.[96] This trial had an identical design to the trial in adults.[95] Objective WASO, sleep latency, and sleep duration all improved on both 2-night PSG assessment periods.

On subjective sleep outcomes, there was significant improvement versus placebo in patient global impression items on day 2, night 15, and night 22. The actual percentage of patients who reported improvement is not presented in the poster, and the patient global impression items are not specified. Subjective sleep quality was significantly improved on day 1-2. Subjective sleep quality at other endpoints is not reported.

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

Because the objective sleep data are baseline-adjusted, and subjective data are either given only as the percentage of patients improved or not reported, it is not possible to make indirect comparisons about the efficacy and safety of zolpidem extended release and other newer insomnia drugs from these trials.

Eszopiclone vs Zaleplon

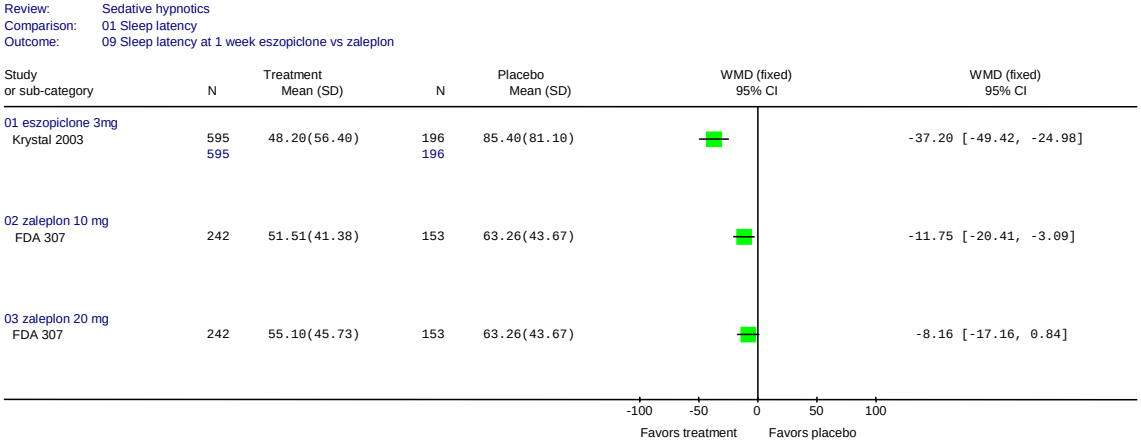
Direct comparisons

There are no head-to-head trials of eszopiclone versus zaleplon.

Indirect comparisons

Indirect comparisons from placebo-controlled trials are available only for the outcome of sleep latency at one week for eszopiclone versus zaleplon (Figure 8). Both drugs were more effective than placebo. There was more of a difference from placebo in the eszopiclone study, but confidence intervals overlap. Additionally, the placebo sleep latency rate was higher in the eszopiclone study than in the zaleplon study (85.4 minutes vs 63.3 minutes), indicating the populations differed in severity and limiting conclusions that can be drawn from comparing these studies.

Figure 8. Sleep latency at one week in placebo-controlled trials of eszopiclone and zaleplon



Zaleplon vs Zopiclone

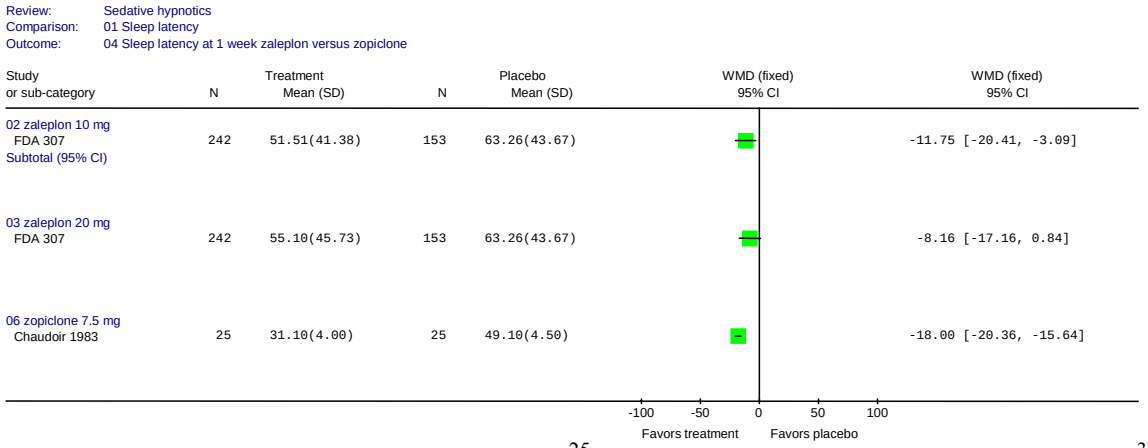
Direct Comparisons

There are no head-to-head studies of zaleplon versus zopiclone.

Indirect comparisons

Indirect comparisons of zaleplon versus zopiclone from placebo-controlled trials are available only for the outcome of sleep latency at one week (Figure 9). Confidence intervals for the mean difference from placebo overlapped, indicating the drugs were similarly effective.

Figure 9. Sleep latency at one week in placebo-controlled trials of zaleplon and zopiclone



One trial compared zaleplon to triazolam[25] and two compared zopiclone to triazolam.[34, 55] On sleep outcomes (time to sleep onset and duration of sleep), both zaleplon and zopiclone were similarly efficacious to triazolam 0.25 mg. It is difficult to draw conclusions about the comparative efficacy of zaleplon versus zopiclone from active-control studies, however, because the duration of treatment and populations differed.

