Drug Class Review

Newer Drugs for Insomnia

Final Report Update 2

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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 about comparative effectiveness and safety profiles of different drugs within a pharmaceutical class. This report does not provide usage guidelines nor should it 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. Variation in estimates depends on different methods of surveying and definitions of insomnia.[1] About three-fourths of people who have trouble sleeping say that the problem is "occasional," averaging about 6 nights per month. The other one-fourth have frequent or chronic insomnia, averaging about 16 nights per month.[2] Individuals with insomnia most often report a combination of difficulty falling asleep and intermittent wakefulness during sleep.[3] The most common symptoms of insomnia are waking up feeling unrefreshed and waking often during the night. The symptoms waking up too early and difficulty falling asleep are less common but still experienced at least a few nights a week by about 25% of adults with insomnia.[1] The risk of insomnia increases with age; affecting approximately 20% to 40% of older adults at least a few nights per month.[2]

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

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

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

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

Scope and Key Questions

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

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

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

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

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

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

Included populations

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

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

Included interventions

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

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

Table 1. Newer drugs for insomnia

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

Included outcomes

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

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

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

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

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

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

METHODS

Literature Search

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

Study Selection

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

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

Data Abstraction

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

Validity Assessment

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

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

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

Data Synthesis

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

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

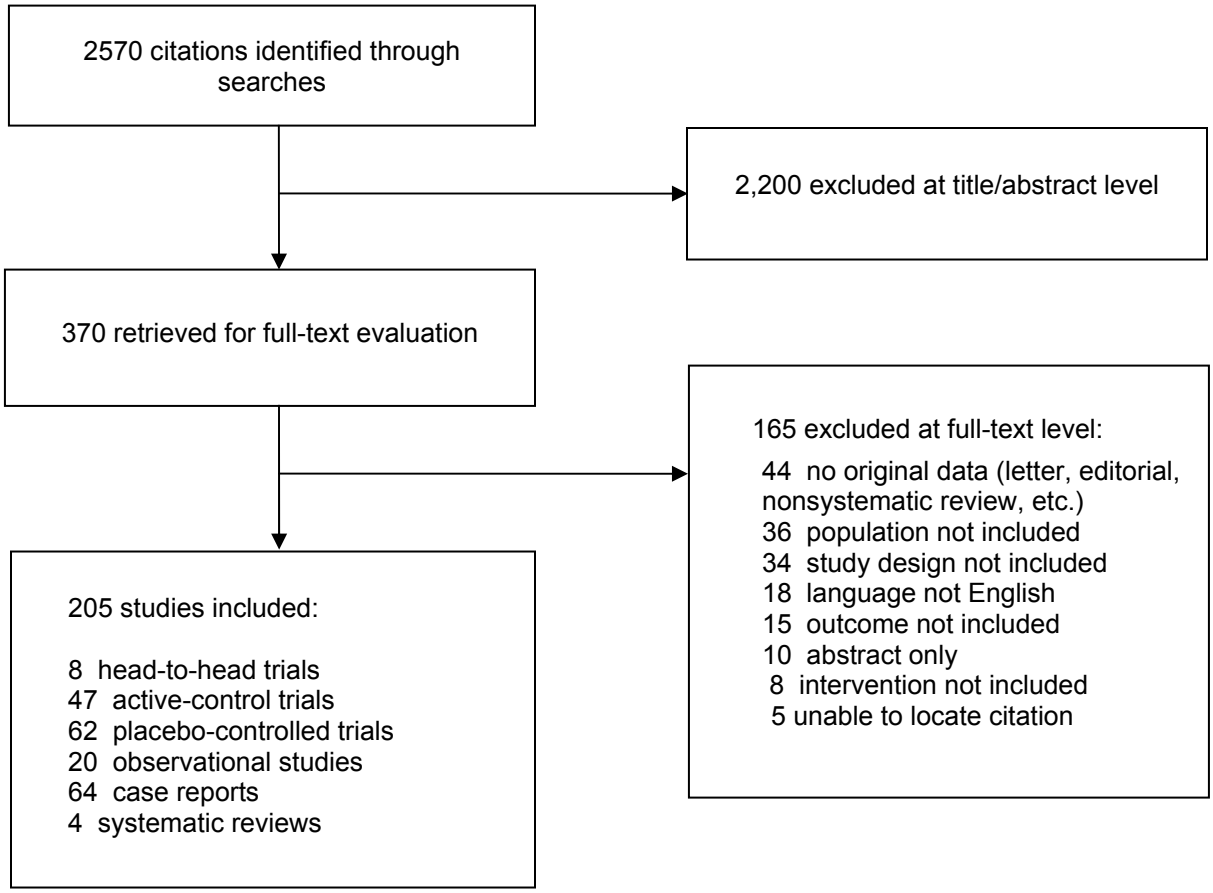
To assess the strength of evidence in a body of literature related to a particular key question, we examined consistency of study design, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty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

RESULTS

Overview of included studies

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

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



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

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

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

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

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

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

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

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

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

Summary of the Evidence

There is no evidence in children.

Direct evidence

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

Indirect evidence

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

Zolpidem extended-release

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

Detailed Assessment

Direct evidence

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

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

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

Eszopiclone compared with zolpidem

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

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

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

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

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

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

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

Zaleplon compared with zolpidem

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

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

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

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

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

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

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

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

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

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

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

Zopiclone compared with zolpidem

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

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

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

Indirect evidence: Meta-analysis of placebo-controlled trials

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

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

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

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

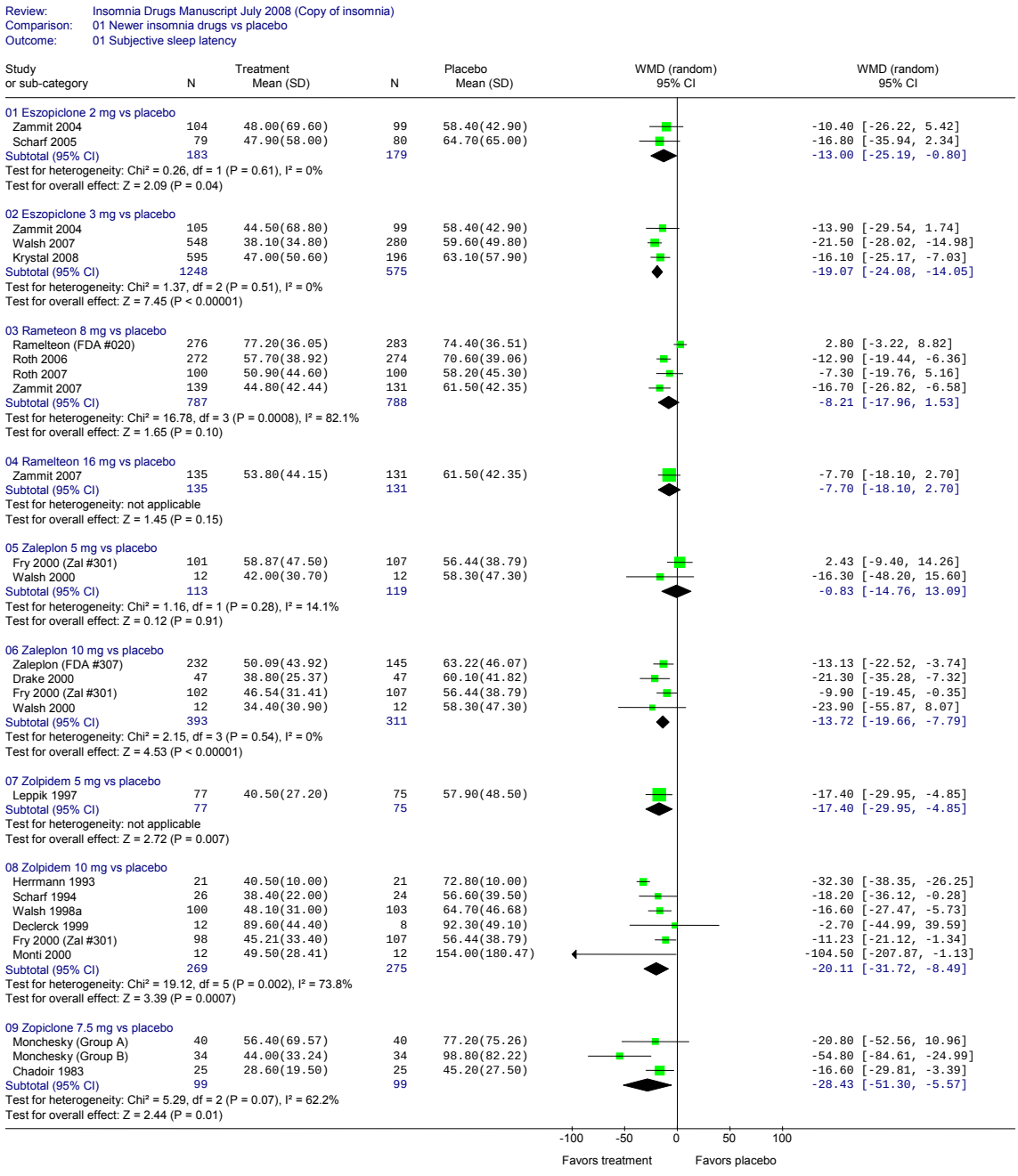
Study, year (Quality)	Interventions	Sample size	Population (Elderly=age 65 or older)	Treatment duration/ Design
(FAIR)				
Roth 2007[106] (FAIR)	Ramelteon 4 mg Ramelteon 8 mg	100	Elderly	2 nights/ Crossover
Zammit 2007[122] (FAIR)	Ramelteon 8 mg Ramelteon 16 mg	405	Adults	5 weeks/ Parallel
Drake 2000[29]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

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

Subjective sleep latency

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

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

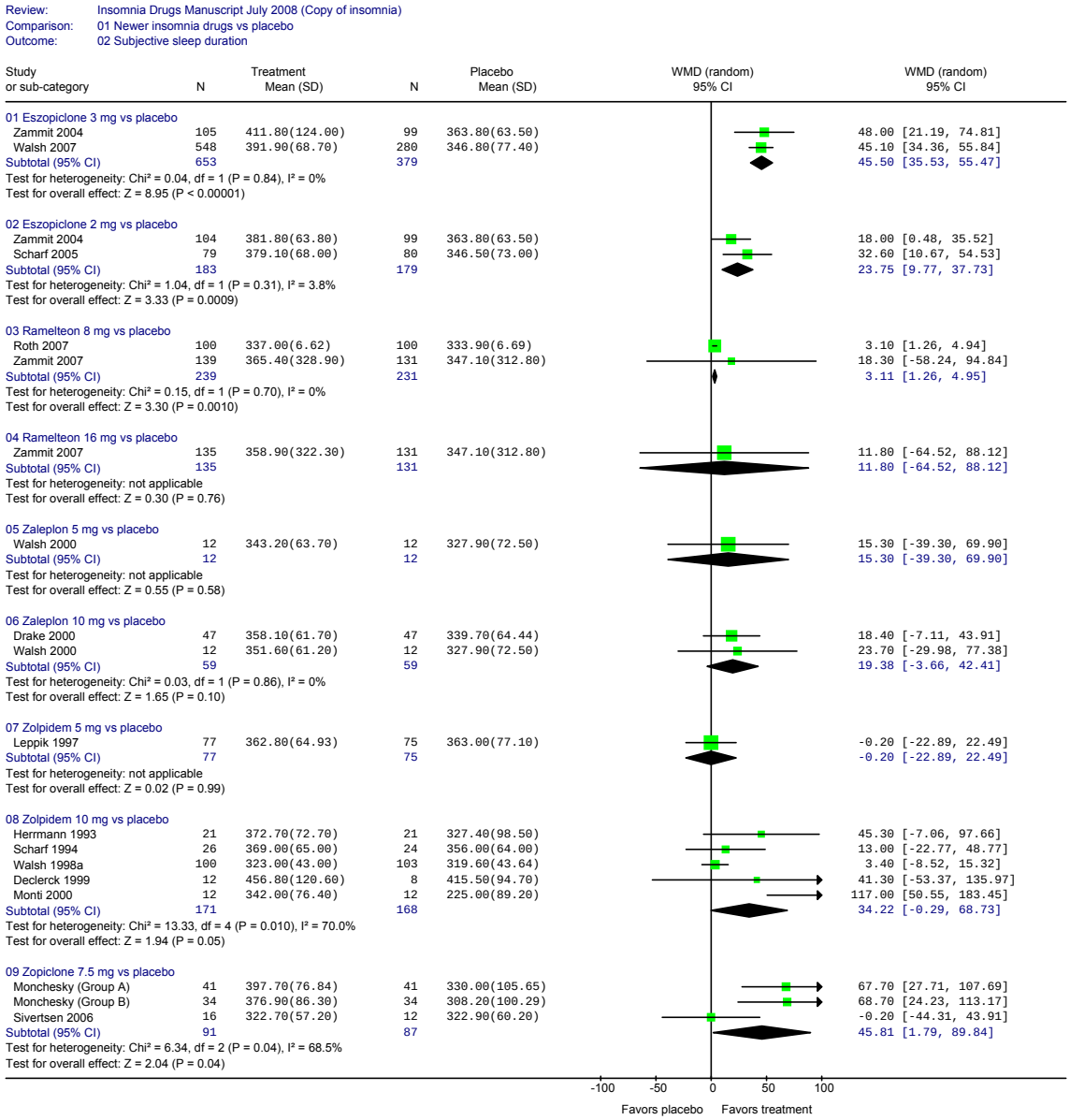


Sleep duration

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

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

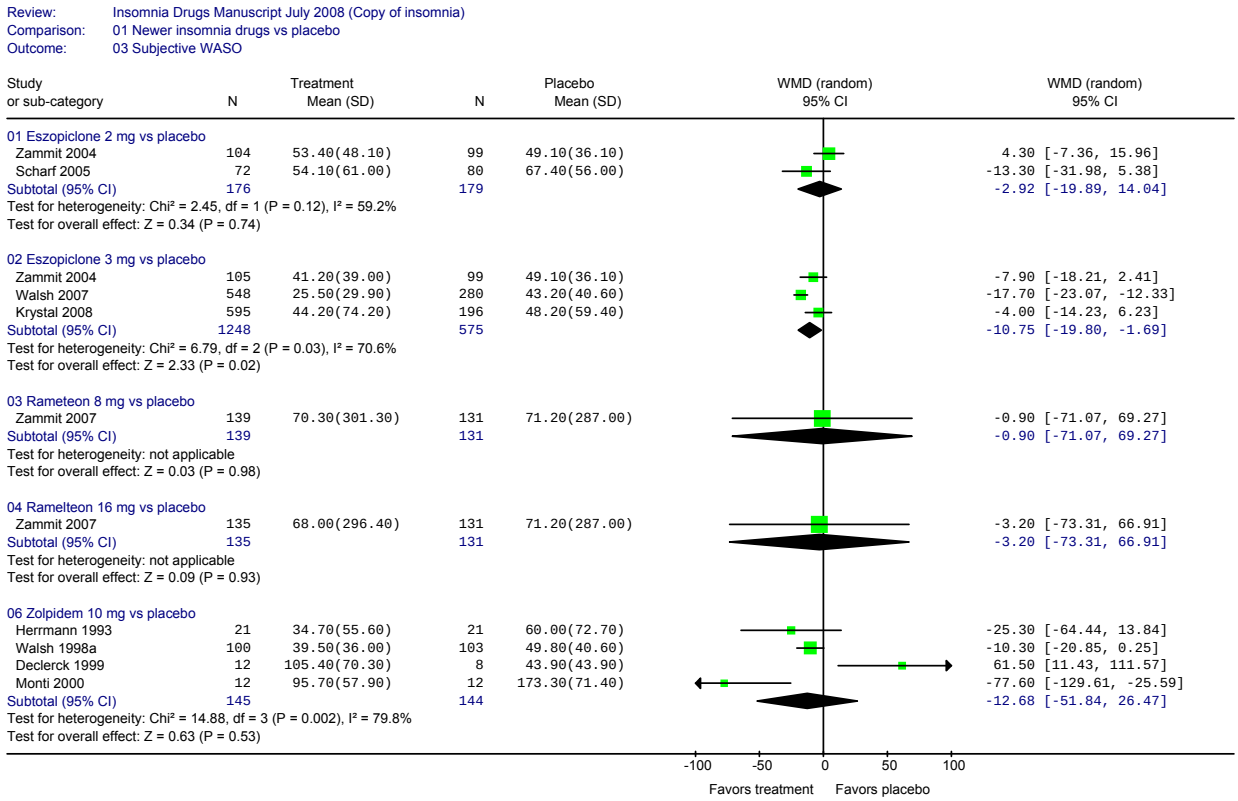
Figure 3. Subjective sleep duration in placebo-controlled trials of newer insomnia drugs



Subjective wake time after sleep onset

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

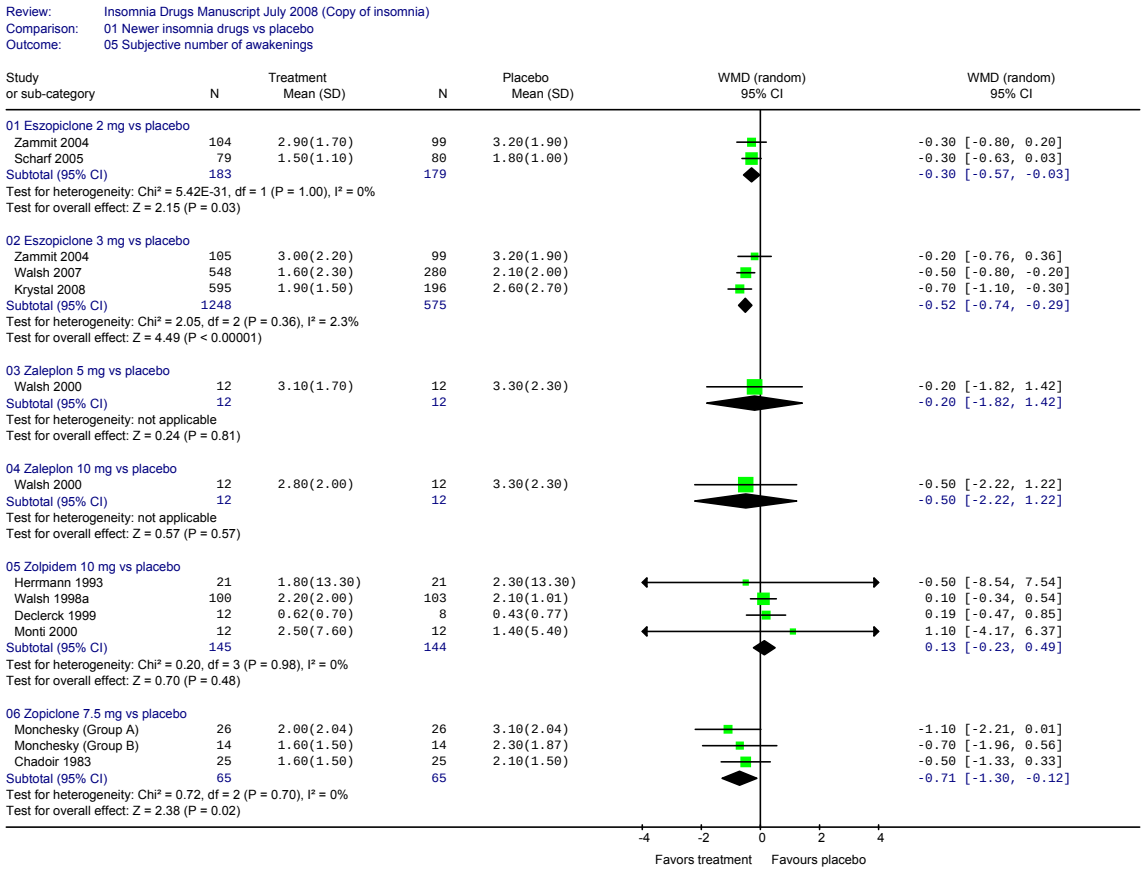
Figure 4. Subjective wake time after sleep onset in placebo-controlled trials of newer insomnia drugs



Subjective number of awakenings

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

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



Results of adjusted indirect meta-analysis

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

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

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

[a] Statistically significant results are in boldface type.

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

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

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

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

[a] Statistically significant results are in boldface type.