Ramelteon vs newer sedative hypnotics

Direct Comparisons

There are no head-to-head studies of ramelteon versus newer sedative hypnotics.

Indirect comparisons

Ramelteon has been compared to placebo in patients with chronic insomnia in 5 placebo-controlled trials.[171] Two of these have been fully published; one in adults and one in older adults.[94, 172] Abstracts of two other trials[173, 174] are available, but these reports do not contain enough information to assess internal validity and are not included in this report.

A fair-quality crossover trial was conducted in 107 adults ages 18 to 64 years, randomized to placebo or ramelteon 4 mg, 8 mg, 16 mg, or 32 mg.[94] The primary outcome measure was sleep latency, measured using PSG in a sleep laboratory after 2 days of treatment.

The design of this study is similar to that of a study of eszopiclone and zolpidem.[14] Table 8 (first 2 rows) shows results of the primary outcome from the ramelteon study.[94] The remaining rows show results from a study of eszopiclone vs zolpidem. These studies are similar in their designs, outcome measures, and placebo response rates, so they allow indirect comparisons of ramelteon, zolpidem, and eszopiclone for the outcome of objective sleep latency. Objective sleep latency was 4 to 8 minutes longer with ramelteon compared with zolpidem and eszopiclone. Confidence intervals for the difference from placebo overlapped, however, indicating that the drugs were similar on this outcome.

Table 8. Objective sleep latency over 2 days in placebo-controlled trials of ramelteon, zolpidem, and eszopiclone

Study, year	Drug, dose	Objective LPS (mean), treatment	Objective LPS (mean), placebo	Mean difference vs placebo (minutes)
Erman 2006[94]	Ramelteon 8 mg	24.3	37.7	-13.7 (-20.4, -7.0)
Erman 2006[94]	Ramelteon 16 mg	24.0	37.7	-13.4 (-20.0, -6.7)
Erman 2005[14]	Zolpidem 10mg	16.6	37.8	-21.2 (-29.6, -12.8)
Erman 2005[14]	Eszopiclone 2 mg	20.1	37.8	-17.7 (-26.5, -8.9)
Erman 2005[14]	Eszopiclone 3 mg	18.3	37.8	-19.2 (-28.1, -10.3)

LPS, latency to persistent sleep

Subjective sleep outcomes (sleep latency, total sleep time, and sleep quality) were also measured in the trial of ramelteon.[94] There was no difference from placebo on any subjective measure, with the exception of sleep latency at the 16 mg dose of ramelteon (-13.1 minutes; 95% CI –24.3, –1.9). There were no significant next-day effects on alertness or ability to concentrate associated with ramelteon.

A fair-quality, placebo-controlled trial of ramelteon 4 mg and 8 mg in 829 older adults has also been published (Evidence Table 13).[172] The primary outcome was sleep latency as measured by patient sleep diaries; outcomes were reported for weeks 1, 3, and 5. Patients taking ramelteon showed improvements in sleep latency at week 1 and week 5 (Table 9). At week 3, the ramelteon 8 mg group was improved over placebo, but not the 4 mg group. Total sleep time was increased in both ramelteon groups compared with placebo at week 1 and with the 4 mg dose at week 3, but there was no difference with either dose at week 5.

Table 9. Subjective sleep outcomes in a placebo-controlled trial of ramelteon in older adults

Outcome	Ramelteon 4 mg (p vs placebo)	Ramelteon 8 mg (p vs placebo)	Placebo
Sleep latency			
Week 1	70.2 minutes (p=0.008)	70.2 minutes (p=0.008)	78.5 minutes
Week 3	64.9 minutes (p=0.142)	60.3 minutes (p=0.003)	69.3 minutes
Week 5	63.4 minutes (p=0.028)	57.7 minutes (p<0.001)	70.6 minutes
Total sleep time			
Week 1	324.6 minutes (p=0.004)	321.1 minutes (p=0.055)	313.9 minutes
Week 3	336.0 minutes (p=0.007)	332.1 minutes (p=0.071)	324.3 minutes
Week 5	337.5 minutes (p=0.104)	334.4 minutes (p=0.347)	330.1 minutes

There were no differences from placebo on other sleep outcomes, including number of awakenings, ease of falling back to sleep after awakening, and sleep quality (data not reported). There was no evidence of rebound insomnia or withdrawal effects, as measured on days 1 through 7 after discontinuation using a placebo run-out.

An unpublished trial in adults in which the primary outcome was subjective sleep latency found no difference between ramelteon and placebo.[171] It is not possible to assess this evidence until the study is fully published with more details.

Summary by Drug and Outcome

Table 10 summarizes the comparative evidence for short-term efficacy by drug and outcome. Although there are some differences between the drugs on some outcomes no one drug appeared to be consistently superior.

Table 10. Summary of short-term efficacy by drug and outcome

	Outcome	Shorter sleep latency	Longer sleep duration	Fewer number of awakenings	Improved sleep quality	Daytime alertness	Less rebound insomnia
Eszopiclone	**Direct evidence**	Similar to zolpidem*		Similar to zolpidem*		Similar to zolpidem	
	Indirect evidence	Similar to zolpidem	Better than zolpidem				
Zaleplon	**Direct evidence**	Better than zolpidem		Similar to zolpidem		Similar to zolpidem	Better than zolpidem
	Indirect evidence	Better than zolpidem Similar to zopiclone					
Zolpidem	**Direct evidence**	Similar to eszopiclone*	Better than zaleplon	Similar to zaleplon and zopiclone	Better than zaleplon	Similar to eszopiclone and zaleplon	Better than zopiclone
	Indirect evidence	Similar to eszopiclone					
Zolpidem extended release	**Direct evidence**						
	Indirect evidence						
Zopiclone	**Direct evidence**	Similar to zolpidem*	Similar to zolpidem	Similar to zolpidem			
	Indirect evidence	Similar to zaleplon Better than zolpidem					
Ramelteon	**Direct evidence**						
	Indirect evidence	Similar to zolpidem* and eszopiclone*					

*measured via PSG in a sleep laboratory

Newer insomnia drugs vs benzodiazepines

Appendix D summarizes results of good or fair quality studies of newer drugs compared with benzodiazepines in the general population of adults and older adults with insomnia. Details of the populations, interventions, and outcomes of these trials are provided in Evidence Tables 4 through 8. We also included six active-control trials in subgroups of patients with comorbid conditions; these are detailed in Evidence Tables 10 through 12.

There are no trials of eszopiclone, ramelteon, or zolpidem extended release versus benzodiazepines, and the evidence for zaleplon versus benzodiazepines is limited to two fair-quality trials versus triazolam. [25, 58]

Zolpidem. We included one study of zolpidem versus flurazepam,[28] two versus temazepam,[36, 56] and four versus triazolam.[36, 40, 46, 49]

In one study of zolpidem 10 mg or 20 mg versus flurazepam 30 mg, zolpidem was more effective for sleep outcomes.[28] Adverse events were similar for zolpidem 10 mg vs flurazepam, but zolpidem 20 mg was associated with more adverse events.

Two studies of zolpidem versus temazepam,[36, 56] found the drugs similar in efficacy and rebound insomnia.

In two studies comparing zolpidem 10 mg to triazolam 0.25 mg,[46, 49] sleep outcomes were similar for the two drugs, but triazolam caused more rebound insomnia. There was also more rebound insomnia with triazolam 0.25 mg compared to zolpidem 5 mg,[46] and with triazolam 0.5 mg compared to zolpidem 10 mg.[40]

The NICE review[97] presents an analysis of two studies of zolpidem versus nitrazepam that were excluded from our review because they are not English language.(Kazamatsuri, 1993 and Kudo, 1993) There were no significant differences between drugs in sleep latency or duration. In one study, more patients reported improved sleep quality with zolpidem (66.7% vs 37.5%, p=0.031),(Kudo, 1993) and there were fewer awakenings with zolpidem in the other.(Kazamatsuri, 1993} There were no differences in adverse event rates (OR 0.70, 95% CI 0.37 to 1.30), and no difference in daytime alertness or global impression of treatment in either study.

Zaleplon**.** In two trials of zaleplon compared to triazolam, the drugs were similar on most sleep outcomes and short-term adverse events.[25, 58] In one study, triazolam 0.25 mg was associated with more nausea than zaleplon 5 mg.[58] However, this outcome was with a low dose of zaleplon (5 mg). In the same study, there was no difference between zaleplon 10 mg and triazolam 0.25 mg.[58]

Zopiclone. Zopiclone has been compared to four benzodiazepines (flurazepam, nitrazepam, temazepam, and triazolam). In five studies of zopiclone versus flurazepam,[22, 27, 39, 41, 50] most comparisons found the two drugs to be similar in efficacy and adverse effects.

Zopiclone and triazolam were similar in efficacy and adverse events.[24, 33, 34] For rebound insomnia, results were mixed in two studies, with one finding triazolam causing more rebound[29] and the other finding no difference.[32]

In studies of zopiclone versus nitrazepam,[18, 35] efficacy and safety were similar, but nitrazepam was associated with more rebound insomnia.

The NICE review[97] presents an analysis of four studies of zopiclone versus temazepam. No significant differences were found in the two studies that made direct comparisons on sleep outcomes (sleep latency, sleep duration, number of awakenings, and sleep quality). Adverse events were similar in the one study that made a direct comparison.

Newer insomnia drugs vs trazodone

We identified one short-term, fair-quality study of zolpidem 10 mg versus trazodone 50 mg.[57] Sleep latency was shorter with zolpidem after 1 week of treatment (48.2 vs 57.7 minutes, p=0.037), but the difference was not significant at week 2 (48.1 vs 54.5 minutes, p not reported). Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2. The total numbers of adverse events and withdrawals due to adverse events were similar between the drugs. More patients reported somnolence with trazodone (16% vs 23%).

A trial of trazodone versus zaleplon, conducted in psychiatric inpatients, was rated poor quality and does not provide additional comparative information about newer insomnia drugs versus trazodone.[48]

Long-term Effectiveness

A fair-quality, 6-month placebo-controlled trial of eszopiclone 3 mg in 788 adults is the longest-term trial of a newer insomnia drug.[76] Results of this trial are summarized in Table 11.