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

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

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

PSG-measured outcomes in trials of ramelteon

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

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

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

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

Zolpidem extended-release

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

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

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

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

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

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

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

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

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

Summary of the Evidence

Direct evidence

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

Indirect evidence

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

Detailed Assessment

Direct evidence

Eszopiclone compared with zolpidem

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

Zaleplon compared with zolpidem

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

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

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

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

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

Zolpidem compared with zopiclone

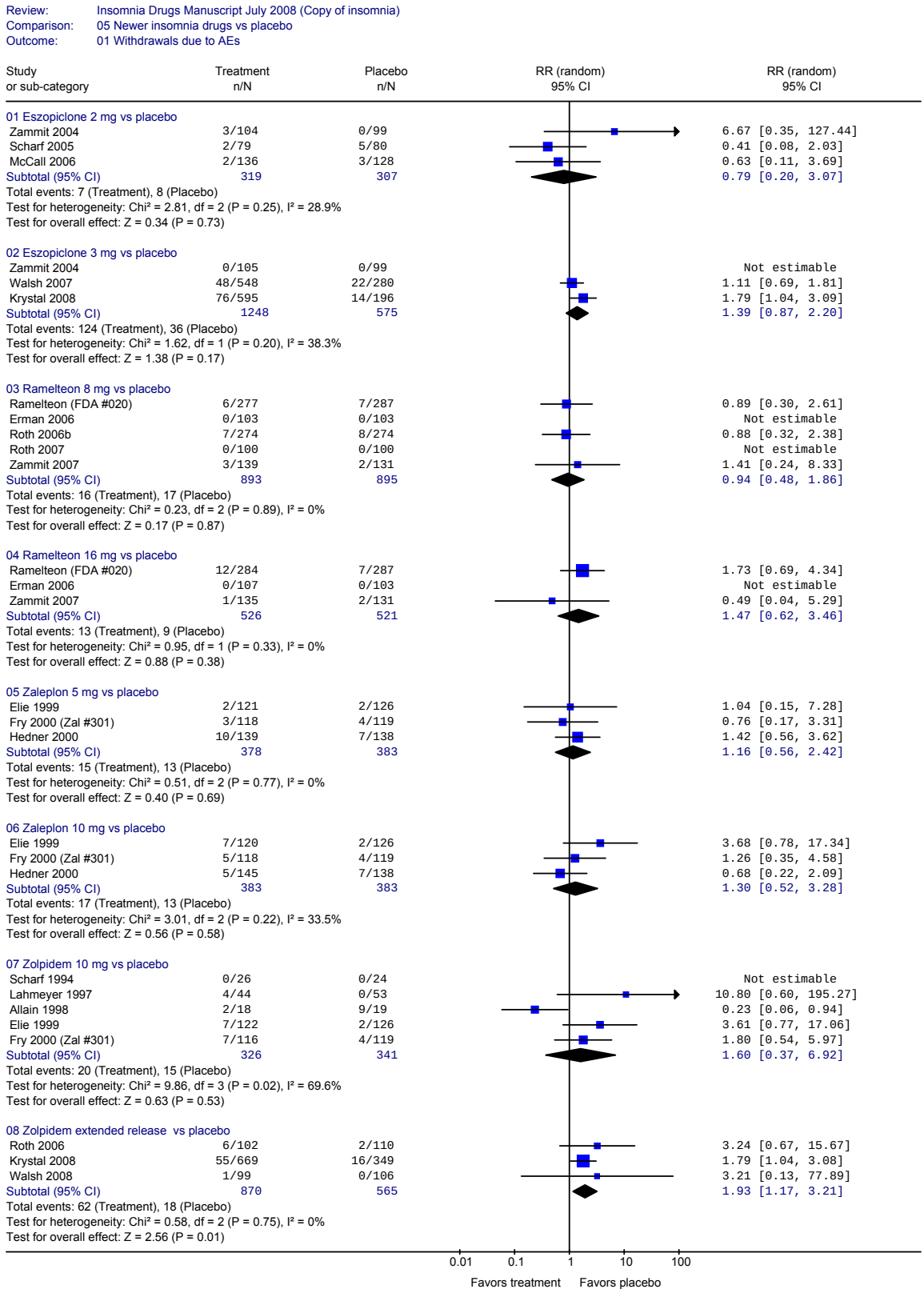
Zolpidem was compared with zopiclone in a study designed to measure withdrawal effects.[13] This was not a head-to-head trial, but 2 trials with the same design conducted simultaneously. The comparison in each trial was the effect of withdrawing treatment compared with continuing treatment. During the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

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

Indirect evidence

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

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



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

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

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

Newer insomnia drugs compared with benzodiazepines

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

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

Zolpidem

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

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

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

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

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

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

Zaleplon

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

Zopiclone

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

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

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

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

Newer insomnia drugs compared with trazodone

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

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

Long-term safety

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

Eszopiclone

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

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

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

Zaleplon

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

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

Zolpidem

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

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

Zolpidem extended-release

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

Zopiclone

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

Abuse and dependence

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

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

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

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

Case reports

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

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

Summary of the Evidence

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

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

Detailed Assessment

Older adults

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

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

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

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

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

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

Pregnancy

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

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

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

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

Comorbid conditions

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

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

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

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

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

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

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

SUMMARY

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

Table 11. Summary of the evidence by key question

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

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

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

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Appendix A. Literature search strategies

Newer Drugs for Insomnia included interventions:

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

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

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

Search Strategy:

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

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

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

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

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

For Controlled Trials

Assessment of Internal Validity

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

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

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

Not reported

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

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

Assessment of External Validity (Generalizability)

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

2. How many patients were recruited?

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

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

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

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

For Studies Reporting Complications, Adverse Effects, or Both

Assessment of Internal Validity

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

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

3. Were the investigated events specified and defined?

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

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

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

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

Assessment of External Validity

1. Was the description of the population adequate?

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

3. How many patients were recruited?

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

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

For Systematic Reviews

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

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

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

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

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

3. Is the validity of included studies adequately assessed?

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

Appendix C. Excluded studies

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

Codes:

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

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

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

Trials	Code
Besset A, Tafti M, Villemin E, Borderies P, Billiard M. Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers. *Drugs under Experimental and Clinical Research.* 1995;21(4):161-169.	6
Billiard M, Besset A, de Lustrac C, Brissaud L. Dose-response effects of zopiclone on night sleep and on nighttime and daytime functioning. *Sleep.* 1987;10(1):27-34.	4
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Excluded Studies	Code
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Appendix D. Summary of results of trials comparing newer insomnia drugs compared with benzodiazepines

(No new trials were identified for Update #2)

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

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

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

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

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

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Drug Class Review

Newer Drugs for Insomnia

Final Report Update 2
Evidence Tables

October 2008

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 about comparative effectiveness and safety profiles of different drugs within a pharmaceutical class. This report does not provide usage guidelines nor should it 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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Evidence Table 1. Characteristics of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Allain, 2003 (Fair)	Age between 40 and 65 years; with a clinical examination judged compatible with difficulties falling asleep, with previous history of recurrent episodes of insomnia and justifying the prescription of hypnotic treatment at the time of inclusion.	Current episode having lasted more than three weeks; any secondary insomnia resulting from medical or psychiatric causes; patients who followed a continuous treatment with the same hypnotic for more than six months; patients who took hypnotic drugs the day before inclusion; patients who took hypnotic drugs the day before inclusion, patients currently treated by zolpidem or zaleplon; night-shift work; current medical treatment including antidepressants, neuroleptics, anxiolytics, H1 antihistamines, barbiturates or hypnotics.	Mean age (SD): 52 (7); 49% female; Race/ethnicity: NR	NR/ NR/ 53	0/ 0/ 53	1 days	Zolpidem; Zaleplon; ; ;
Ancoli-Israel, 1999 (Fair)	Elderly (65 years or older) men and women who had at least a 3-month history of primary insomnia as defined by the DSM-IV at study entry. This history must have included a usual sleep latency of 30 minutes or more and either 3 or more awakenings per night on average or a usual total sleep time of <= 6.5 hours.	Preexisting medical condition that would affect the study results or if raw scores on the Zung Self-Rating Anxiety and Depression scales administered during screening were >=50. Patients were also excluded if they had sleep apnea or restless legs syndrome, if their sleep complaint was considered to be secondary to nicotine use, or if the study physician judged that results of physical examinations or routine clinical laboratory assessments included a clinically important abnormality.	Mean age (SD): 72 (5); 58% female; Race/ethnicity: 3.3% Black; 1.6% Hispanic; 1.3 Asian; 93.6% White	1224/ 551/ 549	2/ NR/ 549	2 weeks	Zaleplon 5 mg; Zaleplon 10 mg; Zolpidem 5 mg; Placebo;
							Zaleplon 5mg; Zaleplon 10mg; Zolpidem 5mg; Placebo;

Evidence Table 1. Characteristics of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Elie, 1999 (Fair)	Met criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on DSM-III-R; ages 18 to 65 years, men or nonpregnant women who were using a medically acceptable method of contraception, or postmenopausal women. During the month preceding study enrollment, patients must have experienced the following symptoms: a typical sleep latency of 30 minutes or longer, daytime impairment due to sleep disturbance, and either a mean total sleep duration per night of less than or equal to 6.5 hours or prolonged (at least 30 minutes) or frequent (3 or more per night) nocturnal awakenings with difficulty returning to sleep.	Transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder and patients whose raw score on either the Zung Self-Rating Anxiety Scale or the Zung Self-Rating Depression Scale was >49.	Mean age (SD): 42.8 (12.4); 64% female; Race/ethnicity: 99% white <1% black <1% Asian	NR/ NR/ 615	41/ NR/ 574	4 weeks	Zaleplon 5 mg; Zaleplon 10 mg; Zaleplon 20 mg; Zolpidem 10 mg; Baseline
							Zaleplon 5 mg; Zaleplon 10 mg; Zaleplon 20 mg; Zolpidem 10 mg; Placebo
							Zaleplon 5 mg; Zaleplon 10 mg; Zaleplon 20 mg; Zolpidem 10 mg; placebo
							Zaleplon 5mg; Zaleplon 10mg; Zaleplon 20mg; Zolpidem 10mg;

Evidence Table 1. Characteristics of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Fry, 2000 (Fair)	Men or non-pregnant women, 18-65 years who met the criteria for primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders based on the DSM-III-R. Women who were capable of becoming pregnant had to use a medically acceptable method of contraception. At initial screening, patients had to report having experienced the following symptoms frequently (at least 3 times per week, according to DSM-III-R) during the month preceding study enrollment: a typical sleep latency of 30 minutes or more, daytime impairment due to sleep disturbance, and either an average total sleep duration per night of 6.5 hours or less or prolonged (30 minutes or more) or frequent nocturnal awakenings (three or more per night) with difficulty returning to sleep.	Patients excluded if they experienced transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder, and patients whose raw score on either the Zung anxiety or depression self-rating scales was 50 or greater.	Mean age (SD): 42 (12); 59% female; Race/ethnicity: 11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Other; 84% White	NR/ 830/ 595	9/ NR/ 586	4 weeks	Zaleplon 5 mg; Zaleplon 10 mg; Zaleplon 20 mg; Zolpidem 10 mg; placebo
							Zaleplon 5mg; Zaleplon 10mg; Zaleplon 20mg; Zolpidem 10mg;
Lemoine, 1995 (Fair)	Males and females aged 18 to 65 years who were treated for insomnia for at least 3 months with zopiclone 7.5 mg or zolpidem 10 mg.	History of depression or other psychiatric disorder, a current depressive episode (total score on the QD2A questionnaire >=7) or any other current psychiatric disorder, severe and evolving physical illness, dementia, alcoholism, drug abuse, or acute pain. Patients were also excluded if they had been taking any psychotropic drug (with the exception of zopiclone or zolpidem) within the previous two weeks. Women were excluded if pregnant or were likely to be or were breast-feeding.	Mean age (SD): ( ); .% female; Race/ethnicity:	NR/ NR/ 394	15/ 2/ 390	s	; ; ;

Evidence Table 1. Characteristics of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
							:
Sepracor Study #190-045 Erman 2008 (Fair)	Patients aged 21 to 64 years with primary insomnia as defined by DSM-IV (<= 6.5 hours of sleep per night, and >= 30 minutes each night to fall asleep for at least one month), who also met the following screening PSG criteria: (1) sleep latency: at least 2 nights >= 20 minutes with none of 3 nights < 15 minutes, plus (2) either total sleep time: at least 2 nights <= 420 minutes, or (3) wake time after onset of persistent sleep (WASO): at least 2 nights >= 20 minutes with none of 3 nights < 15 minutes	Any clinically significant and/or unstable medical condition or chronic disease; DDM-IV Axis I or Axis II psychiatric illness or personality disorder; sleep apnea or restless legs syndrome/periodic leg movements disorder; history of substance abuse/dependence; use of any psychotropic, hypnotic, or other medications (including herbal supplements or melatonin) known to affect sleep; or use of other prescription or over-the-counter medications (including those containing caffeine, diphenhydramine, or ephedrine) known to affect sleep or to be contraindicated for use with hypnotics.	Mean age (SD): 40.6 (9.7); 25% female; Race/ethnicity: 44 (67.7%) white 13 (20.0%) black 3 (4.6%) Asian 5 (67.7%) Hispanic	NR/ NR/ 64	NR/ NR/ 64	2 days	Eszopiclone 1mg; Eszopiclone 2mg; Eszopiclone 2.5mg; Eszopiclone 3mg; Zolpidem

Evidence Table 1. Characteristics of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Tsutsui, 2001 (Fair)	Patients with chronic primary insomnia (I.e., experiencing non-restorative sleep or difficulty for more than a month in initiating or maintaining sleep), experiencing difficulties more than three times a week in sleeping.	Schizophrenia, depression, manic depression, clinically diagnosed diseases in the acute or exacerbation phase or with unstable symptoms, organic cerebral disorders (diagnosed or suspected), serious heart, liver, kidney, or blood disorders, severe respiratory dysfunction, myasthenia gravis or acute narrow-angle glaucoma and cognitive disorders or impaired intelligence. Symptoms interfering with sleep (e.g., pain, fever, diarrhea, pollakiuria, cough), hypersensitivity to benzodiazepines and analogous drugs, zopiclone intake within 3 months prior to the study, requirement for hypnotics at a dose exceeding the standard single dose, history of drug dependence, operation of machinery involving risk, pregnancy or likelihood of pregnancy, breast feeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.	Mean age (SD): 42.2 (12.7); 58% female; Race/ethnicity: NR	NR/ NR/ 479	77/ NR/ 428	2 weeks	Zolpidem; Zopiclone; ; ;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
Allain, 2003 (Fair)	Anxiety mean score	Zolpidem: 29.3; Zaleplon: 26.7; : ; : ; : ; P-value=0.34
	Behavior following wakefulness mean score (lower is better)	Zolpidem: 47.4; Zaleplon: 51.7; : ; : ; : ; P-value=0.31
	Consciousness mean score	Zolpidem: 73.9; Zaleplon: 73.1; : ; : ; : ; P-value=0.18
	Drowsiness duration (minutes)	Zolpidem: 43; Zaleplon: 38; : ; : ; : ; P-value=0.83
	Drowsiness mean score	Zolpidem: 28; Zaleplon: 27.7; : ; : ; : ; P-value=0.53
	Dynamism mean score	Zolpidem: 62.6; Zaleplon: 61.8; : ; : ; : ;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		P-value=0.47
	Ease of waking up mean score (lower is better)	Zolpidem: 43.6; Zaleplon: 43.8; : ; : ; : ; P-value=0.27
	Getting to sleep mean score (lower is better)	Zolpidem: 35.9; Zaleplon: 45.3; : ; : ; : ; P-value=0.03
	Mood mean score	Zolpidem: 21.6; Zaleplon: 20.1; : ; : ; : ; P-value=0.92
	Percentage of patients preferring a drug	Zolpidem: 62; Zaleplon: 38; : ; : ; : ; P-value=0.81
	Quality of sleep mean score	Zolpidem: 68.8; Zaleplon: 50.2; : ; : ; : ; P-value=<0.0001
	Quality of sleep mean score (lower is better)	Zolpidem: 30.6; Zaleplon: 44.3; : ; : ;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=<0.0001
Ancoli-Israel, 1999 (Fair)	Median sleep quality at week 1 (1=excellent, 7=extremely poor)	Zaleplon 5 mg: 3.83; Zaleplon 10 mg: 3.67; Zolpidem 5 mg: 3.50; Placebo: 4.00; : ; P-value=
	Median sleep quality at week 2 (1=excellent, 7=extremely poor)	Zaleplon 5 mg: 3.75; Zaleplon 10 mg: 3.63; Zolpidem 5 mg: 3.50; Placebo: 4.00; : ; P-value=
	Median subjective sleep latency (minutes) at week 1	Zaleplon 5 mg: ; Zaleplon 10 mg: ; Zolpidem 5 mg: ; Placebo: ; : ; P-value=
	Median subjective sleep latency (minutes) at week 2	Zaleplon 5 mg: 39; Zaleplon 10 mg: ; Zolpidem 5 mg: ; Placebo: 56; : ; P-value=
	Median subjective total sleep time at week 1	Zaleplon 5 mg: ; Zaleplon 10 mg: 345; Zolpidem 5 mg: 360; Placebo: 318; : ; P-value=
	Median subjective total sleep time at week 2	Zaleplon 5 mg: ; Zaleplon 10 mg: ; Zolpidem 5 mg: 360;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Placebo: 326; : ; P-value=
	Number of awakenings at week 1	Zaleplon 5 mg: 1.8; Zaleplon 10 mg: 1.8; Zolpidem 5 mg: 1.7; Placebo: 2.0; : ; P-value=
	Number of awakenings at week 2	Zaleplon 5 mg: 1.9; Zaleplon 10 mg: 1.7; Zolpidem 5 mg: 1.6; Placebo: 1.9; : ; P-value=
	rebound insomnia: number of awakenings on discontinuation day 1 (median)	Zaleplon 5mg: 2; Zaleplon 10mg: 2; Zolpidem 5mg: 2; Placebo: 2; : ; P-value=
	rebound insomnia: sleep duration, total sleep time on discontinuation day 1 (minutes, median)	Zaleplon 5mg: 330; Zaleplon 10mg: 315; Zolpidem 5mg: 300; Placebo: 317.50; : ; P-value=
	rebound insomnia: sleep latency on discontinuation day 1 (minutes, median)	Zaleplon 5mg: 30; Zaleplon 10mg: 45; Zolpidem 5mg: 60; Placebo: 44; : ; P-value=
Elie, 1999 (Fair)	Median number of awakenings at baseline	Zaleplon 5 mg: 2; Zaleplon 10 mg: 2;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zaleplon 20 mg: 2; Zolpidem 10 mg: 2; Baseline: 2; P-value=
	Median number of awakenings at week 1	Zaleplon 5 mg: 2; Zaleplon 10 mg: 2; Zaleplon 20 mg: 2; Zolpidem 10 mg: 2; Baseline: 2; P-value=
	Median number of awakenings at week 2	Zaleplon 5 mg: 2; Zaleplon 10 mg: 2; Zaleplon 20 mg: 2; Zolpidem 10 mg: 2; Baseline: 2; P-value=
	Median number of awakenings at week 3	Zaleplon 5 mg: 2; Zaleplon 10 mg: 2; Zaleplon 20 mg: 1; Zolpidem 10 mg: 2; Baseline: 2; P-value=
	Median number of awakenings at week 4	Zaleplon 5 mg: 2; Zaleplon 10 mg: 2; Zaleplon 20 mg: 1; Zolpidem 10 mg: 2; Baseline: 2; P-value=
	Median sleep duration at baseline (minutes)	Zaleplon 5 mg: 313; Zaleplon 10 mg: 331; Zaleplon 20 mg: 328; Zolpidem 10 mg: 330; Placebo: 334; P-value=
	Median sleep duration at week 1 (minutes)	Zaleplon 5 mg: 351;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zaleplon 10 mg: 370; Zaleplon 20 mg: 370; Zolpidem 10 mg: 379; Placebo: 351; P-value=
	Median sleep duration at week 2 (minutes)	Zaleplon 5 mg: 359; Zaleplon 10 mg: 368; Zaleplon 20 mg: 369; Zolpidem 10 mg: 387; Placebo: 359; P-value=
	Median sleep duration at week 3 (minutes)	Zaleplon 5 mg: 384; Zaleplon 10 mg: 371; Zaleplon 20 mg: 374; Zolpidem 10 mg: 385; Placebo: 365; P-value=
	Median sleep duration at week 4 (minutes)	Zaleplon 5 mg: 372; Zaleplon 10 mg: 384; Zaleplon 20 mg: 385; Zolpidem 10 mg: 400; Placebo: 377; P-value=
	Median time to sleep onset at week 2 (median, minutes)	Zaleplon 5 mg: 35; Zaleplon 10 mg: 32; Zaleplon 20 mg: 31; Zolpidem 10 mg: 37; placebo: 47; P-value=
	Median time to sleep onset at week 3 (median, minutes)	Zaleplon 5 mg: 31; Zaleplon 10 mg: 30; Zaleplon 20 mg: 28; Zolpidem 10 mg: 34; placebo: 41; P-value=