Table 11. Results of 6-month placebo-controlled trial of eszopiclone 3 mg

Outcome (difference from placebo)	Week 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Sleep latency (median, minutes)	-30 (p<0.0001)	-21 (p<0.0001)	-20 (p<0.0001)	-15 (p<0.0001)	-15 (p<0.0001)	-14 (p<0.0001)	-15 (p<0.0001)
Sleep duration (median, minutes)	+45 (p<0.0001)	+38 (p<0.0001)	+40 (p<0.0001)	+34 (p<0.0001)	+19 (p<0.0001)	+42 (p<0.0001)	+38 (p<0.0001)
Number of awakenings (median)	0 (p=0.0013)	-0.5 (p<0.0001)	-0.4 (p<0.0001)	-0.3 (p<0.0001)	-0.6 (p<0.0001)	-0.5 (p<0.0001)	-0.4 (p<0.0001)
Sleep quality (scale 1-10, higher is better)	+2.0 (p<0.0001)	+1.0 (p<0.0001)	+1.0 (p<0.0001)	+1.0 (p<0.0001)	+0.8 (p<0.0001)	+1.0 (p<0.0001)	+1.0 (p<0.0001)
Daytime alertness (scale 1-10, higher is better)	+1.0 (p<0.0001)	+0.5 (p<0.0001)	+0.6 (p<0.0001)	+0.8 (p<0.0001)	+0.7 (p<0.0001)	+0.7 (p<0.0001)	+0.8 (p<0.0001)

Eszopiclone 3 mg was more effective than placebo at all time periods through 6 months on sleep latency, sleep duration, number of awakenings, sleep quality, and daytime alertness. Rebound insomnia was not measured in this trial.

Although this trial provides evidence that eszopiclone 3 mg is efficacious versus placebo for up to 6 months, it does not provide any information about the comparative efficacy and safety

of eszopiclone versus other newer drugs for insomnia. There are no long-term trials of eszopiclone at lower doses, although 2 mg is the recommended initial dose.

A second 6-month placebo-controlled trial of eszopiclone is currently available only as a poster presentation.[175] This trial also showed eszopiclone 3 mg was more effective than placebo for sleep latency, WASO, total sleep time, number of awakenings, and sleep quality for each month up to 6 months. There was no evidence of rebound insomnia or discontinuation effects (results are reported graphically only).

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. Results of observational studies of adverse events are shown in Evidence Table 17.

Zaleplon. A one-year, open-label extension of a head-to-head trial[8] was conducted to assess the longer-term safety of zaleplon 5 mg in older patients.[101] In order to qualify for the extension phase, patients were required to have completed the trial and a placebo run-out period of 7 days without adverse effects, so this study is limited to a highly selected sample of patients less likely to experience discontinuation effects. Sixty-four percent of those completing the 2-week trial enrolled in the extension study. Results of this open-label extension are reported in combination with another extension study 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 disturbances (2%). There was a significant increase in rebound 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.[110, 115]

In an open-label study of zolpidem 10 mg or 20 mg,[110] 96 patients over age 40 in general practice in France were followed for 6 months. Forty-nine 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), feeling of drunkenness (1 patient), anterograde amnesia (2 patients), nausea (1 patient), 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 180 days withdrew (8%); two experienced nightmares, but these were not considered to be related to the study drug. There were no reports of withdrawal or rebound phenomena.

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

Eszopiclone. In a 6-month placebo-controlled trial of eszopiclone 3 mg,[76] rates of serious adverse events were 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). Following discontinuation of the drug, there were similar overall rates of "new" events (defined as those not seen during the treatment period, or a worsening of an event) in the placebo (10.7%) and eszopiclone (11.2%) groups. There were no reports of seizures, hallucinations, or perceptual-disturbance events. There was one report of anxiety in the eszopiclone group. Adverse events occurred in 81.1% of the eszopiclone group versus 70.8% of the placebo group.

The most common adverse event was unpleasant taste (26.1% eszopiclone vs 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 vs 1.5% placebo), depression (2.0% vs 0%), unpleasant taste (1.7% vs 0.5%), headache (0% vs 2%), asthenia (1% vs 1.5%), and insomnia (0% vs 1.5%).

A 6-month, open-label extension study of this trial has also been conducted.[176] 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,[176] 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%).

Abuse and Dependence

Cases of abuse and dependence have been associated with zolpidem and zopiclone.[120, 121, 123, 132, 134, 139, 140, 142, 144-146, 149, 156-158, 162, 163, 168] A review of case reports and epidemiological data of zolpidem abuse and dependence potential found most patients had a history of drug or alcohol abuse or other psychiatric conditions.[177]

A 2003 survey of 297 patients admitted to addiction treatment sites in the United Kingdom[109] found that while zopiclone was used by many more subjects than zolpidem (53.7% vs 5.8%), both drugs were similar in their use to induce sleep (88% vs 82%) or to get high (22.9% vs 23.5%).

Eszopiclone, zaleplon, zolpidem extended release, and ramelteon have been in use for a shorter period of time than zolpidem and zaleplon, so there is less information about their effects over the long term. All of 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 that the newer sedative hypnotics have.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one newer insomnia drug 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 of zolpidem vs 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%), but there was no difference in overall adverse events or in withdrawals due to adverse effects.
  - A case-control study of the relationship of the use of zolpidem to hip fracture in 6,110 older women found an increased risk in patients using zolpidem (adjusted

odds ratio vs nonuse 1.95; 95% CI 1.09-3.51). The risk was higher than for benzodiazepines (adjusted odds ratio vs nonuse 1.46; 1.21-1.76)

- 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 $\pm$ 676 grams vs 3624 $\pm$ 536 grams; p=0.01) and gestational age (38.3 $\pm$ 2.7 weeks vs 40.0 $\pm$ 1.6 weeks; p=0.002), but there were no differences in other pregnancy outcomes.
  - A prescription event monitoring study in the UK 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 in pregnancy for other newer insomnia drugs.
- Comorbid conditions
  - There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol, patients with generalized anxiety disorder, and inpatients with stroke.
  - Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in patients with COPD.

Detailed Assessment

Older adults

One head-to-head trial,[8] one placebo-controlled trial[96] (discussed under Key Questions 1 and 2), six active-control trials (Evidence Tables 7-9),[22, 26, 35, 36, 46, 55] and three observational studies (Evidence Table 17)[101, 111, 116] were conducted in older adults.

In a 2-week trial in older adults,[8] 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 (see Table 6). A one-year, open-label extension of this trial was conducted to assess the longer-term safety of zaleplon in older patients.[101] Adverse events were mild (see long-term safety section for more details of this extension study).

A case-control study of the relationship of the use of zolpidem or other medications to hip fracture in 6,110 older women found an increased risk in patients using zolpidem (adjusted Odds Ratio 1.95; 95% CI 1.09-3.51).[116] The risk was higher than for benzodiazepines (adjusted Odds Ratio 1.46; 1.21-1.76). This study did not include other newer insomnia drugs, so it does not provide information about the comparative risk of zolpidem versus 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.[117] These potential confounders were BMI, current smoking status, activities of daily living (ADL) score, cognitive impairment, and Rosow-Breslau physical impairment scale. The authors found that ADL score was the strongest confounder, causing an overestimation of 10% when comparing zolpidem

users with benzodiazepine users. They conclude, however, that the magnitude of the effect of unmeasured confounders is unlikely to explain completely the elevations in hip fracture observed in older sedative hypnotic users.

A good-quality systematic review and meta-analysis of pharmacological treatments for insomnia in older people (at least 60 years) was recently published.[99] The review included studies of newer sedative hypnotics, along with benzodiazepines and over-the-counter medications such as antihistamines. Only subjective sleep measures were included. Results are combined for all sleep agents for most outcomes, so it is not possible to use this review to make conclusions about the comparative efficacy and safety of newer sedative hypnotics to each other or about newer sedative hypnotics to other sleep agents. Studies of zaleplon, zopiclone, and zolpidem (combined) versus 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).[99] For all sedative hypnotics (newer and older), the number needed to harm for all adverse events compared with placebo was 6 (95% CI 4.7 to 7.1), and the number needed to treat compared with placebo 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.

Gender and Racial Groups

We found no evidence that one newer insomnia drug is safer or more effective in subgroups based on gender or race.

Use in Pregnancy

A prospective cohort study in Canada evaluated pregnancy outcomes following first-trimester exposure to zopiclone in 40 women.[106] The sample consisted of women who had initiated contact with a program that provides counseling for pregnant women, so it is not representative of the total population of women who were exposed to zopiclone in pregnancy.

Newborns in the zopiclone group had a significantly lower mean birth weight (3249 $\pm$ 676 grams vs 3624 $\pm$ 536 grams; p=0.01) and lower gestational age (38.3 $\pm$ 2.7 weeks vs 40.0 $\pm$ 1.6 weeks; p=0.002). Once birth weight was adjusted for gestational age, the differences were no longer significant. There were no differences in outcome of pregnancy, delivery method, assisted deliveries, fetal distress, and presence of meconium at birth, preterm deliveries, or neonatal intensive care admissions between study 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 outcomes in 23 women exposed to zolpidem and 18 exposed to zopiclone during pregnancy.[178] In women who had taken zolpidem, there were 2 spontaneous and 6 legal abortions; in those 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 births in women exposed to either drug.

Patients with Comorbid Conditions

There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol,[19] patients with generalized anxiety disorder,[30] and inpatients with stroke.[37]

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.[51]

Placebo-controlled trials of zolpidem have been conducted in patients with depression[64] and other psychiatric conditions,[88] in peri- and postmenopausal women,[68] and in patients with fibromyalgia.[79] Zaleplon has been studied in placebo-controlled trials in patients undergoing kidney dialysis.[85] Zopiclone has been compared to placebo in trials of patients with upper airway resistance syndrome,[78] rheumatoid arthritis,[70] fibromyalgia,[69, 72] and in shiftworkers.[81] Eszopiclone was more effective than placebo for insomnia in patients with rheumatoid arthritis,[179] in patients with depression who were also taking fluoxetine,[180] and in peri- and postmenopausal women.[181] While these studies provide evidence that these drugs are effective for some sleep outcomes in certain patients with co-morbid conditions, they do not provide evidence about the comparative efficacy of newer insomnia drugs in these subgroups.

Overall Summary

Table 12 summarizes the quality of the overall body of evidence for each key question.