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	Median time to sleep onset at week 4 (median, minutes)	Zaleplon 5 mg: 31; Zaleplon 10 mg: 28; Zaleplon 20 mg: 27; Zolpidem 10 mg: 36; placebo: 36; P-value=
	Rebound: Number of awakenings on night +1 (median)	Zaleplon 5mg: 2.3; Zaleplon 10mg: 2.0; Zaleplon 20mg: 1.8; Zolpidem 10mg: 2.6; : ; P-value=
	Rebound: Sleep duration on night +1 (median, minutes)	Zaleplon 5mg: 344.3; Zaleplon 10mg: 349.6; Zaleplon 20mg: 339.2; Zolpidem 10mg: 324.7; : ; P-value=
	Rebound: Sleep latency on night +1 (median, minutes)	Zaleplon 5mg: 51.7; Zaleplon 10mg: 57.6; Zaleplon 20mg: 50.4; Zolpidem 10mg: 91.6; : ; P-value=
	Sleep quality mean score at baseline	Zaleplon 5 mg: 4.6; Zaleplon 10 mg: 4.5; Zaleplon 20 mg: 4.5; Zolpidem 10 mg: 4.4; Baseline: 4.5; P-value=
	Sleep quality mean score at week 1	Zaleplon 5 mg: 4.1; Zaleplon 10 mg: 3.9; Zaleplon 20 mg: 3.8; Zolpidem 10 mg: 3.7; Baseline: 4.1;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		P-value=
	Sleep quality mean score at week 2	Zaleplon 5 mg: 4.0; Zaleplon 10 mg: 3.9; Zaleplon 20 mg: 3.8; Zolpidem 10 mg: 3.6; Baseline: 3.9; P-value=
	Sleep quality mean score at week 3	Zaleplon 5 mg: 3.8; Zaleplon 10 mg: 3.8; Zaleplon 20 mg: 3.6; Zolpidem 10 mg: 3.6; Baseline: 3.9; P-value=
	Sleep quality mean score at week 4	Zaleplon 5 mg: 3.8; Zaleplon 10 mg: 3.7; Zaleplon 20 mg: 3.6; Zolpidem 10 mg: 3.4; Baseline: 3.8; P-value=
	Time to sleep onset at week 1 (median, minutes)	Zaleplon 5 mg: 42; Zaleplon 10 mg: 36; Zaleplon 20 mg: 33; Zolpidem 10 mg: 45; placebo: 50; P-value=
Fry, 2000 (Fair)	Number of awakenings at week 1 (median)	Zaleplon 5 mg: 1.93; Zaleplon 10 mg: 1.69; Zaleplon 20 mg: 1.75; Zolpidem 10 mg: 1.59; placebo: 1.71; P-value=
	Number of awakenings at week 2 (median)	Zaleplon 5 mg: 1.67; Zaleplon 10 mg: 1.69; Zaleplon 20 mg: 1.50; Zolpidem 10 mg: 1.50;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		placebo: 2.00; P-value=
	Number of awakenings at week 3 (median)	Zaleplon 5 mg: 1.71; Zaleplon 10 mg: 1.71; Zaleplon 20 mg: 1.43; Zolpidem 10 mg: 1.71; placebo: 1.86; P-value=
	Number of awakenings at week 4 (median)	Zaleplon 5 mg: 1.71; Zaleplon 10 mg: 1.57; Zaleplon 20 mg: 1.60; Zolpidem 10 mg: 1.67; placebo: 1.71; P-value=
	Sleep quality at week 1 (median)	Zaleplon 5 mg: 3.43; Zaleplon 10 mg: 3.57; Zaleplon 20 mg: 3.43; Zolpidem 10 mg: 3.38; placebo: 3.73; P-value=
	Sleep quality at week 2 (median)	Zaleplon 5 mg: 3.43; Zaleplon 10 mg: 3.57; Zaleplon 20 mg: 3.43; Zolpidem 10 mg: 3.29; placebo: 3.57; P-value=
	Sleep quality at week 3 (median)	Zaleplon 5 mg: 3.43; Zaleplon 10 mg: 3.43; Zaleplon 20 mg: 3.29; Zolpidem 10 mg: 3.29; placebo: 3.57; P-value=
	Sleep quality at week 4 (median)	Zaleplon 5 mg: 3.38; Zaleplon 10 mg: 3.54; Zaleplon 20 mg: 3.29;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zolpidem 10 mg: 3.15; placebo: 3.43; P-value=
	Time to sleep onset at week 1 (median, minutes)	Zaleplon 5 mg: 45.36; Zaleplon 10 mg: 40.71; Zaleplon 20 mg: 35.71; Zolpidem 10 mg: 45.71; placebo: 57.5; P-value=
	Time to sleep onset at week 2 (median, minutes)	Zaleplon 5 mg: 43.57; Zaleplon 10 mg: 36.43; Zaleplon 20 mg: 31.67; Zolpidem 10 mg: 46.43; placebo: 49.29; P-value=
	Time to sleep onset at week 3 (median, minutes)	Zaleplon 5 mg: 40.71; Zaleplon 10 mg: 35.71; Zaleplon 20 mg: 30.00; Zolpidem 10 mg: 44.29; placebo: 45.00; P-value=
	Time to sleep onset at week 4 (median, minutes)	Zaleplon 5 mg: 45.63; Zaleplon 10 mg: 35.00; Zaleplon 20 mg: 30.00; Zolpidem 10 mg: 34.29; placebo: 47.14; P-value=
	Total sleep time at week 1 (median, minutes)	Zaleplon 5 mg: 360.0; Zaleplon 10 mg: 360.6; Zaleplon 20 mg: 368.6; Zolpidem 10 mg: 377.1; placebo: 346.8; P-value=
	Total sleep time at week 2 (median, minutes)	Zaleplon 5 mg: 366.4; Zaleplon 10 mg: 364.3;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zaleplon 20 mg: 368.6; Zolpidem 10 mg: 384.4; placebo: 360.0; P-value=
	Total sleep time at week 3 (median, minutes)	Zaleplon 5 mg: 361.4; Zaleplon 10 mg: 377.1; Zaleplon 20 mg: 386.8; Zolpidem 10 mg: 392.1; placebo: 366.4; P-value=
	Total sleep time at week 4 (median, minutes)	Zaleplon 5 mg: 360.0; Zaleplon 10 mg: 376.3; Zaleplon 20 mg: 377.5; Zolpidem 10 mg: 392.9; placebo: 364.3; P-value=
	rebound : Number of awakenings on discontinuation night 1	Zaleplon 5mg: 2; Zaleplon 10mg: 2; Zaleplon 20mg: 2; Zolpidem 10mg: 2; : ; P-value=
	rebound : Sleep duration on discontinuation night 1 (median, minutes)	Zaleplon 5mg: 360; Zaleplon 10mg: 360; Zaleplon 20mg: 360; Zolpidem 10mg: 330; : ; P-value=
	rebound : Sleep latency on discontinuation night 1 (minutes, median)	Zaleplon 5mg: 45; Zaleplon 10mg: 40; Zaleplon 20mg: 30; Zolpidem 10mg: 60; : ; P-value=
Sepracor Study	daytime ability to function	Eszopiclone 1mg: 58.7;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
#190-045 (Fair)		Eszopiclone 2mg: 59.5; Eszopiclone 2.5mg: 54.1; Eszopiclone 3mg: 56.6; Zolpidem: 56.2; P-value=
		Eszopiclone 1mg: 58; Eszopiclone 2mg: 59; Eszopiclone 2.5mg: 51; Eszopiclone 3mg: 60; Zolpidem: 53; P-value=
	daytime alertness	Eszopiclone 1mg: 52.5; Eszopiclone 2mg: 55.2; Eszopiclone 2.5mg: 50.7; Eszopiclone 3mg: 52.2; Zolpidem: 55.8; P-value=
		Eszopiclone 1mg: 57; Eszopiclone 2mg: 56.5; Eszopiclone 2.5mg: 50; Eszopiclone 3mg: 56; Zolpidem: 27.7; P-value=
	depth of sleep	Eszopiclone 1mg: 46; Eszopiclone 2mg: 56.5; Eszopiclone 2.5mg: 53; Eszopiclone 3mg: 59.9; Zolpidem: 56.5; P-value=
	morning sleepiness	Eszopiclone 1mg: 42.3; Eszopiclone 2mg: 42; Eszopiclone 2.5mg: 45.3; Eszopiclone 3mg: 44.5; Zolpidem: 43.3; P-value=

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Eszopiclone 1mg: 43.8; Eszopiclone 2mg: 44.6; Eszopiclone 2.5mg: 44.7; Eszopiclone 3mg: 45.4; Zolpidem: 43.5; P-value=
	number of awakenings	Eszopiclone 1mg: 7.5; Eszopiclone 2mg: 6.5; Eszopiclone 2.5mg: 7.0; Eszopiclone 3mg: 5.3; Zolpidem: 7.5; P-value=
		Eszopiclone 1mg: 7.8; Eszopiclone 2mg: 7.6; Eszopiclone 2.5mg: 7.1; Eszopiclone 3mg: 6.5; Zolpidem: 7.2; P-value=
	quality of sleep	Eszopiclone 1mg: 47; Eszopiclone 2mg: 58; Eszopiclone 2.5mg: 55; Eszopiclone 3mg: 62; Zolpidem: 56; P-value=
	sleep efficiency (%)	Eszopiclone 1mg: 86.8; Eszopiclone 2mg: 88.9; Eszopiclone 2.5mg: 89.7; Eszopiclone 3mg: 89.2; Zolpidem: 88.8; P-value=
		Eszopiclone 1mg: 88.6; Eszopiclone 2mg: 89.6; Eszopiclone 2.5mg: 90.4; Eszopiclone 3mg: 92.0; Zolpidem: 89.1;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		P-value=
	sleep latency (min)	Eszopiclone 1mg: 16.8; Eszopiclone 2mg: 15.5; Eszopiclone 2.5mg: 13.8; Eszopiclone 3mg: 13.1; Zolpidem: 13.1; P-value=
		Eszopiclone 1mg: 25.2; Eszopiclone 2mg: 20.1; Eszopiclone 2.5mg: 18.6; Eszopiclone 3mg: 18.3; Zolpidem: 16.6; P-value=
	total sleep time (min)	Eszopiclone 1mg: 381.3; Eszopiclone 2mg: 412.5; Eszopiclone 2.5mg: 420.0; Eszopiclone 3mg: 420.0; Zolpidem: 410; P-value=
	wake after sleep onset (min)	Eszopiclone 1mg: 35.5; Eszopiclone 2mg: 30.5; Eszopiclone 2.5mg: 29.5; Eszopiclone 3mg: 25.3; Zolpidem: 30.5; P-value=
		Eszopiclone 1mg: 41.4; Eszopiclone 2mg: 36.0; Eszopiclone 2.5mg: 33.1; Eszopiclone 3mg: 35.9; Zolpidem: 39.3; P-value=
	wake time during sleep (min)	Eszopiclone 1mg: 28; Eszopiclone 2mg: 26; Eszopiclone 2.5mg: 25.3; Eszopiclone 3mg: 23.3;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zolpidem: 24.7; P-value=
Staner, 2005 (Poor)	Ideal route deviation	Zolpidem: -0.17; Zopiclone: -0.31; Lormetazepam: -0.15; Placebo: -0.18; : ; P-value=
	absolute speed deviation	Zolpidem: 123.3; Zopiclone: 122.8; Lormetazepam: 125.1; Placebo: 123.7; : ; P-value=
	awakening from sleep	Zolpidem: 66.1; Zopiclone: 62.6; Lormetazepam: 70.6; Placebo: 65.7; : ; P-value=
	behavior after waking	Zolpidem: 63.1; Zopiclone: 62.5; Lormetazepam: 69.2; Placebo: 63.7; : ; P-value=
	ease to get asleep	Zolpidem: 59.4; Zopiclone: 55.4; Lormetazepam: 55.0; Placebo: 45.8; : ; P-value=
	number of collisions	Zolpidem: 0.15; Zopiclone: 0.66; Lormetazepam: 0.37;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Placebo: 0.21; : ; P-value=
	sleep quality	Zolpidem: 68.8; Zopiclone: 74.5; Lormetazepam: 70.0; Placebo: 61.1; : ; P-value=
	speed limit deviation	Zolpidem: -5.7; Zopiclone: -5.9; Lormetazepam: -3.0; Placebo: -4.6; : ; P-value=
Tsutsui, 2001 (Fair)	Patients rated by the investigator as "markedly improved"	Zolpidem: 18.7; Zopiclone: 16.4; : ; : ; : ; P-value=NS
	Patients rated by the investigator as "moderately improved"	Zolpidem: 49.3; Zopiclone: 45.2; : ; : ; : ; P-value=NS
	Patients rated by the investigator as "slightly improved"	Zolpidem: 26.8; Zopiclone: 31.1; : ; : ; : ; P-value=NS
	Patients rated by the investigator as "unchanged"	Zolpidem: 5.3; Zopiclone: 6.4;

Evidence Table 2. Results of head-to-head trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=NS
	Patients rating the treatment as "ineffective"	Zolpidem: 5.7; Zopiclone: 5.5; : ; : ; : ; P-value=NS
	Patients rating the treatment as "markedly effective"	Zolpidem: 18.2; Zopiclone: 16.0; : ; : ; : ; P-value=NS
	Patients rating the treatment as "moderately effective"	Zolpidem: 46.4; Zopiclone: 45.2; : ; : ; : ; P-value=NS
	Patients rating the treatment as "slightly effective"	Zolpidem: 29.7; Zopiclone: 33.3; : ; : ; : ; P-value=NS
	rebound: patients with an aggravation of sleep onset latency by one grade or more at the end of followup	Zolpidem: 4.5; Zopiclone: 15.4; : ; : ; : ; P-value=0.005

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Allain, 1998 (Fair)	The subjects were suffering from chronic insomnia, being regularly treated with triazolam. They met the following criteria: male and female volunteers over 18 years of age; receiving out-patient treatment from a GP; taking triazolam (0.25 to 0.50 mg/day) for longer than one month.	Patients were not included if any of the following exclusion criteria applied: refusal to participate in the study or susceptible to non-compliance; shift workers; patients suffering from an identifiable mental disorder or treated fro their sleep disorder with hypnotics other than triazolam 0.25 mg/day; pregnant or breast feeding women; liver or respiratory failure, myasthenia, or epilepsy.	Mean age (SD): 51.9 (16.7); 0% female; Race/ethnicity: NR	NR/ NR/ 37	18/ NR/ 37	21 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Allain, 2001 (Fair)	Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterized by sleep disturbance and problems in falling asleep or nocturnal awakenings and resulting in difficulty in performing daytime functions, were eligible for inclusion in the study. In addition, patients were required to have a score of between 7 and 15 on the Epworth Sleepiness Scale. In order to be included in the double-blind phase of the study, patients must present insomnia as characterized by at least two of the following four criteria: sleep latency > 30 minutes, total sleep time > 3 hours and < 6 hours, number of awakenings > 3 per night and wake-time after sleep onset > 30 minutes per night.	Patients were excluded from the study if they were pregnant, breast feeding or were of child-bearing potential and not using an adequate method of contraception, or it they had desynchronisationtype sleep-wake rhythm disorders (such as jet-lag), parasomnia (for example somnambulism), anxiety (>4 on the covi scale), symptoms of depression (>6 on the Raskin scale), acute or chronic pain resulting in insomnia, severe psychiatric disturbances, were receiving treatment with psychotropic/sedative drugs, or had a severe medical condition or known hypersensitivity to imidazopyridine. They were also excluded if their lifestyle was expected to change, if they were suspected of drug/alcohol abuse, if they presented with excessive and abnormal daytime drowsiness, or if they were liable to present with known advance sleep apnoea syndrome. Patients who had received benzodiazepines regularly for more than one month, or for more that 15 days in the month prior to inclusion, were also excluded from the study, as were patients	Mean age (SD): 46.1 (10.5); 77% female; Race/ethnicity: NR	NR/ NR/ 245	NR/ NR/ 245	28 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Asnis, 1999 (?)	Men and women, 18 to 66 years of age, experiencing insomnia. All patients were required to meet DSM-iV criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder based on their psychiatrist's diagnosis or the interview with a study psychiatrist Patients were required to report persistent insomnia as characterized by a typical sleep latency of > 30 minutes, a typical nightly total sleep time of < 6.5 hours, or > 2 awakenings on a typical night and clinically significant daytime impairment. Patients with complaints of insomnia causing clinically significant distress and a reported total sleep time of less than 6.5 hours or reported sleep latency of at least 30 minutes for at least 3 of the previous 7 nights/days were randomly assigned to either zolpidem, 10 mg, or placebo.	Patients with HAM-D score of > 12, a history of suicide attempt or contemplation, or psychotropic medication treatment other than the SSRI or who were pregnant, lactating, or sexually active without approved contraception were also excluded. Patients with histories suggestive of insomnia secondary to any condition other than the depressive disorder or SSRI therapy (e.g. shift work, substance abuse, anxiety disorder), with history consistent with a diagnosis of restless legs or periodic limb movement syndromes, or with a medical condition likely to influence sleep were excluded.	Mean age (SD): NR (NR); 0% female; Race/ethnicity: NR	273/ NR/ 194	37/ 8/ 190	42 days	Zolpidem; Placebo; ; ;
Berry, 2006 (Fair)	Obese adult patients undergoing treatment of severe OSA (AHI>30/hr) with CPAP therapy for at least 6 months.	Difficulty tolerating CPAP, already on hypnotic medications, those with uncontrolled daytime sleepiness suggested by an Epworth Sleepiness Scale Score of greater than 12 and patients with a history of sedative dependance durng last 3 years.	Mean age (SD): 49.4 (12.4); 12% female; Race/ethnicity: NR	NR/ NR/ 16	NR/ NR/ 16	s	Zolpidem; Placebo; ; ;
						1 days	Zolpidem;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
							Placebo; ; ;
Chaudoir, 1983 (Poor)	The study was carried out in patients of both sexes aged between 35 and 65 years. The admission criterion was at least one of the following complaints--unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping less than six hours.	The exclusion criteria were patients with depression or an anxiety state requiring therapy, mental disability, liver or kidney dysfunction, cardiovascular disease for which medication was being received or with significant symptomatology (chest pains), gastro-intestinal disease, drug addiction or consumption of alcohol which would interfere with the assessment of the drug, or history of hypersensitivity to drugs. Patients receiving medication which was likely to induce sedation, patients requiring regular analgesia for the relief of chronic pain, night-shift workers, pregnant women, nursing mothers and women of child-bearing potential and patients weighing less than 7 stone or more than 14 stone were also excluded.	Mean age (SD): 50 (NR); 72% female; Race/ethnicity: NR	NR/ 30/ 25	5/ 0/ 25	7 days	Zopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Declerck, 1999 (Fair)	Patients, male and female aged between 30 and 75 years, were included in the study if they had complaints of insomnia and had been using benzodiazepine as a hypnotic drug in a therapeutic dosage for more than 4 days a week, for more than 3 months. A written statement of informed consent was obtained from each patient.	Exclusion criteria were complaints of excessive daytime sleepiness or an irregular sleep/wake schedule; a history of psychotic, severe affective or neurological illness: apparent cardiovascular, respiratory, hepatic or renal disorders; a history of drug or alcohol abuse; multiple benzodiazepine intake; intake of other psychotropic drugs with sedative side-effects, or of drugs that interfere pharmacokinetically with zolpidem. In addition, subject were excluded if they were pregnant or if there was any possibility of pregnancy before participation in the study.	Mean age (SD): 54 (NR); 77% female; Race/ethnicity: NR	NR/ NR/ 22	NR/ NR/ 20	7 days	Zolpidem; Placebo; ; ;
Dockhorn, 1996 (Fair)	Healthy patients who had experienced acute insomnia (3-9 nights) sue to a recent situational stress related to marriage, work, family, or financial matters were randomized. Insomnia was defined as a sleep duration of 4-6 h per night, a sleep latency of 30 min or more, and daytime complaints associated with disturbed sleep (thereby meeting the DSM-III-R definition of acute insomnia)	None of the patients had any significant psychiatric disorder, a history of insomnia within 2 months of the current episode, depression (criteria adapted from the DSM-III-R Criteria for Major Depression), recurrent thoughts of death or suicide, anxiety requiring treatment with anxiolytics, or a recent history of drug or alcohol abuse; none were regularly taking any medications that could interfere with the assessment of a hypnotics. Patients who normally slept on an unusual schedule (e.g., shift workers) and women who were lactating or at risk on pregnancy were excluded	Mean age (SD): 32.7 (NR); 58% female; Race/ethnicity: NR	NR/ NR/ 138	9/ 2/ 136	7-10 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Dorsey, 2004 (Fair)	Women aged 39 to 60 years were eligible to participate in the study if they had developed insomnia in temporal conjunction with menopausal symptoms. In addition, they had to have complaints of difficulty maintaining sleep or complaints of nonrestorative sleep for >6 months. Sleep maintenance difficult had to occur an average of >3 night per week and had to be accompanied by >2 nocturnal hot flashes, hot flushes, or night sweats. Participant also had to be in good mental and physical health, as determined by medical and psychiatric history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study onset.	Exclusion criteria included the presence of signs or symptoms of clinical depression, as ascertained by clinical interview and a Beck Depression Inventory score of > 10, or any other significant psychiatric disorder, based on DSM-IV criteria; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study onset; positive urine screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbiturates, opiates, cocaine, phenothiazines, amphetamines, and cannabinoids; a history of drug abuse/dependence or alcoholism; and a history of current symptoms of obstructive sleep apnea or periodic limb movement disorder.	Mean age (SD): 50.8 (4.5); 100% female; Race/ethnicity: NR	242/ 141/ 141	16/ 3/ 141	28 days	Zolpidem; Placebo; ; ;
Drewes, 1991 (Fair)	Sleep disorders in patients with fibromyalgia.	NR	Mean age (SD): NR (NR); 0% female; Race/ethnicity: NR	NR/ NR/ 45	4/ 0/ 41	84 days	Zopiclone; Placebo; ; ;
Drewes, 1998 (Fair)	All patients fulfilled the American Rheumatism Association criteria for RA and the protocol was approved by the local Ethics Committee. As sleep disturbance are thought to be an integral part of the	NR	Mean age (SD): 50.9 (9.4);	NR/	NR/	14 days	Zolpidem;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
	disease, patients were included whether or not they had subjective sleep		72% female; Race/ethnicity: NR	41/ 40	NR/ 40		Placebo; ; ;
							Zopiclone; Placebo; ; ;
Erman, 2006 (Fair)	Men and non-pregnant, non-lactating women between the ages of 18 and 64 years who had chronic insomnia were recruited. All pts met the following criteria: a diagnosis of primary insomnia (DSM-IV-TR) for at least three months, a subjective sleep latency (SSL) greater than 30 min, a subjective total sleep time (sTST) of less than 6.5 h per night, and daytime complaints associated with disturbed sleep; a mean LPS > 20 min for two consecutive PSG screening nights with neither night less than 15 min; a mean wake time after sleep onset (WASO) of at least 60 min for two consecutive PSG screening nights, with neither night less than 45 min; an habitual bedtime between 8:30 p.m. and midnight; and a body weight within 20% of the ideal, according to the Metropolitan Life Tables.	Pts were excluded from the study if their histories included a potential medical or psychiatric condition that could have confounded the study. Excluded conditions included depression, anxiety, seizure disorders, drug addiction, sleep apnea, nocturnal myoclonus, mental retardation, a history of alcohol abuse within the past two years, tobacco use within the past 90 days, or psychotropic drug use. Other exclusionary criteria included the use of St. John's wort or melatonin, or consumption of grapefruit or grapefruit juice within three weeks prior to the study. Shift workers and patients who had flown across three or more time zones within seven days prior to screening also were excluded, as were those with a history of hypersensitivity to ramelteon or related compounds.	Mean age (SD): 37.7 ( ); 64% female; Race/ethnicity: 54.7% Caucasian; 22.6 Hispanic; 21.7% Africa-American; 0.9% Asian	319/ 205/ 107	4/ 0/ 103	2 days	Ramelteon 4mg; Ramelteon 8mg; Ramelteon 16mg; Ramelteon 32mg; Placebo