Table 12. Summary of the evidence by key question

Key Questions 1 and 2: Benefits and Harms	Quality of Evidence	Conclusion
Short-term efficacy and safety: Pediatrics	Poor	No evidence
Short-term efficacy and safety: Adults	Good for zolpidem vs zaleplon	There is evidence from four fair-quality head-to-head trials that zaleplon is more effective than zolpidem for sleep latency, but zolpidem is more effective than zaleplon for sleep duration and sleep quality. The drugs were similar for number of awakenings and daytime alertness. Zolpidem caused more rebound insomnia than zaleplon on the first night after discontinuation. Short-term adverse events and withdrawals due to adverse events were similar.
	Fair for zolpidem vs zopiclone	One fair-quality head-to-head trial found that zolpidem and zopiclone were similar in efficacy on patient-rated sleep outcomes and investigator's global assessment of improvement. Zopiclone caused more rebound sleep latency insomnia than zolpidem. Overall adverse events and effects of withdrawal were similar in another study designed to measure withdrawal effects. There is limited indirect evidence that zopiclone was more effective for sleep latency at one week.
	Fair for zolpidem vs eszopiclone	In one fair-quality head-to-head trial, zolpidem and eszopiclone had similar objective sleep latency and Wake Time After Sleep Onset. There was no difference between zolpidem and eszopiclone on subjective measures of next-day effects. Limited indirect comparisons provide evidence that the drugs were similar for sleep latency and number of awakenings, but eszopiclone was more effective for increasing sleep duration.
	Poor for zolpidem extended release vs other newer drugs for insomnia	There are no head-to-head trials, and no active-control trials. Two placebo-controlled trials, one in adults and one in older adults, found zolpidem extended release superior to placebo on objective and subjective sleep outcomes. These trials have not been fully published, and method of reporting limits indirect comparisons.
	Poor for zaleplon vs zopiclone and eszopiclone	There are no head-to-head trials. Limited indirect comparisons suggest the drugs are similar for sleep latency at one week. Indirect comparisons for other sleep outcomes were not possible.
	Poor for ramelteon vs newer sedative hypnotics	There are no trials of ramelteon compared to newer sedative hypnotics, benzodiazepines, or trazodone in patients with insomnia. One placebo-controlled crossover trial of 2 nights of treatment in adults has been fully published. This trial provides indirect evidence that ramelteon is similar to zolpidem and eszopiclone for objective sleep latency. There was no difference between ramelteon and placebo on any subjective measure, with the exception of sleep latency at the 16 mg dose. There were no significant next-day effects on alertness or ability to concentrate associated with ramelteon A 5-week placebo-controlled trial in older adults found ramelteon 4 mg and 8 mg more effective than placebo for subjective sleep latency and total sleep time at some time points, but no different from placebo on other subjective sleep outcomes. There was no rebound insomnia. Abstracts of additional placebo-controlled trials of ramelteon do

		not provide sufficient information to assess internal validity and are not included.
	Fair to poor for newer insomnia drugs vs benzodiazepines	There are no trials of eszopiclone versus benzodiazepines. Most comparisons found the newer sedative hypnotics to be similar to benzodiazepines in efficacy and short-term adverse events. Some studies found less rebound insomnia with newer sedative hypnotics.
	Poor for newer insomnia drugs vs trazodone	We identified one fair-quality, short-term trial of zolpidem versus trazodone. Sleep latency was shorter with zolpidem after 1 week of treatment, but the difference was not significant at week 2. Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2. More patients reported somnolence with trazodone. Withdrawals due to adverse events and overall adverse events were similar between the drugs. A trial of zaleplon versus trazodone was rated poor quality.
Long-term efficacy and safety	Fair for eszopiclone, poor for others	Evidence about long-term efficacy and safety is limited; there is no comparative evidence. Two longer-term placebo-controlled trials (one available only as a poster) provide evidence that eszopiclone 3 mg is efficacious for up to 6 months, but do not add any information about the *comparative* efficacy and safety of eszopiclone versus other sedative drugs for insomnia. No withdrawal effects were observed. There was no rebound insomnia in one trial; rebound insomnia was not assessed in the other. In a 6-month open-label extension of one trial, improvements in sleep outcomes were sustained; 3.8% of patients discontinued due to adverse events. Withdrawal effects and rebound insomnia were not assessed. A one-year open-label extension study of zaleplon in older adults found most adverse events were mild. Sleep outcomes worsened after discontinuation, but did not approach baseline levels. There are case reports of dependence with both zolpidem and zopiclone.
Key Question 3: Subgroups	**Quality of Evidence**	**Conclusion**
Older adults (age ≥ 65 years)	Fair	In a 2-week head-to-head trial of zolpidem vs 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 a placebo-controlled trial in older adults, zolpidem extended release was superior to placebo for objective and subjective sleep outcomes. A case-control study of the relationship of the use of zolpidem to hip fracture in 6,110 older women found an increased risk in patients using zolpidem (adjusted odds ratio vs nonuse 1.95; 95% CI 1.09-3.51).
Gender and race	Poor	We found no evidence that one newer drug for insomnia is safer or more effective in any subgroup based on gender or race.
Pregnancy	Fair for zopiclone, poor for others	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 and gestational age, but there were no differences in other pregnancy outcomes. A prescription event monitoring study in the UK 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 in pregnancy for other newer drugs for insomnia.
Patients with comorbid conditions.	Poor	There is no comparative evidence in patients with comorbid conditions. There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol, patients with generalized anxiety disorder, and inpatients with stroke. Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in patients with COPD. Placebo-controlled trials do not provide additional comparative evidence.

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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 (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing 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 has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *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, published by the CRD.

All studies or systematic reviews that are included 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 which meet all criteria, are rated good quality; the remainder are 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 are only probably valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the 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, birth dates or week days
    - 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 numbers, birth dates or week days
        - 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 to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

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

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom 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 followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

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

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

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

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

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

7. Did the duration of followup correlate to reasonable timing for 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 population to the population to whom 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?