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Fava, 2006 (Fair)	All patients were required to be 21 - 64 years old (inclusive) and meet DSM-IV criteria for MDD and for insomnia associated with MDD. The current depressive episode was required to have lasted 2 weeks to 6 months (inclusive), and the insomnia symptoms must not have predated the symptoms of MDD by more than 10 weeks. Additionally, patients were required to have a score of >= 14 after subtracting the three sleep-related item scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17; Hamilton 1960). Patients had to report total sleep time (TST) <= 6.5 hours, sleep latency >= 30 min, and wake time after sleep onset (WASO) >= 45 min per night at least three times per week for the preceding month. Finally, patients were required to either not be taking antidepressant medications at screening or to be taking a sub-therapeutic antidepressant dose with the approval of the investigator to taper the medication.	Patients were required to have not been receiving antidepressant medication for at least 14 days before randomization for all drugs except fluoxetine (35 days) and antipsychotic medications (30 days). Patients were additionally excluded if they: 1) had a known sensitivity to any selective serotonin reuptake inhibitor (SSRI), zopiclone, or eszopiclone; 2) were a significant suicide risk as determined by clinical interview; 3) had a previous episode of MDD that was refractory to treatment with an SSRI; 4) had a psychiatric or personality disorder that might compromise the ability to evaluate safety and efficacy of study medication; 5) had insomnia associated with another sleep disorder or had any condition that impacted or was likely to impact sleep; 6) had a history of drug or alcohol abuse or dependence in the previous 6 months or positive urine test at screening; or 7) had evidence of clinically unstable or uncontrolled serious medical conditions.	Mean age (SD): 41.0 ( ); 67% female; Race/ethnicity: Caucasian: 62.9% African American: 24.2% Other: 12.8%	985/ NR/ 545	172/ 50/ 373	8 weeks	Eszopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Goldenberg, 1994 (Poor)	Patients of either sex aged between 25 and 60 years were recruited to the study if they had suffered at least two of the following symptoms for between 2 to 12 weeks: sleep duration less than 6 hours per night, at least 2 nightly awakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.	The following exclusion criteria applied: depression or other psychiatric problems; alcohol or drug dependency; concurrent medication with CNS effects; history of allergy; acute or chronic illness affecting sleep; important negative life events (bereavement, divorce, unemployment, etc.) within the previous month; pregnancy or risk or pregnancy. Nursing mothers, and those performing skilled tasks, shift work or travelling frequently by air were also excluded from the study, as were those unable to complete the questionnaire or who were planning to go on holiday within the period of the trial.	Mean age (SD): NR (NR); .% female; Race/ethnicity: NR	NR/ NR/ 524	NR/ NR/ 458	44 days	Zopiclone; Placebo; ;
						48 days	Zopiclone; Placebo; ;
Gronblad, 1993 (Fair)	patients with primary fibromyalgia	NR	Mean age (SD): NR (NR); 0% female; Race/ethnicity: NR	NR/ 59/ 33	10/ NR/ 33	56 days	Zopiclone; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Hedner, 2000 (Fair)	This study evaluated patients of both sexes who were at least 65 years old and who had a history of insomnia of at least 3 months' duration. Inclusion to this study was also dependent on the absence of any significant psychiatric or central nervous system (CNS) disorder. Primary insomnia, based on criteria in the Diagnostic and Statistical Manual, 4th edition (DSM-IV; American Psychiatric Association, 1994), was characterized by a sleep latency of 30 minutes or more and either three or more awakenings per night or a total sleep time of 6.5 hours or less.	Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled.	Mean age (SD): 72.5 (NR); .% female; Race/ethnicity: NR	NR/ NR/ 437	22/ NR/ 422	14 days	Zaleplon 5mg; Zaleplon 10mg; Placebo; ;
Herrmann, 1993 (Poor)	For inclusion in the study, patients had to meet two of the following three polysomnographic criteria: (i) sleep onset latency of more than 30 min; (ii) total sleep time of less than 6 h or time awake more than 1 h; and (iii) five awakenings of at least 5 min each.	Other criteria were an absence of medical, psychiatric and organic mental disorders, and normal results on routine laboratory testing and on urine drug screening for amphetamines, cannabinoids, morphine derivatives, barbiturates and benzodiazepines. Patients presenting with caffeinism or alcoholism, or shift workers were excluded.	Mean age (SD): NR (NR); 43% female; Race/ethnicity: NR	NR/ 25/ 21	NR/ NR/ 21	14 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Hindmarch, 1995 (Fair)	patients aged between 25 and 60 years suffering from at least two of the following symptoms for two or more weeks: sleep duration less than 6 hours per night; at least 2 nightly awakenings; sleep onset latency of 30 minutes or more; and daily symptoms attributable to sleep disorders.	Depression or other psychiatric disorders, alcohol or substance dependency, concurrent medication with CNS effects, acute or chronic illness affecting sleep, important negative life events within the previous month, and pregnancy were considered as exclusion criteria.	Mean age (SD): 42.9 (8.9); 0% female; Race/ethnicity: NR	NR/ NR/ 458	NR/ NR/ 458	42 days	Zolpidem; Placebo; ;
						48 days	Zolpidem; Placebo; ;
Kryger (Fair)	Men and women aged 21-64 years with a diagnosis of mild [AHI =5 and <10 or moderate AHI = 10 and = 20] obstructive or mixed sleep apnea and a habitual bedtime between 8:30 p.m. and 12 a.m. and who reported sleeping more than 4 hour per night. Confirmatory AHI = 5 and = 20 per hour of sleep and an arterial blood oxygen saturation >80% during screenign night, did not have periodic leg movements with an arousal index of >20 per hour of sleep during screening night.	History of surgical intervention for sleep apnea or had used a continuous airway pressure device or dental appliance for sleep apnea within the preceeding 30 days. Known hypersensitivity to remelteon; a recent acute, clinically significant illness or hospitalization; uncontrolled systematic illness; hepatitis, recent use of sleep medications, recent sleep scheudle changes; a rcent history of psychiatric disorder or drug or alcohol abuse; history of seizure, COPD, restless leg syndrome, periodic leg movement disorder or other known sleep disorder or other known sleep disorders; or ther clinically important abnormal findings.	Mean age (SD): 47.4 (9.45); 69% female; Race/ethnicity: NR	NR/ NR/ 26	0/ 0/ 26	s	Ramelteon; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Krystal (Fair)	Male and female 18-64 years of age meeting criteria for chronic primary insomnia from the DSM-IV. History of 3 months of difficulty falling asleep, difficulty maintaining sleep, or experiencing nonrestorative sleep with reports of clinically significant impairment in social, occupational and other important areas of functioning, = h of wakefulness for at least 4 nights per week, over the past month, and to have spent >6.5 hrs, but <8.5 hrs/night in bed trying to sleep over the past 2 weeks.	Shift workers, napped more than 3 times per week, consuming >5 xanthine containing beverages per day as well as patients who had been using over the counter sleep remedies or prescription sleep medications within two weeks or 5 half-lives(whichever was longer) before screening. Use of any substance associated with effects on sleep-wake function within 1 week or 5 half-lives before screening not permitted. Primary hypersomnia, narcolepsy, breathing related sleep diroders, circadian rhythm sleep disorders, parasomnia, or dyssomnia not otherwise specified. Patients having current severe neuropsychiatric disorder (DSM IV), history of substance abuse or dependencewithin the past year, myasthenia gravis, severe respiratory insufficiency, any unstable medical condition, sensitivity to Zolpidem or its excipient were not entered into the study.	Mean age (SD): 45.7 (11.0); 61% female; Race/ethnicity: White: 662(65%) Black: 183 (18%) Asian/Oriental: 14 (1.4%) Other: 159(15.6%)	1701/ NR/ 1025	405/ 77/ 1016	24 weeks	Zolpidem; Placebo; ;
Krystal 2005 (poster)	DSM-IV diagnosis of chronic primary insomnia; Patient-reported average sleep time <=	NR	Mean age: 45.6 (range 21-64); 61% female;	NR/ NR/	350/ 80/	180 days	Eszopiclone; Placebo;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
	6.5 hrs/night and/or sleep latency >30 min		Race/ethnicity: Caucasian: 71% Black: 16% Hispanic: 13%	830	828		; ;
Krystal, 2003 (Fair)	Patients receiving a DSM IV diagnosis of primary insomnia and/or a usual sleep latency of more than 30 minutes each night for at least 1 month prior to screening were eligible for randomization, provided they did not (1) meet criteria for a DSM-IV Axis I psychiatric diagnosis other than primary insomnia, sexual and gender-identity disorders, or Axis II personality disorders (excluded by medical history); (2) have a history of substance abuse or substance dependence; (3) consume more than 2 alcoholic beverages per day or more than 14 per week; (4) use any psychotropic, hypnotic, or other medications known to infect sleep or to be contraindicated for use with hypnotics; (5) use over-the-counter analgesics that contain caffeine or herbal supplements, including products with herbs, melatonin, or St. John's Wort.	NR	Mean age (SD): 44 (11.3); 63.2% female; Race/ethnicity: 80% Caucasian 13.2% African American 7.9% other	1194/ 791/ 788	320/ 60/ 788	180 days	Eszopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Lahmeyer, 1997 (Fair)	Patients had to have a history of a minimum of 3 months of disturbed sleep, characterized by a typical sleep duration of between 4 and 6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints.	Patients were excluded if they: (a) had used any investigational drug (i.e. a drug still under clinical trial, prior to FDA approval) within 30 days of the start of the study; (b) had used alcohol or a short acting CNS medication within 1q year; (c) had a positive urine drug screen (for benzodiazepines, barbiturates, opiates and amphetamines) performed at screening-patients then took placebo for the first 3 mights of week 1; (d) had a history of exaggerated responses to benzodiazepines or other CNS depressants; (e) had been an illicit drug addict within the previous year; (f) had subjective symptoms of sleep apnoea; or (g) had nocturnal myoclonus or seizures. Patients who were shiftworkers and women who were breastfeeding were also excluded. In addition, patients with coexisting medical or psychiatric conditions (based on a prestudy evaluation of medical and sleep history, physical examination, vital signs, clinical and laboratory tests, ECG and urinalysis) were excluded from the study.	Mean age (SD): 44.9 (11.6); 56% female; Race/ethnicity: 92% Caucasian 6% black <1% Hispanic 1% Asian	178/ 33/ 145	27/ 0/ 118	31 days	Zolpidem 10mg; Zolpidem 15mg; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Lofaso, 1997 (Fair)	All included patients were subjects with UARS taken from a group of heavy snorers who complained of daytime tiredness and/or sleepiness.	Patients were excluded if physical examination, laboratory tests (serum creatinine and hepatic enzymes) electrocardiograph (ECG), vital capacity, or forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) were abnormal. Subjects with a current medical illness or a history of serious psychiatric disease or who were taking medication known to affect sleep or vigilance were excluded. Patients were also required to have a habitual consumption of more than four caffeine-containing beverages per day and to have no history of alcohol abuse. Beverages containing alcohol or caffeine were prohibited during the days of study.	Mean age (SD): 46 (9); 0% female; Race/ethnicity: NR	NR/ NR/ 8	NR/ NR/ 8	7 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
McCall 2006 (Fair)	Patients aged 64-86 years who met DSM-IV criteria for Insomnia and who self reported sleeping = 6.5 hrs per night and taking more than 30 mins to fall asleep each night for at least 1 month. A mean WASO of 20 mins or more, with no night<15 mins, a mean LPS of 20 mins or more with no night < 15 mins. Patients with comorbid conditions that were not expected to disrupt sleep were allowed if their disease was stable.	Patients were excluded if they had secondary insomnia or any condition that may have affected sleep (including sleep apnea). restless leg syndrome, periodic leg movement dosorder, chronic pain, severe COPD or advanced sleep phase syndrome, or if they used drugs known to affect sleep within 3 days, melatonin or any herbal supplements with alleged CNS effects within 14 days or ST. John's Wort within 30 days. Medical abnormalities or unstable chronic disease, medical or psychiatric disorder, a hisotry of significant hepatis or renal dysfunction or the use of any drugs affecting hepatic or renal clearance capacity within 30 days prior to dosing, or consumption of more than 2 alcoholic beverages daily.	Mean age (SD): 71.1 (range 64-86);	782/	9/	2 weeks	Eszopiclone;
			67% female; Race/ethnicity: 89.4% Caucasian 7.2% black 2.7% Hispanic 0.8% Asian	NR/ 264	NR/ NR		Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Moldofsky, 1996 (Fair)	Diagnosis of FM was based on the American College of Rheumatology criteria to diffuse myalgia, at least 11 to 18 tender points in specific anatomic regions, chronic fatigue, and nonrestful sleep of at least 3 months' duration. Patients had been assessed by an overnight polysomnography as part of their evaluation for FM and were found to have the alpha EEG NREM sleep abnormally.	Patients were excluded if they had a serious medical or psychiatric disorder or either sleep apnea or sleep related periodic involuntary limb movement disorder on polysomnography. Other reasons for exclusion included pregnancy or the potential of becoming pregnant; use of short acting central nervous system (CNS) medication, including alcohol or caffeine within 12 h of study entry; use of triazolam within 3 mights of the first treatment night; use of temazepam, flurazepam, and other intermediate or long acting hypnotics; use of analgesics (excluding ASA or acetaminophen), antidepressants, or psychotropic drugs within 14 nights of the first treatment; and a history of exaggerated response or hypersensitivity to the benzodiazepines or other CNS depressants. Otherwise, all patients were determined to be in good health based on a medical history, examination, electrocardiogram, and laboratory analyses of blood and urine samples.	Mean age (SD): 42 (2); .% female; Race/ethnicity: NR	NR/ 26/ 19	3/ 0/ 16	4 days	Zolpidem 5mg; Zolpidem 10mg; Zolpidem 15mg; Placebo;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Monchesky, 1986 (Fair)	Adults patients were enrolled who had suffered from insomnia for at least three months and met at least two of the following criteria: (1) sleep latency of 45 minutes or more, (2) more than three nightly awakenings with difficulty in falling asleep again, (3) early final morning awakening, and (4) total sleep time of usually less than five hours and always less than six hours.	Pregnancy and breast-feeding; concomitant use of neuroleptics, sedatives, analgesics, or antidepressants; a history of drug abuse or addiction; a history of serious psychiatric, hepatic, renal, or metabolic disorders; epilepsy; a known hypersensitivity to hypnotic drugs; abnormal liver or renal function; abnormal hemogram values; and an established diagnosis of sleep apnea	Mean age (SD): NR (NR); 0% female; Race/ethnicity: NR	NR/ NR/ 99	0/ 2/ 91	7 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Monchesky, 1989 (Fair)	Male and female shift workers between the ages of 22 and 55 were recruited from the General Motors of Canada assembly plant in Oshawa, Ontario, Canada. To be included in the study, participants had to alternate between a two-week day shift (07:00 to 15:30 h) and a two-week night shifts (18:00 to 02:30 h) for at least one year. In both cases, subjects worked from Monday to Friday. During each shift, two 10-min breaks, an 15-min "personal relief" pause and a 35-min lunch period were allowed. Shift workers had to present a history of insomnia of three or more consecutive day or night shifts characterized by at least three of the following four criteria: (a) a sleep latency of 30 min or more; (b) two or more nightly awakenings with difficulty in returning to sleep; (c) a total sleep time of < 6 h and (d) a poor quality of sleep. All participants gave written, informed consent to participate	Subjects previously receiving hypnotic medication were eligible to participate in this study provided the above criteria were met after a 4-d wash-out period. Females were excluded if they were pregnant, lactating or were not using a medically recognized contraceptive method. Subjects whose sleep performance was disrupted by external factors and those taking neuroleptics, sedatives, analgesics, anti-depressants, or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnia was considered secondary to a psychiatric or medical disorder were also excluded as were those with a history of alcoholism, drug abuse or caffeine overuse.	Mean age (SD): 34.9 (1.24); 6% female; Race/ethnicity: NR	NR/ NR/ 50	NR/ NR/ 50	12 days	Zopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Monti, 1996 (Fair)	All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.	Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.	Mean age (SD): 44.25 (4.8); 83% female; Race/ethnicity: NR	NR/ NR/ 12	NR/ NR/ 12	27 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Monti, 2000 (Poor)	Patients aged between 27 and 59 years, with chronic primary insomnia according to the DSM-IV participated in the study.	Patients with poor health, acute or chronic pain, decompensated hepatic, renal or cardiac disease, known drug allergy or abuse, periodic leg movements during sleep, restless legs or sleep apnea were excluded from the study, and so were pregnant women and breast-feeding mothers. Patients with poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac, or neuropsychiatric diseases [subjects with a score of HAMD > 18, or a score of HAMA(14 items)>16 were not included]; known drug allergy or abuse; periodic leg movements during sleep; restless legs; or sleep apnea were excluded from the study, as also were pregnancy women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with clinically significant deviations in their laboratory tests. Alcohol abuse, intake of hypnotics or anxiolytics in the seven days prior to baseline period, or a positive benzodiazepine urine screening also led to exclusion.	Mean age (SD): 51.9 (3.6); 100% female; Race/ethnicity: NR	NR/ NR/ 12	NR/ NR/ 12	15 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Parrino (Fair)	Hypnotic naïve subjects and met all criteria for diagnosis of primary sleep maintenance insomnia persisting for at least 1 month.	history of anxiety disorders, major depression critical medical condition, substance abuse or comcommitant treatment with psychoactive drugs. Sleep apnea, periodic limb movement and other sleep disorders	Mean age (SD): 32.8 (9); 50% female; Race/ethnicity: NR	NR/ NR/ 12	4/ 0/ 8	6 days	Zolpidem; Placebo; Zolpidem; Placebo;
Perlis, 2004 (Fair)	Patients aged 18 to 64 years were eligible for the study provided they met the DSM-IV criteria for primary insomnia and were deemed to be in good mental and physical health as ascertained by a medical history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study start.	Exclusion criteria included presence of any significant psychiatric disorder; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study start; positive urine screen for medication that could interfere with the assessment of study medication; history of drug addiction, alcoholism, or drug abuse; and history of or current symptoms compatible with sleep apnea or periodic leg movements during sleep. Additionally, female patients were ineligible if they were breastfeeding, pregnant, or not using double-barrier contraceptive methods.	Mean age (SD): 40.8 (12.7); 71% female; Race/ethnicity: 70% Euro American	322/ 277/ 199	10/ 3/ 192	84 days	Zolpidem; Placebo; ; ;
Roehrs (poster) (Fair)	DSM-IV-defined primary insomnia, WASO 1 hour per night for at least 3 nights per week during preceding month, and time in bed of 6.5 to 9 hours per night for 2 weeks prior to enrollment. A 2-night (screening) mean PSG WASO	Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.	Mean age (SD): 70.2 ( ); 57% female;	NR/ NR/	7/ NR/	21 days	Zolpidem MR; Placebo;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
	>= 40 minutes (not <30 minutes on either night), and total sleep time 3 to 7 hours each screening night was		Race/ethnicity: 95.1% Caucasian; 4.9% other	205	NR		; ;
Rosenberg (Fair)	Patients aged 35-64 years, wit mild to moderate OSAS (AHI range =10 and = 40) that required CPAP treatment. Patients had to have reported using CPAP most every night for atleast 3 months.	Severe OSAS patients, DSM-IV axis I psychiatric diagnosis other than sexual and gender identity disorders; known sensitivity to racemic zopiclone, or substance contained in the formulation; diagnosis of central sleep apnea syndrome; history of restless leg syndromeor periodic leg movement syndromeor any clinically significant unstable medical abnormality of the cardiovascular, respiratory, hepatic or renal systems. Tested positive for hepatitis B surface antigen or hepatitis C antibody; had a history of psychotropic medication use within 30 days prior to the study; had nay other condition that may have affected sleep; history of substance abuse in the previous 10 yrs, use of herbal supplements 14 days prior to screening or St John's Wort 30 days prior to screening, consumption of alcoholic beverages daily, rotating or third shift workder.	Mean age (SD): 48.4 (9.0); 32% female; Race/ethnicity: White: 72.7% Black: 18.2% Asian: 9.1%	41/ NR/ 22	1/ 0/ 21	2 days	Eszopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Roth ( )	Adults 18-64 years of age with primary insomnia, DSM-IV diagnosis of primary insomnia, reporting at least 1 hour of wakefulness at least 3 nights a wk over the preceding month and soent between 6.5 and 9 hrs in bed per night over the 2 preceding weeks, were invited to complete a 2 night PSG screen. Two night mean WASO of at least 30 mins and TST between 3 and 7 hour each screening night	DSM=IV axis I psychiatric disorderor any sleep disorder , circadian rhythm disorder, parasomnia or dyssomnia, having a history of substance abuse or dependence or lifestyle that precludes the diagnosis of primary insomnia, having received any other sleep medication within 2 weeks prior to screening or within 1 wk prior to screening having received any substance with CNS effects	Mean age (SD): 44.3 (13); 58% female; Race/ethnicity: Caucasian 90%	NR/ NR/ 212	20/ 1/ 212	21 days	Zolpidem; Placebo; ; ;
	At screening: 65 years or older , diagnosis of chronic primary insomnia and daytime impariment or distress associated wth disturbed sleep, BMI between 18-34 (inclusive) and a self reported habitual bedtime between 8:30 p.m. and 12:00 a.m. At randomization: mean LPS =20 mins on 2 nights with neither night <15 mins and a mean WASO =60 mins with a wake time =45 mins on each of the 2 nights.	Significant psychiatric or medical illness as determined by the investigator within 1 year of baseline; use of medicationns or supplements known to affect the sleep-wake cycle within 5 days of baseline; use of any other CNS active medications(other than ramelteon) including sleep aids and herbal preparations with CNS effects, within 3 weeks of baseline or who had flown across more than 3 time zones within 7 days of screening. At randomization: AHI>15 or periodic leg movements with arousal index >20 on PSG.	Mean age (SD): 70.7 ( ); 63% female; Race/ethnicity: Caucasian: 95% Asian:1% Hispanic:4% Black, Native American, Other: 0%	NR/ NR/ 100	0/ 0/ 100	9 weeks	Ramelteon 4mg; Ramelteon 8 mg; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
							Ramelteon 4mg; Ramelteon 8mg; Placebo; ;
Roth 2006 (Fair)	Age 65 years or older with a diagnosis of primary insomnia as defined by the DSM-IV-TR for at least 3 months, a reported sleep latency >=45 minutes, and a total sleep time <=6.5 hours per night for at least 3 nights during the week of the single-blind lead-in period. Body mass index must have been between 18 and 34, inclusive, and habitual bedtime must have been between 8:30 pm and 12:00 am. For subset of patients with severe sleep onset difficulties (sSL =60) receiving 8 mg or placebo were included in post hoc analysis	Patients could not have had any significant medical or psychiatric disorder or have used any medications that affected the central nervous system or sleep/wake function within 1 week (or 5 half lives, whichever is longer) prior to the first day of the placebo lead-in period.	Mean age (SD): 72.4 (72.4); 0% female; Race/ethnicity: Not reported	NR/ NR/ 829	128/ NR/ NR	5 weeks	Ramelteon 4 mg; Ramelteon 8 mg; Placebo; ;
Scharf, 2005 (Fair)	Men and women between the ages of 65 and 85 years who met the DSM-IV for primary insomnia and who reported sleeping 6.5 hours per night or less and took more than 30 minutes to fall asleep each night for at least 1 month	Patients with a prior history of allergies to zopiclone or any sedative hypnotic, history of severe chronic obstructive pulmonary disease, history of any condition that could interfere with the absorption of orally administered medicine, or prior participation in the investigational study less than 30 days prior to screening were	Mean age (SD): 72.3 (4.9); 58% female;	353/ NR/	21/ NR/	14 days	Eszopiclone 1mg; Eszopiclone 2mg;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
		excluded.	Race/ethnicity: 89.4% Caucasian 2.2% black 1.3% Hispanic	231	231		Placebo; ;
Schnitzer (poster) (?)	Subjects (aged 25-64) diagnosed with rheumatoid arthritis (RA)(as defined by the ACR) must have been on stable regimen for treatment of rheumatoid arthritis for a minimum of 90 days prior to Visit 2; Self-reported WASO of >= 45 minutes and TST <= 6.5 hours ar least three times a week over the previous month and symptoms of insomnia must have post-dated onset of rheumatoid arthritis;	NR	Mean age (SD): 52.1 ( ); 87% female; Race/ethnicity: Caucasian: 85.0% Black: 11.8% Hispanic: 3.2%	NR/ NR/ 153	11/ NR/ 153	4 weeks	Eszopiclone; Placebo; ; ;
Shaw, 1992 (?)	Patients of either sex, between ages of 65 and 85 years, who had been hospitalized for psychiatric conditions but who were without serious systematic medical conditions, were recruited. Patients with insomnia of at least 2 weeks' duration and fulfilling at least two of the following conditions were included: latency of onset of sleep greater than 30 min; awake for more than 1 h during the night; two or more waking periods during the night; and total sleep time of less than 6 h.	Exclusion criteria included: anaemia; significant cardiac, hepatic or renal dysfunction, or other serious medical condition; history of alcohol abuse; significant abnormalities in routine laboratory tests; and concomitant use of benzodiazepines or hypnotic drugs.	Mean age (SD): 74.5 ( ); 68% female; Race/ethnicity: NR	NR/ NR/ 119	9/ NR/ 119	21 days	Zolpidem 10mg; Zolpidem 20mg; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Soares 2006	Women aged 40-60 yrs who met DSM-IV criteria for insomnia in the context of menopausal transition, peri menopausal or early post menopausal with variable cycle length; late menopausal transition with two or more skipped cycles and an interval of amenorrhea for a period of upto 12 months. Additional criteria for insomnia defined as reported sleep latency 45 or more minutes and sleep duration 6 or few hours for greater than 3 times per week for 1 month	obstructive sleep apnea, history of substance abuse or dependence, consumption of more than 2 alcoholic beverages per day or 14 per week, use of prescription medications known to affect sleep , and the use of over the counter medication affecting sleep or mood. Patients with major depressive disorder or other other major Axis I psychiatric disorders.	Mean age (SD): 49 ( ); 100% female; Race/ethnicity: majority white	642/ NR/ 410	51/ 4/ 410	4 weeks	Eszopiclone; Placebo; ; ;
Soares (poster) (?)	Stages of Reproductive Aging Workshop (STRAW) Criteria: 1. Early Menopausal Transition (Stage-2); 2. Late Menopausal Transition (Stage-1); 3. Early post menopause (Stage+1a). Age 40-60 yrs. Sleep latency >= 45 min and sleep duration <= 6h, >= 3x/wk for 1 month; insomnia symptoms post-date onset of peri-menopausal symptoms, with no other cause of secondary insomnia	NR	Mean age (SD): 49.1 ( ); 100% female; Race/ethnicity: Caucasian: 77% Black: 15% Hispanic: 8%	NR/ NR/ 410	51/ NR/ 410	28 days	; ; ; ;
Soubrane (poster) (Fair)	DSM-IV-defined primary insomnia, WASO 1 hour per night at least 3 nights per week during the preceding month, and time in bed of 6.5 to 9 hours per night during the 2	Any DSM-IV Axis I psychiatric disorder, sleep disorder, history of substance abuse, use of any substance with CNS effects known to affect sleep, or use of over-the-counter or prescription sleep	Mean age (SD): 44.4 (13.0); 58% female;	NR/ NR/	20/ NR/	3 weeks	Zolpidem MR; Placebo;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
	hours per night during the 2 weeks prior to enrollment.	counter or prescription sleep medication within 1 and 2 weeks prior to screening, respectively.	Race/ethnicity: 90% Caucasian, 10% other	212	NR		; ;
Terzano, 1992 (Poor)	patients met the criteria for the diagnosis of persistent psychophysiological insomnia and self-reported at least two of the following complaints: difficulties in falling asleep, inadequate sleep length and frequent nocturnal awakenings.	patients had nocturnal myoclonus or sleep apnea syndrome	Mean age (SD): 49.6 (5.1); 67% female; Race/ethnicity: NR	NR/ NR/ 12	NR/ NR/ 12	1 days	Zolpidem; Placebo; ; ;
Walsh ( )	Patients between 65-87 years meeting DSM-IV-TR primary insomnia diagnostic criteria were eligible if they reported at least 1 hour of wakefulness after sleep onset at least 3 nights a week over the precding month and spent between 6.5-9 hours in bed per night over the 2 preceding weeks. WASO of at least 30 mins on each night with a mean WASO of at least 40 mins, a total sleep time of between 3 and 7 hours on each night	History of hypersensitivity to zolpidem or it's excipients, night shift workers consumer's of high amounts of xanthine-containing beverages and those with body mass index higher than 32. Presence of any other DSM-IV Axis I psychiatric disorders (including primary hypersomnia, narcolepsy, breathing related sleep disorder, circadian rhythm disorder, parasomnia, and dyssomnia), history of epilpesy, parasomnia and dissomnia), history of epilepsy, myasthenia gravis, evidence of any clinically significant, severe or unstable progressive, progressive, medical or surgical disorder, hisotry of substance abuse, lifestyle that precludes diagnosis of primary insomnia, use of sleep medication in the previous 2 weeks, concommitant use of any psychotropic drug or other substance known to affect sleep within the previous week.	Mean age (SD): 70.2 (4.5);	396/	7/	3 weeks	Zolpidem;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
			57% female; Race/ethnicity: White: 95.1% Other: 4.9%	NR/ 205	0/ 203		Placebo; ; ; ;
	Subjects age 21-65 years, meeting DSM-IV criteria for primary insomnia and reporting = 6.5 hours sleep and/or >30 mins to fall asleep on a typical night for at least the past month.	Unstable medical conditions, DSM-IV axis I or personality disorder diagnosis ; difficulty in sleep initiation or maintenance associated with known medical condition (e.g. sleep apnea, restless leg syndrome, chronic pain, BPH); hisotry of substance abuse or dependence . Patients had to be off of other insomnia medications at screening.	Mean age (SD): ( ); 0% female; Race/ethnicity:	1436/ NR/ 830	350/ 80/ 828	6 months	Eszopiclone; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Walsh, 2000a (Poor)	Males and female aged 60 to 80 years who reported sleep disturbance of > 3 months' duration with associated daytime impairment were eligible. Historical inclusion criteria included the following occurring three or more times each week: a subjective sleep latency of > 30 minutes and either > 3 awakenings per night (with difficulty returning to sleep) or a total sleep time between 180 and 360 minutes.	any chronic or recurrent medical illness considered to affect sleep or to potentially require medical attention or medication changes during the study was cause for exclusion. Additionally, patients with a present or past history of a major psychiatric illness [e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnoses of depressive or psychotic disorders, dementia or mental retardation] that was considered to influence sleep or study outcome were excluded. Additional exclusion criteria included a urine drug screen positive for drugs of abuse or sedative/hypnotic/anxiolytic agents; a history of severe adverse reactions to sedative hypnotics; bodyweight more than 5% below or more than 25% above Metropolitan Life Insurance Company standards; use of any medication with significant CNS effects within the prior 2 weeks (4 weeks for slowly eliminated drugs such as fluoxetine); or a history of drug/alcohol abuse within the past 12 months.	Mean age (SD): 67.5 (NR); 35% female; Race/ethnicity: NR	311/ 54/ 48	NR/ NR/ 48	2 days	Zaleplon 2mg; Zaleplon 5mg; Zaleplon 10mg; Placebo;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Walsh, 2000b, 2002 (Fair)	1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or total sleep time (TST) < 6.5 hours, and insomnia-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; bedtime and rise time varying by < 3 hours during baseline week. 4) negative pregnancy test, non breast-feeding and, continued contraceptive measures for women of child-bearing potential. 5) absence of a current medical condition, or current or past major psychiatric illness which may influence the study. 6) a Hamilton Depression Scale score < 8 (excluding sleep-related items). 7) no illicit drug use or excessive alcohol use or abuse in the past 12 months. 8) urine drug screen negative for any illicit drug or psychotropic medication. 9) no use of a prescription or non-prescription drugs that affect sleep-wake function within 7 to 25 days (depending on half life), or an investigational drug within 30 days. 10) smoking < 10 cigarettes per day.	NR	Mean age (SD): 44.1 (1.2); 71% female; Race/ethnicity: 83.4% Caucasian 16.6% other	365/ 163/ 163	29/ 5/ NR	56 days	Zolpidem; Placebo; ; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Zammit, 2004 (Fair)	Adults aged 21 years-64 years who met DSM-IV criteria for primary insomnia, and who additionally reported no more than 6.5 h of sleep per night and required more than 30 min to fall asleep each night for at least 1 month, were eligible for screening.	Patients with any unstable medical abnormality or acute illness, any pertinent drug sensitivities, abnormalities in drug metabolism, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, or sleep apnea were excluded.	Mean age (SD): 39.8 (11.7); 61% female; Race/ethnicity: 66.2% Caucasians 16.6% black 13% Hispanic 4.2% other	NR/ 669/ 308	16/ 0/ 308	44 days	Eszopiclone 2mg; Eszopiclone 3mg; ; ;
							Eszopiclone 2mg; Eszopiclone 3mg; Placebo; ;

Evidence Table 3. Characteristics of Placebo-controlled trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Number Screened Eligible Enrolled	Number Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Zammit, 2007 ( )	Adults with a diagnosis of primary insomnia (DSM-IV-TR) present at the time of evaluaton for at least 3 months, reporting an sSL of at least 30 minutes, an sTST of less than 6.5 hours, and daytime complaints associated with their disturbed sleep. Eligibilty in DB phase mean LPS=20 mins on the 2 nights of PSG monitoring, with an LPS of no less than 15 mins on either night, mean wake time =60 mins per night during the two nights of monitoring, with no less than 45 mins of wake time on either night	Participation in any previous studies of remelteon, had taken any other investigational drug within 30 days, or if they had sleep schedule changes associated with shift work or had taken a flight across more than 3 time zones in 7 days preceeding the initial screening. Medications known to affect sleep wake function must not have been taken within 5 days or 5 half-lives of the start of the study. History of sleep apnea, COPD, seizures, anxiety, depression, schizophrenia, bipolar disorder, mental retardation, cognitive disorder, significant neurological, hepatic, renal, endocrine, cardio vascular, gastro intestinal, pulmonary, hematologic, or metabolic diseases, history of drug addiction or abuse within 12 months of the study. At screening, subjects were excluded if they had apnea-hypoapnea index >10 or a periodic leg movement arousal index >10.	Mean age (SD): NR ( ); .% female; Race/ethnicity:	1078/ NR/ 405	38/ 1/ NR	5 weeks	Ramelteon 8mg; Ramelteon 16 mg; Placebo; ;
							Remelteon 8mg; Remelteon 16 mg; Placebo; ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
Allain, 1998	amount of sleep	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.0001
	anxiety	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.0003
	daytime alertness	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	energy	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.01
	less nightmare	Zolpidem: 93; Placebo: less; : ; : ; : ; P-value=<0.04
	number of awakenings	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	overall no different except day 21, where zolpidem was more effective, p<0.007	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	total sleep time (hr) at day 28	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	total sleep time (hr) at day 7	Zolpidem: 6.13; Placebo: 6.40; : ; : ; : ; P-value=NR
Allain, 2001	anxiety during the day (1=worse; 100=better), change from baseline	Zolpidem: -1.5; Placebo: -2.9; : ; : ; : ; P-value=0.55
	bodily pain, change from baseline	Zolpidem: 4.7; Placebo: 3.7; : ; : ; : ; P-value=NS
	daytime drowsiness (1=worse; 100=better), change from baseline	Zolpidem: -1.8; Placebo: -5.3; : ; : ; : ; P-value=0.048

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	daytime sleep duration (min), change from baseline	Zolpidem: -2.6; Placebo: -0.9; : ; : ; : ; P-value=NR
	efficacy index- when efficacy outseighs safety)	Zolpidem: 108; Placebo: 84; : ; : ; : ; P-value=0.0004
	general health perception, change from baseline	Zolpidem: 3.4; Placebo: 2.5; : ; : ; : ; P-value=NS
	general mental health, change from baseline	Zolpidem: 5.9; Placebo: 5.1; : ; : ; : ; P-value=NS
	global impression- much or very much improved	Zolpidem: 67; Placebo: 29; : ; : ; : ; P-value=<0.0001
	lucidity in the morning (1=worse; 100=better), change from baseline	Zolpidem: 2.9; Placebo: 2.3; : ; : ; : ; P-value=0.77

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	number of nocturnal awakenings, change from baseline	Zolpidem: -1.2; Placebo: -1.2; : ; : ; : ; P-value=<0.05
	physical function, change from baseline	Zolpidem: 2.5; Placebo: 2.7; : ; : ; : ; P-value=NS
	role limitations due to emotional problems, change from baseline	Zolpidem: 7.9; Placebo: -0.3; : ; : ; : ; P-value=NS
	role limitations due to physical problem, change from baseline	Zolpidem: 7.5; Placebo: 4.9; : ; : ; : ; P-value=NS
	sadness during the day (1=worse; 100=better), change from baseline	Zolpidem: -0.6; Placebo: -2.8; : ; : ; : ; P-value=0.30
	severity of illness- not ill to mildly ill	Zolpidem: 69; Placebo: 46; : ; : ; : ; P-value=0.002

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep onset latency (min), change from baseline	Zolpidem: -23; Placebo: -18.8; : ; : ; : ; P-value=<0.05
	sleep quality (1=worse; 100=better), change from baseline	Zolpidem: 14.1; Placebo: 20.6; : ; : ; : ; P-value=0.01
	social functioning, change from baseline	Zolpidem: 6.1; Placebo: 2.8; : ; : ; : ; P-value=NS
	total sleep time (min), change from baseline, all condition	Zolpidem: 74.6; Placebo: 63.2; : ; : ; : ; P-value=NS
	total sleep time (min), change from baseline, with pill	Zolpidem: 82.7; Placebo: 62.8; : ; : ; : ; P-value=<0.05
	vitality in the morning (1=worse; 100=better), change from baseline	Zolpidem: 9.1; Placebo: 9.6; : ; : ; : ; P-value=0.83

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	vitality, change from baseline	Zolpidem: 6.5; Placebo: 5.7; : ; : ; : ; P-value=NS
	wake time after sleep onset (min), change from baseline	Zolpidem: -32.8; Placebo: -31.4; : ; : ; : ; P-value=NR
Asnis, 1999	ease of falling asleep, change from baseline, withdrawal week, rebound	Zolpidem: -3.5; Placebo: -13; : ; : ; : ; P-value=0.013
	next-morning sleepiness, week 4	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.05
	non-insomnia, week 4	Zolpidem: -0.62; Placebo: -0.60; : ; : ; : ; P-value=0.695
	number of awakenings (%), change from baseline	Zolpidem: 38; Placebo: 18; : ; : ; : ; P-value=<0.05

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	number of awakenings , change from baseline, withdrawal week, rebound	Zolpidem: -0.43; Placebo: -0.66; : ; : ; : ; P-value=0.163
	patients with insomnia improvement of minimal or more	Zolpidem: more; Placebo: NR; : ; : ; : ; P-value=<0.05
	patients with insomnia of mild or less-than-mild severity	Zolpidem: more; Placebo: NR; : ; : ; : ; P-value=<0.05
	refreshed feeling	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.05
	sleep items, week 4	Zolpidem: -2.13; Placebo: -1.33; : ; : ; : ; P-value=<0.001
	sleep latency (min), change from baseline, withdrawal week, rebound	Zolpidem: -4.7; Placebo: -25.3; : ; : ; : ; P-value=0.027