Systematic Reviews:

1. Is there a clear review question and inclusion/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 decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., 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, details of the search terms used, 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, e.g. if 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 (e.g., 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 have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers 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 studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of 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 (e.g., according to sample size, or 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 Trials

307 trials were excluded with the exclusion code shown below (new trials from Update 1 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, non-systematic 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.	(AO)
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

Trials	Code
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
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.	(AO)
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

Trials	Code
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
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

Trials	Code
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)
Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of ropinirole in restless legs syndrome. *Sleep Medicine.* 2005;6(2):141-147.	3
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
Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. *Psychopharmacology.* 1999;143(4):373-379.	4
Boissl K, Dreyfus JF, Delmotte M. Studies on the dependence-inducing potential of zopiclone and triazolam. *International Pharmacopsychiatry.* 1982;17(2):242-247.	4
Bond A, Lader M. Correlations among measures of response to benzodiazepines in man. *Pharmacology, Biochemistry & Behavior.* Feb 1983;18(2):295-298.	6
Boniface PJ, Martin IC, Nolan SL, Tan ST. Development of a method for the determination of zopiclone in whole blood. *Journal of Chromatography - Biomedical Applications.* 1992;584(2):199-206.	2
Borgen L. Trial effects of oral Xyrem and Zolpidem on sleep-disordered breathing in obstructive sleep apnea patients. *clinicaltrials.gov.* 2004.	2
Boulanger-Rostowsky L, Fayet H, Benmoussa N, Ferrandi J. Dependence on zolpidem: a report of two cases. *Encephale.* Mar-Apr 2004;30(2):153-155.	1
Brunelle E, Rotily M, Lancon C, et al. Letter to the Editor: Zolpidem: Intravenous misuse in drug abusers. *Addiction.* Sep 2005;100(9):1377-1378.	4
Burton JH, Lyon L, Dorfman T, Tomassoni AJ. Continuous flumazenil infusion in the treatment of zolpidem (Ambien(registered trademark)) and ethanol coingestion [1]. *Journal of Toxicology - Clinical Toxicology.* 1998;36(7):743-746.	2

Trials	Code
Busto UE, Sproule BA, Knight K, Herrmann N. Use of prescription and nonprescription hypnotics in a Canadian elderly population. *Canadian Journal of Clinical Pharmacology.* 2001;8(4):213-221.	6
Caldwell J, Caldwell JL. Comparison of the effects of zolpidem-induced prophylactic naps to placebo naps and forced rest periods in prolonged work schedules. *Sleep.* 1998;21(1):79-90.	4
Cashman JN, Power SJ, Jones RM. Assessment of a new hypnotic imidazo-pyridine (zolpidem) as oral premedication. *British Journal of Clinical Pharmacology.* 1987;24(1):85-92.	4
Cashman JN, Power SJ. An evaluation of tests of psychomotor function in assessing recovery following a brief anaesthetic. *Acta Anaesthesiologica Scandinavica.* 1989;33(8):693-697.	2
Caville P. Homeopathy in dementia and agitation. *Homeopathy.* 2002;91(2):109-112.	5
Chang M-Y, Lin J-L. Irreversible Ischemic Hand Following Intraarterial Injection of Zolpidem Powder. *Journal of Toxicology - Clinical Toxicology.* 2003;41(7):1025-1028.	2
Channer KS, Dent M, Roberts CJC. The effect of posture at the time of administration on the central depressant effects on the new hypnotic zopiclone. *British Journal of Clinical Pharmacology.* 1984;18(6):879-886.	2
Cialdella P, Boissel JP, Belon P. Homeopathic specialities as a substitute for benzodiazepines: A double-blind vs. placebo study. *Therapie.* 2001;4:397-402.	3
Cipriani A, Brambilla P, Furukawa T, et al. Fluoxetine versus other types of pharmacotherapy for depression [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2005;4:4.	2
Clauss RP, Guldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem. *South African Medical Journal.* 2000;90(1):68-72.	2
Cluydts R, De Roeck J, Cosyns P, Lacante P. Antagonizing the effects of experimentally induced sleep disturbance in healthy volunteers by lormetazepam and zolpidem. *Journal of Clinical Psychopharmacology.* 1995;15(2):132-137.	4
Cluydts R, Heyde K, De Volder I. Polysomnographic findings during non-continuous administration of zolpidem. *Sleep Medicine Reviews.* 2002;6(SUPPL. 1):S13-S19.	6

Trials	Code
Cluydts R, Peeters K, De Bouyalsky I, Lavoisy J. A pilot, randomized, double-blind study of zolpidem 10 mg comparing intermittent versus continuous administration. *Sixth World Congress of Biological Psychiatry, Nice, France. June.* 1997.	6
Cluydts R, Peeters K, de Bouyalsky I, Lavoisy J. Comparison of continuous versus intermittent administration of zolpidem in chronic insomniacs: a double-blind, randomized pilot study. *Journal of International Medical Research.* 1998;26(1):13-24.	6
Cluydts RJ, De Roeck JM, Jolie AM. A three week multicentre general practitioner study of zoldipem in 651 patients with insomnia. *Acta Therapeutica.* 1993;19(1):73-91.	6
Cohn MA. Effects of zolpidem, codeine phosphate and placebo on respiration. A double-blind, crossover study in volunteers. *Drug Safety.* 1993;9(4):312-319.	4
Coleman DE, Ota K. Hallucinations with zolpidem and fluoxetine in an impaired driver. *Journal of Forensic Sciences.* Mar 2004;49(2):392-393.	4
Colle M, Rosenzweig P, Bianchetti G, et al. Nocturnal profile of growth hormone secretion during sleep induced by zolpidem: a double-blind study in young adults and children. *Hormone Research.* 1991;35(1):30-34.	2
Colle M, Rosenzweig P, Bianchetti G, et al. Nocturnal profile of growth hormone secretion during sleep induced by zolpidem: a double-blind study in young adults and children. *Hormone Research.* 1991;35(1):30-34.	2
Conway DH, Turner SJ, Eddleston J, Guthrie E. Sedation on intensive care: A pathway into dependence. *Care of the Critically Ill.* 2001;17(5):170-171.	6
Corrigan MH, Gallen CC, Bonura ML, Merchant KM. Effectiveness of the selective D4 antagonist sonepiprazole in schizophrenia: A placebo-controlled trial. *Biological Psychiatry.* 2004;55(5):445-451.	3
Coskunol H, Gokden O, Ercan ES, Bayraktar E, Tuglular I, Saygili R. Long-term efficacy of sertraline in the prevention of alcoholic relapses in alcohol-dependent patients: A single-center, double-blind, randomized, placebo-controlled, parallel-group study. *Current Therapeutic Research - Clinical and Experimental.* 2002;63(11):759-771.	3
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Appendix D. Summary of results of trials of newer insomnia drugs versus benzodiazepines