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep latency, week 4	Zolpidem: 34; Placebo: 42.5; : ; : ; : ; P-value=0.079
	sleep quality (%), change from baseline	Zolpidem: 18; Placebo: 9; : ; : ; : ; P-value=<0.05
	sleep quality, change from baseline, withdrawal week, rebound	Zolpidem: -0.07; Placebo: -0.37; : ; : ; : ; P-value=0.04
	sleep-related daytime functioning	Zolpidem: better; Placebo: NR; : ; : ; : ; P-value=<0.05
	total score, change from baseline	Zolpidem: 12.0; Placebo: 2.9; : ; : ; : ; P-value=0.002
	total sleep time (min), change from baseline, average	Zolpidem: more; Placebo: NR; : ; : ; : ; P-value=<0.05

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	total sleep time (min), change from baseline, withdrawal week, rebound	Zolpidem: 0.6; Placebo: 26.3; : ; : ; : ; P-value=0.045
	total, week 4	Zolpidem: -2.75; Placebo: -1.99; : ; : ; : ; P-value=0.075
	wake after sleep onset (min), change from baseline, average	Zolpidem: -30; Placebo: -11; : ; : ; : ; P-value=<0.05
	wake after sleep onset (min), change from baseline, withdrawal week, rebound	Zolpidem: -9.6; Placebo: -16.6; : ; : ; : ; P-value=0.161
Berry, 2006	Arousal index, no./hr	Zolpidem: 16.5; Placebo: 19.0; : ; : ; : ; P-value=<0.03
	Sleep latency, mins	Zolpidem: 13.1; Placebo: 23.5; : ; : ; : ; P-value=<0.02

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Sleep period time, mins	Zolpidem: 434.2; Placebo: 428.3; : ; : ; : ; P-value=NS
	Total sleep time, mins	Zolpidem: 401.9; Placebo: 384.7; : ; : ; : ; P-value=NS
	WASO, mins	Zolpidem: 7.4; Placebo: 10.5; : ; : ; : ; P-value=NS
Chaudoir, 1983	feelings after awakening (VAS mm), 0=very badly; 100=very well	Zopiclone: 67; Placebo: 67; : ; : ; : ; P-value=NS
	feelings after wakening (VAS - mm), 0=very badly; 100=very well	Zopiclone: 59; Placebo: 59; : ; : ; : ; P-value=NS
	mood rating scales (mm) - factor I alertness	Zopiclone: 59; Placebo: 59; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	mood rating scales (mm) - factor II contentedness	Zopiclone: 61; Placebo: 63; : ; : ; : ; P-value=NS
	mood rating scales (mm) - factor III calmness	Zopiclone: 57; Placebo: 59; : ; : ; : ; P-value=NS
	number of night awakenings	Zopiclone: 1.5; Placebo: 2.1; : ; : ; : ; P-value=<0.05
		Zopiclone: 1.6; Placebo: 2.1; : ; : ; : ; P-value=NS
	percentage of patients with early awakenings (%)	Zopiclone: 44; Placebo: 56; : ; : ; : ; P-value=NS
	sleep onset latency (min)	Zopiclone: 28.6; Placebo: 45.2; : ; : ; : ; P-value=<0.05

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		Zopiclone: 31.1; Placebo: 49.1; : ; : ; : ; P-value=<0.001
	sleep quality (VAS - mm), 0=very badly; 100=very well	Zopiclone: 67; Placebo: 51; : ; : ; : ; P-value=<0.05
	sleep quality (VAS mm), 0=very badly; 100=very well	Zopiclone: 63; Placebo: 48; : ; : ; : ; P-value=<0.01
Declerck, 1999	anxiety	Zolpidem: 14.1; Placebo: 14.3; : ; : ; : ; P-value=0.25
	depression	Zolpidem: 22.4; Placebo: 23.3; : ; : ; : ; P-value=0.09
	number of awakenings, day 14	Zolpidem: 0.62; Placebo: 0.43; : ; : ; : ; P-value=0.96

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep latency time (min), day 14	Zolpidem: 89.6; Placebo: 92.3; : ; : ; : ; P-value=0.41
	sleep latency to stage 1 (min), day 14	Zolpidem: 15.3; Placebo: 48.8; : ; : ; : ; P-value=0.019
	total score	Zolpidem: 129.6; Placebo: 134.1; : ; : ; : ; P-value=0.39
	total sleep duration (min), day 14	Zolpidem: 340.5; Placebo: 324.1; : ; : ; : ; P-value=0.38
	total sleep time (min), day	Zolpidem: 456.8; Placebo: 415.5; : ; : ; : ; P-value=0.29
	wake time after sleep onset (min), day 14	Zolpidem: 105.4; Placebo: 43.9; : ; : ; : ; P-value=0.80

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
Dockhorn, 1996	ability to concentrate (1=excellent; 4=poor), day 3-10	Zolpidem: 2.3; Placebo: 2.4; : ; : ; : ; P-value=0.358
	change during posttreatment days- much or somewhat better	Zolpidem: 75; Placebo: 40; : ; : ; : ; P-value=0.002
	change in amount of sleep	Zolpidem: 79; Placebo: 43; : ; : ; : ; P-value=<0.001
	change in sleep- improved a lot or somewhat	Zolpidem: 84; Placebo: 48; : ; : ; : ; P-value=<0.001
	change in time to fall asleep	Zolpidem: 81; Placebo: 42; : ; : ; : ; P-value=<0.001
	ease of falling asleep (0=very easy; 100= not all easy), day 3-10	Zolpidem: 34.8; Placebo: 45.2; : ; : ; : ; P-value=0.004

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	morning sleepiness (0=very sleepy; 100=not at all sleepy), day 3-10	Zolpidem: 53.6; Placebo: 52.1; : ; : ; : ; P-value=0.762
	number of awakenings, day 3-10	Zolpidem: 0.8; Placebo: 1.2; : ; : ; : ; P-value=0.014
	quality of sleep (1=excellent; 4=poor), day 3-10	Zolpidem: 2.2; Placebo: 2.5; : ; : ; : ; P-value=0.007
	quality of sleep- excellent or good	Zolpidem: 78; Placebo: 42; : ; : ; : ; P-value=<0.001
	sleep latency (min), day 3-10	Zolpidem: 43.2; Placebo: 64.0; : ; : ; : ; P-value=0.001
	strength of medication- just right	Zolpidem: 62; Placebo: 28; : ; : ; : ; P-value=<0.001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	total sleep time (min), day 3-10	Zolpidem: 422.2; Placebo: 389; : ; : ; : ; P-value=0.054
	wake time after sleep onset (min), day 3-10	Zolpidem: 18.1; Placebo: 34.6; : ; : ; : ; P-value=0.008
Dorsey, 2004	average summary score (lower score=better sleep)	Zolpidem: 5.53; Placebo: 6.71; : ; : ; : ; P-value=
	change in sleep duration (min), 4 weeks average	Zolpidem: 56.5; Placebo: 20.5; : ; : ; : ; P-value=<0.01
	number of awakenings, 4 weeks average	Zolpidem: 1.4; Placebo: 2; : ; : ; : ; P-value=<0.05
	number of patients with better sleep	Zolpidem: 76.8; Placebo: 43.8; : ; : ; : ; P-value=<0.001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	quality of life	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	sleep latency (min), 4 weeks average	Zolpidem: 31.25; Placebo: 34.25; : ; : ; : ; P-value=NS
	sleep-related difficulty with daytime functioning	Zolpidem: 2.1; Placebo: 2.2; : ; : ; : ; P-value=<0.05
	wake after sleep onset (min), 4 weeks average	Zolpidem: 29.75; Placebo: 52.75; : ; : ; : ; P-value=<0.05
Drewes, 1991	awakenings at night (score), week 12	Zopiclone: 3.3; Placebo: 3.7; : ; : ; : ; P-value=NR
	condition in the morning (score), week 12	Zopiclone: 3.6; Placebo: 3.8; : ; : ; : ; P-value=NR

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	dreams (score), week 12	Zopiclone: 3.1; Placebo: 2.8; : ; : ; : ; P-value=NR
	duration of sleep (score), week 12	Zopiclone: 3.0; Placebo: 3.5; : ; : ; : ; P-value=NR
	feeling now (score), week 12	Zopiclone: -4.5; Placebo: -6.0; : ; : ; : ; P-value=NS
	feeling on waking (score), week 12	Zopiclone: -3.2; Placebo: -6.3; : ; : ; : ; P-value=NS
	general evaluation (score), week 12	Zopiclone: 2.9; Placebo: 3.5; : ; : ; : ; P-value=<0.05
	number of awakenings	Zopiclone: 36; Placebo: 62.5; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	pattern of awakening (score), week 12	Zopiclone: 2.9; Placebo: 0.2; : ; : ; : ; P-value=NS
	quality of sleep (score), week 12	Zopiclone: 14.5; Placebo: 1.7; : ; : ; : ; P-value=<0.05
		Zopiclone: 3.0; Placebo: 3.3; : ; : ; : ; P-value=NR
	sense of balance and coordination (score), week 12	Zopiclone: 1.9; Placebo: -0.4; : ; : ; : ; P-value=NS
	sleep onset latency (score), week 12	Zopiclone: 15.3; Placebo: 3.8; : ; : ; : ; P-value=<0.05
		Zopiclone: 2.5; Placebo: 3.2; : ; : ; : ; P-value=NR

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
Drewes, 1998	No. of awakenings <2 min, week 2	Zopiclone: 10.3; Placebo: 9.9; : ; : ; : ; P-value=
	No. of awakenings >2 min, week 2	Zopiclone: 2.7; Placebo: 2.3; : ; : ; : ; P-value=
	condition in the morning (score), week 2	Zopiclone: 3.2; Placebo: 2.9; : ; : ; : ; P-value=NR
	duration of sleep (score), week 2	Zopiclone: 3.3; Placebo: 3.1; : ; : ; : ; P-value=NR
	feeling now (score), week 2	Zolpidem: 50.0; Placebo: 60.2; : ; : ; : ; P-value=NS
	feeling on waking (score), week 2	Zolpidem: 50.8; Placebo: 51.7; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	frequency of awakenings (score), week 2	Zopiclone: 3.3; Placebo: 2.7; : ; : ; : ; P-value=NR
	frequency of dreams (score), week 2	Zopiclone: 4.3; Placebo: 3.9; : ; : ; : ; P-value=NR
	general evaluation of treatment on sleep (score), week 2	Zopiclone: 3.8; Placebo: 2.1; : ; : ; : ; P-value=<0.05
	pattern of awakenings (score), week 2	Zolpidem: 49.6; Placebo: 48.7; : ; : ; : ; P-value=NS
	quality of sleep (score), week 2	Zolpidem: 36.6; Placebo: 45.9; : ; : ; : ; P-value=<0.05
		Zopiclone: 3.6; Placebo: 3.0; : ; : ; : ; P-value=NR

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sense of balance and coordination	Zolpidem: 49.2; Placebo: 49.5; : ; : ; : ; P-value=NS
	sleep onset latency (score), week 2	Zolpidem: 37.8; Placebo: 49.8; : ; : ; : ; P-value=<0.05
		Zopiclone: 3.8; Placebo: 3.1; : ; : ; : ; P-value=NR
	wake after sleep onset (min), week 2	Zopiclone: 22.5; Placebo: 23.7; : ; : ; : ; P-value=
Erman, 2006	PSG latency to persistent sleep, min	Ramelteon 4mg: 24.0; Ramelteon 8mg: 24.3; Ramelteon 16mg: 24.0; Ramelteon 32mg: 22.9; Placebo: 37.7; P-value=
	PSG total sleep time, min	Ramelteon 4mg: 411.0; Ramelteon 8mg: 412.9; Ramelteon 16mg: 411.2; Ramelteon 32mg: 418.2; Placebo: 400.2; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	PSG wake after sleep onset (WASO), min	Ramelteon 4mg: 48.8; Ramelteon 8mg: 48.3; Ramelteon 16mg: 48.3; Ramelteon 32mg: 43.0; Placebo: 45.5; P-value=
	Subjective sleep latency, min	Ramelteon 4mg: 50.9; Ramelteon 8mg: 46.7; Ramelteon 16mg: 43.9; Ramelteon 32mg: 46.5; Placebo: 57.0; P-value=
	Subjective sleep quality	Ramelteon 4mg: 3.6; Ramelteon 8mg: 3.7; Ramelteon 16mg: 3.7; Ramelteon 32mg: 3.7; Placebo: 3.8; P-value=
	Subjective total sleep time, min	Ramelteon 4mg: 364.1; Ramelteon 8mg: 370.4; Ramelteon 16mg: 370.9; Ramelteon 32mg: 372.8; Placebo: 360.6; P-value=
	next day, ability to concentrate	Ramelteon 4mg: 3.5; Ramelteon 8mg: 3.5; Ramelteon 16mg: 3.5; Ramelteon 32mg: 3.6; Placebo: 3.6; P-value=
	next day, level of alertness	Ramelteon 4mg: 3.5; Ramelteon 8mg: 3.6; Ramelteon 16mg: 3.5; Ramelteon 32mg: 3.6; Placebo: 3.6; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
Fava, 2006	Bech subscale mean changed from clinician administered, week 4	Eszopiclone: -4.9; Placebo: -4; : ; : ; : ; P-value= 0.01
	Bech subscale mean changed from clinician administered, week 8	Eszopiclone: -6.8; Placebo: -5.9; : ; : ; : ; P-value= 0.01
	Bech subscale mean changed from patients report, week 4	Eszopiclone: -4.9; Placebo: -4.8; : ; : ; : ; P-value=0.91
	Bech subscale mean changed from patients report, week 8	Eszopiclone: -6.4; Placebo: -5.7; : ; : ; : ; P-value= 0.09
	HAM-D-17 mean changed excluding insomnia items from all patients, week 4	Eszopiclone: -6.7; Placebo: -6; : ; : ; : ; P-value= 0.16
	HAM-D-17 mean changed excluding insomnia items from all patients, week 8	Eszopiclone: -9.5; Placebo: -8.4; : ; : ; : ; P-value=0.04

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	HAM-D-17 mean changed excluding insomnia items from patients with more severe depression, week 4	Eszopiclone: -8.7; Placebo: -7; : ; : ; : ; P-value<0.05
	HAM-D-17 mean changed excluding insomnia items from patients with more severe depression, week 8	Eszopiclone: -12; Placebo: -10.1; : ; : ; : ; P-value=0.01
	HAM-D-17 mean changed in all items from all patients, week 4	Eszopiclone: -9.6; Placebo: -8; : ; : ; : ; P-value=0.01
	HAM-D-17 mean changed in all items from all patients, week 8	Eszopiclone: -12.9; Placebo: -10.9; : ; : ; : ; P-value=0.02
	HAM-D-17 mean changed in all items from patients with more severe depression, week 4	Eszopiclone: -12; Placebo: -9.1; : ; : ; : ; P-value=0.005
	HAM-D-17 mean changed in all items from patients with more severe depression, week 8	Eszopiclone: -16; Placebo: -12.7; : ; : ; : ; P-value=0.0007

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Sleep latency (min), week 1	Eszopiclone: 54.6; Placebo: 86.6; : ; : ; : ; P-value<0.0001
	Sleep latency (min), week 4	Eszopiclone: 30.0; Placebo: 60.0; : ; : ; : ; P-value<0.0001
	Sleep latency (min), week 8	Eszopiclone: 30.0; Placebo: 47.5; : ; : ; : ; P-value=0.0001
	TST (min), week 1	Eszopiclone: 360.0; Placebo: 292.5; : ; : ; : ; P-value=<0.0001
	TST (min), week 4	Eszopiclone: 390.0; Placebo: 334.3; : ; : ; : ; P-value=0.0001
	TST (min), week 8	Eszopiclone: 405.0; Placebo: 360.0; : ; : ; : ; P-value=0.0004

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	WASO (min), week 1	Eszopiclone: 30.0; Placebo: 48.0; : ; : ; : ; P-value<0.0001
	WASO (min), week 4	Eszopiclone: 15.0; Placebo: 2530; : ; : ; : ; P-value=0.002
	WASO (min), week 8	Eszopiclone: 8.8; Placebo: 26.7; : ; : ; : ; P-value<0.0001
Goldenberg, 1994	Activity	Zopiclone: 20; Placebo: 9.9; : ; : ; : ; P-value=<0.0001
	Global	Zopiclone: 10.8; Placebo: 5.7; : ; : ; : ; P-value=NS
	PGWBI	Zopiclone: 11.8; Placebo: 9.1; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Profession	Zopiclone: 23.3; Placebo: 12.9; : ; : ; : ; P-value=<0.01
	SEQ	Zopiclone: 14.6; Placebo: 2.7; : ; : ; : ; P-value=<0.0001
	Social	Zopiclone: 13.1; Placebo: 5.7; : ; : ; : ; P-value=<0.01
	feeling of well being during the day	Zopiclone: 1.3; Placebo: 0.8; : ; : ; : ; P-value=<0.0001
	physician's overall evaluation: average, good or excellent	Zopiclone: 187; Placebo: 125; : ; : ; : ; P-value=<0.0001
	quality of sleep	Zopiclone: 1.9; Placebo: 1.3; : ; : ; : ; P-value=<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	quality of waking up	Zopiclone: 1.5; Placebo: 1.0; : ; : ; : ; P-value=<0.0001
Gronblad, 1993	morning stiffness at week 4 - better	Zopiclone: 6; Placebo: 5; : ; : ; : ; P-value=NR
	morning stiffness at week 8 - better	Zopiclone: 8; Placebo: 7; : ; : ; : ; P-value=NR
	sleep score at week 4 - better	Zopiclone: 13; Placebo: 9; : ; : ; : ; P-value=NS
	sleep score at week 8 - better	Zopiclone: 11; Placebo: 9; : ; : ; : ; P-value=NS
Hedner, 2000	rebound insomnia: number of awakenings	Zaleplon 5mg: 7; Zaleplon 10mg: 4; Placebo: 7; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	rebound insomnia: subjective sleep latency	Zaleplon 5mg: 11; Zaleplon 10mg: 12; Placebo: 7; : ; : ; P-value=
	rebound insomnia: subjective total sleep time	Zaleplon 5mg: 14; Zaleplon 10mg: 17; Placebo: 6; : ; : ; P-value=
	rebound: subjective number of awakenings, withdrawal day 1	Zaleplon 5mg: 2; Zaleplon 10mg: 2; Placebo: 2; : ; : ; P-value=
	rebound: subjective sleep latency (min), withdrawal day 1	Zaleplon 5mg: 45; Zaleplon 10mg: 50; Placebo: 60; : ; : ; P-value=
	rebound: subjective total sleep time (min), withdrawal day 1	Zaleplon 5mg: 330; Zaleplon 10mg: 300; Placebo: 330; : ; : ; P-value=
	subjective number of awakenings, week 1	Zaleplon 5mg: 2; Zaleplon 10mg: 2; Placebo: 2; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	subjective number of awakenings, week 2	Zaleplon 5mg: 2; Zaleplon 10mg: 1; Placebo: 2; : ; : ; P-value=
	subjective sleep latency (min), week 1	Zaleplon 5mg: 43; Zaleplon 10mg: 40; Placebo: 60; : ; : ; P-value=
	subjective sleep latency (min), week 2	Zaleplon 5mg: 40; Zaleplon 10mg: 37; Placebo: 50; : ; : ; P-value=
	subjective sleep quality, improvement in sleep quality- week 1	Zaleplon 5mg: 48; Zaleplon 10mg: 55; Placebo: 36; : ; : ; P-value=
	subjective sleep quality, improvement in sleep quality- week 2	Zaleplon 5mg: 53; Zaleplon 10mg: 63; Placebo: 36; : ; : ; P-value=
	subjective sleep quality, week 1 (score). 1=excellent; 7=extremely poor	Zaleplon 5mg: 3.8; Zaleplon 10mg: 3.8; Placebo: 3.9; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	subjective sleep quality, week 2 (score). 1=excellent; 7=extremely poor	Zaleplon 5mg: 3.7; Zaleplon 10mg: 3.7; Placebo: 3.8; : ; : ; P-value=
	subjective total sleep time (min), week 1	Zaleplon 5mg: 342; Zaleplon 10mg: 342.9; Placebo: 346.1; : ; : ; P-value=
	subjective total sleep time (min), week 2	Zaleplon 5mg: 351.7; Zaleplon 10mg: 351.4; Placebo: 342.9; : ; : ; P-value=
Herrmann, 1993	calm/restless, fresh/fatigued, relaxed/anxious, lying down during the day	Zolpidem: multi-data; Placebo: multi-data; : ; : ; : ; P-value=NS
	no. of awakenings, day 15-21 treatment	Zolpidem: 1.8; Placebo: 2.3; : ; : ; : ; P-value=NS
	no. of awakenings, day 22-28 withdrawal, rebound	Zolpidem: 2.4; Placebo: 2.5; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep efficiency (%), day 21 treatment	Zolpidem: 86.2; Placebo: 78.3; : ; : ; : ; P-value=<0.05
	sleep efficiency (%), day 28 withdrawal, rebound	Zolpidem: 77.4; Placebo: 68.9; : ; : ; : ; P-value=<0.05
	sleep onset latency (min), day 15-21 treatment	Zolpidem: 40.5; Placebo: 72.8; : ; : ; : ; P-value=<0.05
	sleep onset latency (min), day 21 treatment	Zolpidem: 28; Placebo: 41.7; : ; : ; : ; P-value=NS
	sleep onset latency (min), day 22-28 withdrawal, rebound	Zolpidem: 60.8; Placebo: 70.8; : ; : ; : ; P-value=NS
	sleep onset latency (min), day 28 withdrawals, rebound	Zolpidem: 50.7; Placebo: 36.3; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	time awake (min), day 21 treatment	Zolpidem: 34.7; Placebo: 60; : ; : ; : ; P-value=NS
	time awake (min), day 28 withdrawal, rebound	Zolpidem: 53.7; Placebo: 99.3; : ; : ; : ; P-value=<0.05
	total sleep time (min), day 15-21 treatment	Zolpidem: 372.7; Placebo: 327.4; : ; : ; : ; P-value=NS
	total sleep time (min), day 21 treatment	Zolpidem: 381.3; Placebo: 360.3; : ; : ; : ; P-value=NS
	total sleep time (min), day 22-28 withdrawal, rebound	Zolpidem: 341.8; Placebo: 310.9; : ; : ; : ; P-value=NS
	total sleep time (min), day 28 withdrawal, rebound	Zolpidem: 341.3; Placebo: 298.3; : ; : ; : ; P-value=<0.05