Comparators	KQ outcome	Hypnotic		Benzodiazepine	(No. of Studies) Citations
Zaleplon vs Triazolam					
	Effectiveness outcomes	Zaleplon 5, 10mg	=,=	Triazolam 0.25mg	(2) [1, 2]
	Effectiveness outcomes	Zaleplon 20mg	≤	Triazolam 0.25mg	(1) [2]
	Effectiveness outcomes	Zaleplon 40-60mg	Mixed	Triazolam 0.25mg	(1) [2]
	Safety outcomes	Zaleplon 5, 10mg	=	Triazolam 0.25mg	(1) [1]
	Nausea	Zaleplon 5mg	>	Triazolam 0.25mg	(1) [1]
Zolpidem vs Flurazepam					
	Effectiveness outcomes	Zolpidem 10, 20mg	>	Flurazepam 30mg	(1) [3]
	Safety outcomes	Zolpidem 10mg	=	Flurazepam 30mg	(1) [3]
	Safety outcomes	Zolpidem 20mg	<	Flurazepam 30mg	(1) [3]
Zolpidem vs Temazepam					
	Effectiveness outcomes	Zolpidem 5mg	=	Temazepam 15mg	(1) [4]
	Effectiveness outcomes	Zolpidem 10mg	=	Temazepam 20mg	(1) [5]
	Less rebound	Zolpidem 10mg	=	Temazepam 20mg	(1) [5]
Zolpidem vs Trazodone					
	Effectiveness outcomes	Zolpidem 10mg	=	Trazodone 50mg	(1) [6]
Zolpidem vs Triazolam					
	Effectiveness outcomes	Zolpidem 5mg	>	Triazolam 0.125mg	(1) [4]
	Effectiveness outcomes	Zolpidem 10mg	=,=	Triazolam 0.25mg	(2) [7, 8]
	Effectiveness outcomes	Zolpidem 10mg	>	Triazolam 0.5mg	(1) [9]
	Less rebound	Zolpidem 5mg	>	Triazolam 0.25mg	(1) [7]
	Less rebound	Zolpidem 10mg	≥,>	Triazolam 0.25mg	(2) [7, 8]
	Less rebound	Zolpidem 10mg	>	Triazolam 0.5mg	(1) [9]
Zopiclone vs Flurazepam					
	Effectiveness outcomes	Zopiclone 3.75mg	=	Flurazepam 30mg	(1) [10]
	Effectiveness outcomes	Zopiclone 7.5mg	=,≥,=	Flurazepam 30mg	(3) [10-12]

Comparators	KQ outcome	Hypnotic		Benzodiazepine	(No. of Studies) Citations
	Effectiveness outcomes	Zopiclone 11.5mg	=,≥	Flurazepam 30mg	(2) [10, 11]
	Effectiveness outcomes	Zopiclone 15mg	=	Flurazepam 30mg	(1) [10]
	Safety outcomes	Zopiclone 7.5mg	=,=	Flurazepam 30mg	(1) [13, 14]
	Less rebound	Zopiclone 7.5mg	≤	Flurazepam 30mg	(1) [12]
Zopiclone vs Nitrazepam					
	Effectiveness outcomes	Zopiclone 7.5mg	=,=	Nitrazepam 5mg	(2) [15, 16]
	Daytime alertness	Zopiclone 7.5mg	>,≥	Nitrazepam 5mg	(2) [15, 16]
	Safety outcomes	Zopiclone 7.5mg	=	Nitrazepam 5mg	(1) [15]
Zopiclone vs Temazepam					
	Effectiveness outcomes	Zopiclone 7.5mg	=,=,=	Temazepam 20, 30mg	(3) [17-19]
	Safety outcomes	Zopiclone 7.5mg	=	Temazepam 20mg	(1) [17]
Zopiclone vs Triazolam					
	Effectiveness outcomes	Zopiclone 7.5mg	=,=,=	Triazolam 0.25mg	(3) [20-22]
	Safety outcomes	Zopiclone 7.5mg	=	Triazolam 0.25mg	(1) [20]
	Less rebound	Zopiclone 7.5mg	>,≤	Triazolam 0.25mg	(2) [21, 23]

**Efficacy outcomes*: Sleep Duration, total sleep time, length of sleep, total sleep time; Sleep Quality, sleep efficiency, No. 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: Overall adverse events, side effects, safety,
Rebound insomnia: Rebound, withdrawal effects

***Explanation of symbols for individual studies*:
"≥" 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;
"mixed" some outcomes showed a preference for the newer sedative hypnotic and others showed a preference for the benzodiazepine.
(See Evidence Tables 4 through 9 for details of the population, interventions, and outcomes of these studies).

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