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
Hindmarch, 1995	activity, change from baseline, day 14	Zolpidem: 20; Placebo: 9.9; : ; : ; : ; P-value=<0.0001
	activity, change from baseline, endpoint	Zolpidem: 21.6; Placebo: 14.2; : ; : ; : ; P-value=<0.0001
	global, change from baseline, day 14	Zolpidem: 10.8; Placebo: 5.7; : ; : ; : ; P-value=NS
	global, change from baseline, endpoint	Zolpidem: 13.8; Placebo: 8.9; : ; : ; : ; P-value=NS
	physician's overall evaluation of treatment efficacy as "excellent" or "good" at endpoint	Zolpidem: 76.7; Placebo: 51.4; : ; : ; : ; P-value=
	profession, change from baseline, day 14	Zolpidem: 23.3; Placebo: 12.9; : ; : ; : ; P-value=<0.01

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	profession, change from baseline, endpoint	Zolpidem: 24.5; Placebo: 18.7; : ; : ; : ; P-value=NS
	psychological general well-being index (PGWBI), change from baseline, day 14	Zolpidem: 11.8; Placebo: 9.1; : ; : ; : ; P-value=NS
	psychological general well-being index (PGWBI), change from baseline, endpoint	Zolpidem: 15.2; Placebo: 12.9; : ; : ; : ; P-value=NS
	sleep evaluation questionnaire (SEQ), change from baseline, day 14	Zolpidem: 14.6; Placebo: 2.7; : ; : ; : ; P-value=<0.0001
	sleep evaluation questionnaire (SEQ), change from baseline, endpoint	Zolpidem: 20.9; Placebo: 12.5; : ; : ; : ; P-value=<0.0001
	social, change from baseline, day 14	Zolpidem: 13.4; Placebo: 5.7; : ; : ; : ; P-value=<0.01

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	social, change from baseline, endpoint	Zolpidem: 14.9; Placebo: 9.1; : ; : ; : ; P-value=<0.01
Kryger	AHI-events per hour	Ramelteon: 11.4; Placebo: 11.1; : ; : ; : ; P-value=0.812
	Ability to concentrate	Ramelteon: 3.1; Placebo: 3.0; : ; : ; : ; P-value=0.920
	Awake time, mins	Ramelteon: 54.1; Placebo: 59.8; : ; : ; : ; P-value=
	Latency to persistant sleep (min)	Ramelteon: 17.0; Placebo: 22.5; : ; : ; : ; P-value=0.184
	Level of alertness	Ramelteon: 3.4; Placebo: 3.3; : ; : ; : ; P-value=0.633

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Number of awakenings	Ramelteon: 3.8; Placebo: 3.6; : ; : ; : ; P-value=
	Sleep Latency, mins	Ramelteon: 30.8; Placebo: 40.9; : ; : ; : ; P-value=0.067
	Sleep Quality- rated on 7 point likert scale	Ramelteon: 3.8; Placebo: 3.7; : ; : ; : ; P-value=0.668
	Sleep efficinecy	Ramelteon: 84.8; Placebo: 84.9; : ; : ; : ; P-value=0.899
	Total Sleep Time, mins	Ramelteon: 399.9; Placebo: 385.2; : ; : ; : ; P-value=0.120
	Total sleep time (min)	Ramelteon: 406.5; Placebo: 407.7; : ; : ; : ; P-value=0.856

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	WASO (mins)	Ramelteon: 8.2; Placebo: 7.7; : ; : ; : ; P-value=0.453
Krystal	Decrease in WASO at 6 months, mins	Zolpidem: 68; Placebo: 52; : ; : ; : ; P-value=<0.0001
	Decrease in number of nocturnal awakenings at 6 months	Zolpidem: 1.8; Placebo: 1.3; : ; : ; : ; P-value=0.0001
	Decrease in sleep onset latency at 6 months, mins	Zolpidem: 37.5; Placebo: 27.5; : ; : ; : ; P-value==0.0014
	Increase inTST at 6 months, mins	Zolpidem: 110; Placebo: 85; : ; : ; : ; P-value=0.0001
	Rebound effect on night 1-Increase in TST compared to baseline, mins in run-out period	Zolpidem: 17.7; Placebo: 55.8; : ; : ; : ; P-value=<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Rebound effect on night-2--Increase in TST compared to baseline, mins, run-out period	Zolpidem: 44.5; Placebo: 54.4; : ; : ; : ; P-value=0.2106
	Rebound effect on night-3-Increase in TST compared to baseline, mins, run-out period	Zolpidem: 42.9; Placebo: 49.8; : ; : ; : ; P-value=0.3969
	Rebound effect-decrease in WASO (mins), run out period, Day 1	Zolpidem: -21.1; Placebo: -42.2; : ; : ; : ; P-value=0.0010
	Rebound effect-decrease in WASO (mins), run out period, Day 2	Zolpidem: -31.4; Placebo: -36.9; : ; : ; : ; P-value=0.3648
	Rebound effect-decrease in WASO (mins), run out period, Day 3	Zolpidem: -35.9; Placebo: -38.3; : ; : ; : ; P-value=0.6543
Krystal 2005 (poster)	attention/concentration	Eszopiclone: 1.1; Placebo: 1.6; : ; : ; : ; P-value<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	daytime fatigue	Eszopiclone: 1.4; Placebo: 2.0; : ; : ; : ; P-value<0.0001
	feeling refreshed/rested	Eszopiclone: 2.3; Placebo: 1.8; : ; : ; : ; P-value<0.0001
	mood disturbance	Eszopiclone: 0.9; Placebo: 1.4; : ; : ; : ; P-value<0.0001
	number of awakenings, estimate from figures (data not reported) at month 1	Eszopiclone: 1.5; Placebo: 2.2; : ; : ; : ; P-value<0.0005
	number of awakenings, estimate from figures (data not reported) at month 6	Eszopiclone: 1.4; Placebo: 1.8; : ; : ; : ; P-value<0.0005
	relationship enjoyment	Eszopiclone: 0.7; Placebo: 1.0; : ; : ; : ; P-value<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep difficulties (nights/wk)	Eszopiclone: 3.4; Placebo: 5.1; : ; : ; : ; P-value<0.0001
	sleep latency, estimate from figures (data not reported) at month 1, min	Eszopiclone: 29; Placebo: 53; : ; : ; : ; P-value<0.0001
	sleep latency, estimate from figures (data not reported) at month 6, min	Eszopiclone: 25; Placebo: 42; : ; : ; : ; P-value<0.0001
	sleep quality	Eszopiclone: 2.5; Placebo: 1.7; : ; : ; : ; P-value<0.0001
	total sleep time, estimate from figures (data not reported) at month 1, min	Eszopiclone: 380; Placebo: 330; : ; : ; : ; P-value<0.0001
	total sleep time, estimate from figures (data not reported) at month 6, min	Eszopiclone: 380; Placebo: 330; : ; : ; : ; P-value<0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	wake time after sleep onset, estimate from figures (data not reported) at month 1, min	Eszopiclone: 18; Placebo: 33; : ; : ; : ; P-value<0.0001
	wake time after sleep onset, estimate from figures (data not reported) at month 6, min	Eszopiclone: 15; Placebo: 25; : ; : ; : ; P-value<0.0001
Krystal, 2003	daytime ability to function, month 6	Eszopiclone: 6.8; Placebo: 6.2; : ; : ; : ; P-value=<0.0001
	daytime alertness, month 6	Eszopiclone: 6.5; Placebo: 5.9; : ; : ; : ; P-value=<.0001
	number of awakenings, month 6	Eszopiclone: 1.9; Placebo: 2.6; : ; : ; : ; P-value=<0.0001
	number of night awakenings per week, month 6	Eszopiclone: 3.9; Placebo: 4.7; : ; : ; : ; P-value=0.0001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sense of physical well-being, month 6	Eszopiclone: 6.7; Placebo: 6.1; : ; : ; : ; P-value=0.0002
	sleep latency, month 6	Eszopiclone: 47.0; Placebo: 63.1; : ; : ; : ; P-value=<0.001
	sleep quality, month 6	Eszopiclone: 6.4; Placebo: 5.5; : ; : ; : ; P-value=<0.0001
	total sleep time, month 6	Eszopiclone: 378.3; Placebo: 339.3; : ; : ; : ; P-value=<0.001
	wake after sleep onset, month 6	Eszopiclone: 44.2; Placebo: 48.2; : ; : ; : ; P-value=0.0032
Lahmeyer, 1997	medication helped me - fall asleep faster	Zolpidem 10mg: 84; Zolpidem 15mg: 78; Placebo: 51; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	medication helped me - get a better night's sleep	Zolpidem 10mg: 84; Zolpidem 15mg: 84; Placebo: 49; : ; : ; P-value=
	medication helped me - sleep longer	Zolpidem 10mg: 78; Zolpidem 15mg: 76; Placebo: 51; : ; : ; P-value=
	medication strength - strong enough	Zolpidem 10mg: 71; Zolpidem 15mg: 72; Placebo: 44; : ; : ; P-value=
	medication strength - too strong	Zolpidem 10mg: 0; Zolpidem 15mg: 0; Placebo: 0; : ; : ; P-value=
	medication strength - too weak	Zolpidem 10mg: 29; Zolpidem 15mg: 28; Placebo: 56; : ; : ; P-value=
	number of awakenings - at week 4	Zolpidem 10mg: 1.4; Zolpidem 15mg: 1.2; Placebo: 1.7; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	number of awakenings - post-treatment	Zolpidem 10mg: 1.7; Zolpidem 15mg: 1.9; Placebo: 1.9; : ; : ; P-value=
	number of awakenings - 4 weeks average	Zolpidem 10mg: 1.3; Zolpidem 15mg: 1.3; Placebo: 1.9; : ; : ; P-value=
	sleep latency (min), change from baseline - at week 4	Zolpidem 10mg: -31; Zolpidem 15mg: -31; Placebo: -16; : ; : ; P-value=
	sleep latency (min), change from baseline - post-treatment	Zolpidem 10mg: -10; Zolpidem 15mg: -11; Placebo: -25; : ; : ; P-value=
	sleep latency (min), change from baseline - 4 weeks average	Zolpidem 10mg: -30; Zolpidem 15mg: -33.5; Placebo: -9; : ; : ; P-value=
	sleep quality (1=excellent; 4=poor) - at week 4	Zolpidem 10mg: 2.4; Zolpidem 15mg: 2.4; Placebo: 2.6; : ; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep quality (1=excellent; 4=poor) - post-treatment	Zolpidem 10mg: 2.8; Zolpidem 15mg: 2.9; Placebo: 2.8; : ; : ; P-value=
	sleep quality (1=excellent; 4=poor) - 4 weeks average	Zolpidem 10mg: 2.4; Zolpidem 15mg: 2.4; Placebo: 2.8; : ; : ; P-value=
	total sleep time (min) - at week 4	Zolpidem 10mg: 390; Zolpidem 15mg: 385; Placebo: 360; : ; : ; P-value=
	total sleep time (min) - post-treatment	Zolpidem 10mg: 354; Zolpidem 15mg: 332; Placebo: 359; : ; : ; P-value=
	total sleep time (min) - 4 weeks average	Zolpidem 10mg: 379; Zolpidem 15mg: 381; Placebo: 346; : ; : ; P-value=
Lofaso, 1997	multiple sleep latency data (min)	Zolpidem: 14.8; Placebo: 10.3; : ; : ; : ; P-value=<0.01

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep onset latency (min)	Zolpidem: 11; Placebo: 34; : ; : ; : ; P-value=NS
	sleep onset latency/total in bed (%)	Zolpidem: 91; Placebo: 84; : ; : ; : ; P-value=<0.05
	total sleep time (min)	Zolpidem: 421; Placebo: 399; : ; : ; : ; P-value=NS
	wake after sleep onset (min)	Zolpidem: 34; Placebo: 37; : ; : ; : ; P-value=NS
McCall 2006	Awakenings/night- mean change from baseline	Eszopiclone: -0.7; Placebo: -0.5; : ; : ; : ; P-value=0.009
	Mean change from baseline WTDS, mins	Eszopiclone: -25.3; Placebo: -11.6; : ; : ; : ; P-value=0.004

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Mean change from baseline in LPS, mins	Eszopiclone: -33.5; Placebo: -17.0; : ; : ; : ; P-value=<0.001
	Mean change from baseline, WASO, mins	Eszopiclone: -25.3; Placebo: -12.5; : ; : ; : ; P-value=0.013
	Mean no. of awakenings/night change from baseline	Eszopiclone: -0.8; Placebo: -0.5; : ; : ; : ; P-value=0.805
	Sleep efficiency-mean change from baseline	Eszopiclone: 11.7; Placebo: 5.8; : ; : ; : ; P-value=<0.001
	Sleep latency, mins mean change from baseline	Eszopiclone: -40.8; Placebo: -29.6; : ; : ; : ; P-value=<0.001
	TST, mins, mean change from baseline	Eszopiclone: 56.2; Placebo: 27.6; : ; : ; : ; P-value=<0.001

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	TSTmins, mean change from baseline	Eszopiclone: 48.6; Placebo: 32.4; : ; : ; : ; P-value=<0.001
	WASO, mins, mean change from baseline	Eszopiclone: -31.3; Placebo: -24.5; : ; : ; : ; P-value=0.022
Moldofsky, 1996	number of awakenings (score)	Zolpidem 5mg: 2.3; Zolpidem 10mg: 1.7; Zolpidem 15mg: 2.0; Placebo: 2.7; : ; P-value=
	sleep improvement (score)	Zolpidem 5mg: 3.0; Zolpidem 10mg: 2.4; Zolpidem 15mg: 2.4; Placebo: 3.1; : ; P-value=
	sleep quality (score)	Zolpidem 5mg: 3.1; Zolpidem 10mg: 2.7; Zolpidem 15mg: 2.6; Placebo: 3.1; : ; P-value=
	time to fall asleep (score)	Zolpidem 5mg: 3.1; Zolpidem 10mg: 3.5; Zolpidem 15mg: 3.8; Placebo: 3.0; : ; P-value=

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	total sleep time (score)	Zolpidem 5mg: 2.7; Zolpidem 10mg: 2.5; Zolpidem 15mg: 2.8; Placebo: 3.3; : ; P-value=
Monchesky, 1986	duration of sleep (min), treatment day 14 (switch)	Zolpidem: 376.7; Placebo: 299.5; : ; : ; : ; P-value=NR
	duration of sleep (min), treatment day 7	Zolpidem: 384.8; Placebo: 307.4; : ; : ; : ; P-value=NR
	morning state of rest, treatment day 14 (switch)	Zolpidem: 2.9; Placebo: 2.15; : ; : ; : ; P-value=NR
	morning state of rest, treatment day 7	Zolpidem: 2.85; Placebo: 1.95; : ; : ; : ; P-value=NR
	number of awakenings, treatment day 14 (switch)	Zolpidem: 2.0; Placebo: 2.45; : ; : ; : ; P-value=NR

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	number of awakenings, treatment day 7	Zolpidem: 1.8; Placebo: 3.5; : ; : ; : ; P-value=NR
	quality of sleep, treatment day 14 (switch)	Zolpidem: 4.35; Placebo: 2.95; : ; : ; : ; P-value=NR
	quality of sleep, treatment day 7	Zolpidem: 4.15; Placebo: 3.15; : ; : ; : ; P-value=NR
	sleep induction time (min), treatment day 14 (switch)	Zolpidem: 53.8; Placebo: 119.3; : ; : ; : ; P-value=NR
	sleep induction time (min), treatment day 7	Zolpidem: 51.85; Placebo: 89.9; : ; : ; : ; P-value=NR
	sleepiness during the day, treatment day 14 (switch)	Zolpidem: 2.3; Placebo: 2.9; : ; : ; : ; P-value=NR

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleepiness during the day, treatment day 7	Zolpidem: 2.3; Placebo: 2.65; : ; : ; : ; P-value=NR
	soundness of sleep, treatment day 14 (switch)	Zolpidem: 4.0; Placebo: 2.4; : ; : ; : ; P-value=NR
	soundness of sleep, treatment day 7	Zolpidem: 3.8; Placebo: 2.75; : ; : ; : ; P-value=NR
Monchesky, 1989	depression, anxiety, irritability	Zopiclone: multi-data; Placebo: multi-data; : ; : ; : ; P-value=NS
	morning equilibrium, day 12	Zopiclone: 9.3; Placebo: 9.4; : ; : ; : ; P-value=NS
	sleep duration (score), day 12	Zopiclone: 6.9; Placebo: 5.6; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep latency (score), day 12	Zopiclone: 8; Placebo: 6.2; : ; : ; : ; P-value=<0.05
	sleep quality (score), day 12	Zopiclone: 11.4; Placebo: 9.6; : ; : ; : ; P-value=<0.05
Monti, 1996	daytime alertness (higher score indicates more positive response), night 29-30	Zolpidem: 69.0; Placebo: 44.2; : ; : ; : ; P-value=NS
	daytime alertness (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem: 73.8; Placebo: 54.1; : ; : ; : ; P-value=<0.05
	disturbed sleep (higher score indicates more positive response), night 29-30	Zolpidem: 73.1; Placebo: 48.5; : ; : ; : ; P-value=<0.01
	disturbed sleep (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem: 64.9; Placebo: 63.7; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	movement time, nights 29-30	Zolpidem: 6.9; Placebo: 4.3; : ; : ; : ; P-value=NS
	movement time, nights 31-33, withdrawal, rebound	Zolpidem: 3.7; Placebo: 2.9; : ; : ; : ; P-value=NS
	number of awakenings (lower score indicates more positive response), night 29-30	Zolpidem: 2.6; Placebo: 1.9; : ; : ; : ; P-value=NS
	number of awakenings (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem: 2.3; Placebo: 2.6; : ; : ; : ; P-value=NS
	sleep duration (higher score indicates more positive response), night 29-30	Zolpidem: 2.3; Placebo: 2.5; : ; : ; : ; P-value=NS
	sleep duration (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem: 2.1; Placebo: 2.4; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep efficiency (%), nights 29-30	Zolpidem: 87.3; Placebo: 77.3; : ; : ; : ; P-value=NS
	sleep efficiency (%), nights 31-33, withdrawal, rebound	Zolpidem: 79.0; Placebo: 75.3; : ; : ; : ; P-value=NS
	sleep latency (lower score indicates more positive response), night 29-30	Zolpidem: 2.0; Placebo: 1.8; : ; : ; : ; P-value=NS
	sleep latency (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem: 2.4; Placebo: 1.9; : ; : ; : ; P-value=NS
	stage 2 sleep latency (min), nights 29-30	Zolpidem: 23.6; Placebo: 35.1; : ; : ; : ; P-value=NS
	stage 2 sleep latency (min), nights 31-33, withdrawal, rebound	Zolpidem: 47.2; Placebo: 32.3; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	total number of awakenings, nights 29-30	Zolpidem: 24.8; Placebo: 25.5; : ; : ; : ; P-value=NS
	total number of awakenings, nights 31-33, withdrawal, rebound	Zolpidem: 28.7; Placebo: 26.1; : ; : ; : ; P-value=NS
	total sleep time (min), nights 29-30	Zolpidem: 419.3; Placebo: 370.9; : ; : ; : ; P-value=<0.05
	total sleep time (min), nights 31-33, withdrawal, rebound	Zolpidem: 378.6; Placebo: 361.2; : ; : ; : ; P-value=NS
	total wake time (min), nights 29-30	Zolpidem: 53.8; Placebo: 104.8; : ; : ; : ; P-value=<0.05
	total wake time (min), nights 31-33, withdrawal, rebound	Zolpidem: 97.7; Placebo: 115.9; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	wake time after sleep onset (min), nights 29-30	Zolpidem: 26.3; Placebo: 85.3; : ; : ; : ; P-value=NS
	wake time after sleep onset (min), nights 31-33, withdrawal, rebound	Zolpidem: 54.9; Placebo: 92.0; : ; : ; : ; P-value=NS
Monti, 2000	alert in the morning - night 17-18 (1=agree; 100=disagree)	Zolpidem: 30.3; Placebo: 65.9; : ; : ; : ; P-value=NS
	alert in the morning - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem: 37.9; Placebo: 61.5; : ; : ; : ; P-value=NS
	alert in the morning - night 4-5 (1=agree; 100=disagree)	Zolpidem: 20.8; Placebo: 57.5; : ; : ; : ; P-value=NS
	disturbed sleep - night 17-18 (1=agree; 100=disagree)	Zolpidem: 74.6; Placebo: 40.1; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	disturbed sleep - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem: 62.7; Placebo: 56.8; : ; : ; : ; P-value=NS
	disturbed sleep - night 4-5 (1=agree; 100=disagree)	Zolpidem: 78.4; Placebo: 46.4; : ; : ; : ; P-value=NS
	sleep duration (min) - night 17-18	Zolpidem: 342.0; Placebo: 225.0; : ; : ; : ; P-value=NS
	sleep duration (min) - night 19-21, withdrawal, rebound	Zolpidem: 342.0; Placebo: 207.4; : ; : ; : ; P-value=NS
	sleep duration (min) - night 4-5	Zolpidem: 384.0; Placebo: 180.0; : ; : ; : ; P-value=NS
	sleep efficiency (%) - night 17-18	Zolpidem: 75.4; Placebo: 55.1; : ; : ; : ; P-value=<0.01

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep efficiency (%) - night 19-21, withdrawal, rebound	Zolpidem: 69.7; Placebo: 58.6; : ; : ; : ; P-value=NS
	sleep efficiency (%) - night 4-5	Zolpidem: 79.9; Placebo: 61.9; : ; : ; : ; P-value=<0.006
	sleep latency (min) - night 17-18	Zolpidem: 49.5; Placebo: 154.0; : ; : ; : ; P-value=<0.01
	sleep latency (min) - night 19-21, withdrawal, rebound	Zolpidem: 94.3; Placebo: 118.4; : ; : ; : ; P-value=NS
	sleep latency (min) - night 4-5	Zolpidem: 34.6; Placebo: 228.0; : ; : ; : ; P-value=<0.01
	stage 2 sleep latency - night 17-18	Zolpidem: 29.2; Placebo: 48.3; : ; : ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	stage 2 sleep latency - night 19-21, withdrawal, rebound	Zolpidem: 55.7; Placebo: 69.7; : ; : ; : ; P-value=NS
	stage 2 sleep latency - night 4-5	Zolpidem: 26.1; Placebo: 67.4; : ; : ; : ; P-value=<0.02
	total number of awakenings - night 17-18	Zolpidem: 26.9; Placebo: 26.5; : ; : ; : ; P-value=NS
	total number of awakenings - night 19-21, withdrawal, rebound	Zolpidem: 25.4; Placebo: 32.2; : ; : ; : ; P-value=NS
	total number of awakenings - night 4-5	Zolpidem: 29.4; Placebo: 32.2; : ; : ; : ; P-value=NS
	total sleep time (min) - night 17-18	Zolpidem: 361.2; Placebo: 264.4; : ; : ; : ; P-value=<0.02

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	total sleep time (min) - night 19-21, withdrawal, rebound	Zolpidem: 334.6; Placebo: 281.6; : ; : ; : ; P-value=NS
	total sleep time (min) - night 4-5	Zolpidem: 378.8; Placebo: 279.3; : ; : ; : ; P-value=<0.01
	waking time after sleep onset (min) - night 17-18	Zolpidem: 95.7; Placebo: 173.3; : ; : ; : ; P-value=NS
	waking time after sleep onset (min) - night 19-21, withdrawal, rebound	Zolpidem: 75.1; Placebo: 137.5; : ; : ; : ; P-value=NS
	waking time after sleep onset (min) - night 4-5	Zolpidem: 75.1; Placebo: 137.5; : ; : ; : ; P-value=<0.03
Parrino	Sleep efficiency zol night 6, placebo night 7	Zolpidem: 86; Placebo: 88; Zolpidem: ; Placebo: ; : ; P-value=0.0001 vs baseline

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Sleep efficiency zolpidem night 2, placebo night 3, zolpidem night 4, placebo night 5	Zolpidem: 88; Placebo: 83; Zolpidem: 87; Placebo: 87; : ; P-value=0.0001 vs baseline
	Sleep latency (mins) zolpidem night 2, placebo night 3, zolpidem night 4, placebo night 5	Zolpidem: 16; Placebo: 16; Zolpidem: 12; Placebo: 18; : ; P-value=NS
	Sleep latency (mins) zolpidem night 6, placebo night 7	Zolpidem: 17; Placebo: 12; Zolpidem: ; Placebo: ; : ; P-value=NS
	TST-mins zolpidem night 2, placebo night 3, zolpidem night 4, placebo night 5	Zolpidem: 443; Placebo: 417; Zolpidem: 436; Placebo: 435; : ; P-value=0.0001 vs baseline
	TST-mins zolpidem night 6, placebo night 7	Zolpidem: 431; Placebo: 440; Zolpidem: ; Placebo: ; : ; P-value=0.0001 vs baseline
	Waso (mins) night 6 zolpidem, night 7 placebo.	Zolpidem: 45; Placebo: 35; Zolpidem: ; Placebo: ; : ; P-value=NS

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	Waso (mins) zolpidem night 2 placebo night 3, zolpidem night 4, placebo night 5	Zolpidem: 40; Placebo: 60; Zolpidem: 17; Placebo: 43; : ; P-value=0.046 vs baseline night 4 with zolpidem
Perlis, 2004	IGR scale	Zolpidem: 6; Placebo: 4.5; : ; : ; : ; P-value=<0.001
	number of awakenings, all condition, significant at week 2 and 12 only	Zolpidem: 1.38; Placebo: 1.69; : ; : ; : ; P-value=NS
	number of awakenings, with pill	Zolpidem: 1.03; Placebo: 1.64; : ; : ; : ; P-value=<0.05
	number of awakenings, without pill	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	sleep latency (min), all condition significant at week 10 only	Zolpidem: NR; Placebo: NR; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=NS
	sleep latency (min), with pill	Zolpidem: 38.4; Placebo: 55.1; : ; : ; : ; P-value=<0.05
	sleep latency (min), without pill	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	total sleep time (min), all condition	Zolpidem: 394.1; Placebo: 355.6; : ; : ; : ; P-value=<0.05
	total sleep time (min), with pill	Zolpidem: 417; Placebo: 359.8; : ; : ; : ; P-value=<0.05
	total sleep time (min), without pill	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
	wake after sleep onset (min), all condition, significant at week 2 only	Zolpidem: NR; Placebo: NR; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=NS
	wake after sleep onset (min), with pill	Zolpidem: 32.6; Placebo: 55.4; : ; : ; : ; P-value=<0.05
	wake after sleep onset (min), without pill	Zolpidem: NR; Placebo: NR; : ; : ; : ; P-value=NS
Roehrs (poster)	Patient global impression and sleep quality, data NR	Zolpidem MR: better; Placebo: NR; : ; : ; : ; P-value=0.0001
	Subjective sleep estimate, data NR	Zolpidem MR: better; Placebo: NR; : ; : ; : ; P-value=<0.05
	latency to persistent sleep (LPS), mean change from baseline, Night 1 and 2	Zolpidem MR: -17; Placebo: -6; : ; : ; : ; P-value=0.0001
	latency to persistent sleep (LPS), mean change from baseline, Night 15 and 16	Zolpidem MR: -14; Placebo: -8; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=0.0255
	sleep efficiency (SE), total sleep time/time in bed x100	Zolpidem MR: 10.2; Placebo: 3; : ; : ; : ; P-value=<0.0001
		Zolpidem MR: 5.9; Placebo: 3.5; : ; : ; : ; P-value=0.0509
	wake time after sleep onset (WASO), mean change from baseline, Night 1 and 2	Zolpidem MR: -32; Placebo: -6; : ; : ; : ; P-value=0.0042
	wake time after sleep onset (WASO), mean change from baseline, Night 15 and 16	Zolpidem MR: -18; Placebo: -6; : ; : ; : ; P-value=<0.001
Rosenberg	LPS-mins (2 night means)	Eszopiclone: 13.0; Placebo: 15.4; : ; : ; : ; P-value=0.4493
	Number of awakenings, total (2 night means)	Eszopiclone: 9.5; Placebo: 10.1; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=0.4260
	Sleep efficiency (2 night means)	Eszopiclone: 84.4; Placebo: 85.1; : ; : ; : ; P-value=0.0075
	Total sleep time, mins (2 night means)	Eszopiclone: 424.2; Placebo: 408.7; : ; : ; : ; P-value=0.0080
	WASO, mins (2 nignt means)	Eszopiclone: 48.1; Placebo: 61.8; : ; : ; : ; P-value=0.0125
	Wake time during sleep, mins (2 night means)	Eszopiclone: 43.2; Placebo: 55.9; : ; : ; : ; P-value=0.0133
Roth	6 hr WASO-adjusted mean of the diff , night 1,2(mins)	Zolpidem: -23:25; Placebo: ; : ; : ; : ; P-value=<0.0001
	6 hr WASO-adjusted mean of the diff , night 15,16(mins)	Zolpidem: -16:29; Placebo: ; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=<0.0001
	6 hr WASO-adjusted mean-night 1,2 (mins)	Zolpidem: -33:49; Placebo: -10:24; : ; : ; : ; P-value=
	6 hr WASO-adjusted mean-night 15,16 (mins)	Zolpidem: -30:12; Placebo: -13:43; : ; : ; : ; P-value=
	LPS (min) LS mean	Ramelteon 4mg: 28.7; Ramelteon 8mg: 30.8; Placebo: 38.4; : ; : ; P-value=<0.001
	LPS -mean-night 22 difference from baseline	Zolpidem: 10:40; Placebo: -12:03; : ; : ; : ; P-value=<0.05 vs baseline
	LPS- mean night 23 difference from baseline	Zolpidem: -7:40; Placebo: -13:42; : ; : ; : ; P-value=
	LPS: mins adjusted mean of the diff night 15,16	Zolpidem: -7:33; Placebo: ; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=0.338
	LPS:mins night 15,16	Zolpidem: -21:20; Placebo: -13:47; : ; : ; : ; P-value=
	LPS:mins, adjusted mean of the diff night 1,2	Zolpidem: -10:17; Placebo: ; : ; : ; : ; P-value=<0.0001
	LPS:mins, adjusted mean, night 1,2	Zolpidem: -23:48; Placebo: -13:30; : ; : ; : ; P-value=
	Morning level of alertness -LS mean	Ramelteon 4mg: 3.5; Ramelteon 8 mg: 3.7; Placebo: 3.6; : ; : ; P-value=0.306
	Sleep Quality-LS mean	Ramelteon 4mg: 3.7; Ramelteon 8mg: 3.8; Placebo: 3.8; : ; : ; P-value=0.792
	Sleep efficiency, night 1,2 adjusted mean	Zolpidem: 0.130; Placebo: 0.055; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=
	Sleep efficiency, night 1,2 adjusted mean of the diff	Zolpidem: 0.075; Placebo: ; : ; : ; : ; P-value=<0.0001
	Sleep efficiency, night 15,16 adjusted mean	Zolpidem: 0.094; Placebo: 0.064; : ; : ; : ; P-value=
	Sleep efficiency, night 15,16 adjusted mean of the difference	Zolpidem: 0.030; Placebo: ; : ; : ; : ; P-value=0.0172
	Sleep efficiency:	Ramelteon 4mg: 74.9; Ramelteon 8mg: 75.5; Placebo: 73.1; : ; : ; P-value=0.018
	Sleep efficinecy-mean night 23 difference from baseline	Zolpidem: 0.033; Placebo: 0.085; : ; : ; : ; P-value=
	Sleep efficinecy: mean night 22 difference from baseline	Zolpidem: -0.086; Placebo: 0.051; : ; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=<0.05 vs baseline
	TST (min) LS mean	Ramelteon 4mg: 359.4; Ramelteon 8mg: 362.0; Placebo: 350.4; : ; : ; P-value=0.018
	Waso-Night 22: mean difference from baseline	Zolpidem: 26:25; Placebo: -13:27; : ; : ; : ; P-value=<0.05 vs baseline
	Waso-night 23: mean difference from baseline	Zolpidem: -10:33; Placebo: -28:39; : ; : ; : ; P-value=
	sSleep Latency(min)-LS mean	Ramelteon 4mg: 48.2; Ramelteon 8mg: 50.9; Placebo: 58.2; : ; : ; P-value=0.096
	sTotal Sleep time LS mean	Ramelteon 4mg: 337.8; Ramelteon 8mg: 337.0; Placebo: 333.9; : ; : ; P-value=0.756
Roth 2006	Sleep latency at week 1, minutes (not reported if mean or median)	Ramelteon 4 mg: 64.9; Ramelteon 8 mg: 60.3; Placebo: 69.3; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=
	Sleep latency at week 3, minutes (not reported if mean or median)	Ramelteon 4 mg: 64.9; Ramelteon 8 mg: 60.3; Placebo: 69.3; : ; : ; P-value=
	Total sleep time at week 1, minutes (not reported if mean or median)	Ramelteon 4 mg: 324.6; Ramelteon 8 mg: 321.1; Placebo: 313.9; : ; : ; P-value=
	Total sleep time at week 3, minutes (not reported if mean or median)	Ramelteon 4 mg: 336.0; Ramelteon 8 mg: 332.1; Placebo: 324.3; : ; : ; P-value=
	Total sleep time at week 5, minutes (not reported if mean or median)	Ramelteon 4 mg: 337.5; Ramelteon 8 mg: 334.4; Placebo: 330.1; : ; : ; P-value=
Scharf, 1994	ease of falling sleep (0=very easy; 100=not easy), posttreatment	Zolpidem 10mg: 63.7; Zolpidem 15mg: 64.0; Placebo: 44.4; : ; : ; P-value=
	ease of falling sleep (0=very easy; 100=not easy), week 6	Zolpidem 10mg: 50.7; Zolpidem 15mg: 35.7; Placebo: 48.4; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=
	sleep efficiency (%), week 6	Zolpidem 10mg: 83.1; Zolpidem 15mg: 79.9; Placebo: 81.9; : ; : ; P-value=
		Zolpidem 10mg: 87.9; Zolpidem 15mg: 87.3; Placebo: 80.7; : ; : ; P-value=
	sleep latency (min), posttreatment	Zolpidem 10mg: 62.3; Zolpidem 15mg: 78.2; Placebo: 47.5; : ; : ; P-value=
	sleep latency (min), week 6	Zolpidem 10mg: 25.8; Zolpidem 15mg: 28.1; Placebo: 48; : ; : ; P-value=
		Zolpidem 10mg: 38.4; Zolpidem 15mg: 31.7; Placebo: 56.6; : ; : ; P-value=
		Zolpidem 10mg: 47.1; Zolpidem 15mg: 47.7; Placebo: 48.0; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=
	sleep quality (1=excellent; 4=poor), posttreatment	Zolpidem 10mg: 2.9; Zolpidem 15mg: 3.1; Placebo: 2.6; : ; : ; P-value=
	sleep quality (1=excellent; 4=poor), week 6	Zolpidem 10mg: 2.5; Zolpidem 15mg: 2.5; Placebo: 2.6; : ; : ; P-value=
	tolerance assessment, change from week 2 to week 6	Zolpidem 10mg: multi-data; Zolpidem 15mg: multi-data; Placebo: multi-data; : ; : ; P-value=
	total sleep time (min), posttreatment	Zolpidem 10mg: 333; Zolpidem 15mg: 341; Placebo: 333; : ; : ; P-value=
	total sleep time (min), week 6	Zolpidem 10mg: 369; Zolpidem 15mg: 394; Placebo: 356; : ; : ; P-value=
Scharf, 2005	daily ability to function (0=poor; 10=excellent), average	Eszopiclone 1mg: 7.4; Eszopiclone 2mg: 7.6; Placebo: 7.2; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0579
	daytime alertness (0=drowsy; 10=alert), average	Eszopiclone 1mg: 7.1; Eszopiclone 2mg: 7.3; Placebo: 6.8; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0223
	duration per nap (min), average	Eszopiclone 1mg: 47.7; Eszopiclone 2mg: 52.7; Placebo: 59.2; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=<0.05; 0.0113
	morning sleepiness (0=very sleepy; 10=not at all sleepy), average	Eszopiclone 1mg: 6.9; Eszopiclone 2mg: 7.2; Placebo: 6.6; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0547
	number of awakenings - average	Eszopiclone 1mg: 2; Eszopiclone 2mg: 1.7; Placebo: 1.9; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; NS
	number of naps taken, total	Eszopiclone 1mg: 5.0; Eszopiclone 2mg: 4.3; Placebo: 5.9; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0276
	physical well-being (0=poor; 10=excellent), average	Eszopiclone 1mg: 7.5; Eszopiclone 2mg: 7.7; Placebo: 7.2; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0474
	sleep depth (0=very light; 10=very deep) - average	Eszopiclone 1mg: 6.5; Eszopiclone 2mg: 7.1; Placebo: 6.2; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0015
	sleep latency (min) - average	Eszopiclone 1mg: 53.6; Eszopiclone 2mg: 50; Placebo: 85.5; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=<0.05; 0.0034
	sleep quality (0=poor; 10=excellent) - average	Eszopiclone 1mg: 6.6; Eszopiclone 2mg: 7.2; Placebo: 6.3; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0006
	total sleep time (min) - average	Eszopiclone 1mg: 349.8; Eszopiclone 2mg: 372.3; Placebo: 328.2; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.0003
	wake after sleep onset (min) - average	Eszopiclone 1mg: 72.6; Eszopiclone 2mg: 58.5; Placebo: 74.1; : ; : ; P-value (1 mg vs placebo; 2 mg vs placebo)=NS; 0.423
Schnitzer 2005 (poster)	attention/concentration	Eszopiclone: 1.3; Placebo: 1.4; : ; : ; : ; P-value=0.2
	daytime fatigue	Eszopiclone: 1.6; Placebo: 2.0; : ; : ; : ; P-value=0.005
	feeling refreshed/rested	Eszopiclone: 2.3; Placebo: 1.8; : ; : ; : ; P-value<0.001
	mood disturbance	Eszopiclone: 1.3; Placebo: 1.5; : ; : ; : ; P-value<0.3
	relationship enjoyment	Eszopiclone: 1.0; Placebo: 1.3; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value<0.05
	sleep difficulties (nights/wk)	Eszopiclone: 3.0; Placebo: 4.7; : ; : ; : ; P-value<0.001
	sleep quality	Eszopiclone: 2.6; Placebo: 1.9; : ; : ; : ; P-value=<0.0001
	total score =< 7 (no insomnia)	Eszopiclone: 30.4; Placebo: 47.9; : ; : ; : ; P-value=0.0338
Shaw, 1992	daytime residual effects (1=very drowsy; 4=very alert), change from baseline, day 28	Zolpidem 10mg: 3.21; Zolpidem 20mg: 3.19; Placebo: 3.26; : ; : ; P-value=
	daytime residual effects (1=very drowsy; 4=very alert), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: 3.22; Zolpidem 20mg: 3.28; Placebo: 3.00; : ; : ; P-value=
	number of awakenings (%), change from baseline, day 28	Zolpidem 10mg: -26; Zolpidem 20mg: -23; Placebo: -31;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=
	number of awakenings (%), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: -34; Zolpidem 20mg: -15; Placebo: -16; : ; : ; P-value=
	sleep duration (min), change from baseline, day 28	Zolpidem 10mg: 32; Zolpidem 20mg: 27; Placebo: 14; : ; : ; P-value=
	sleep duration (min), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: 32; Zolpidem 20mg: 28; Placebo: 16; : ; : ; P-value=
	sleep latency (min), change from baseline, day 28	Zolpidem 10mg: 38; Zolpidem 20mg: 28; Placebo: 23; : ; : ; P-value=
	sleep latency (min), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: 36; Zolpidem 20mg: 21; Placebo: 9; : ; : ; P-value=
	sleep quality (1=poor; 4=good), change from baseline, day 28	Zolpidem 10mg: -27; Zolpidem 20mg: -29; Placebo: -30;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=
	sleep quality (1=poor; 4=good), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: -29; Zolpidem 20mg: -14; Placebo: -14; : ; : ; P-value=
	total wake time (min), change from baseline, day 28	Zolpidem 10mg: -28; Zolpidem 20mg: -15; Placebo: -22; : ; : ; P-value=
	total wake time (min), change from baseline, day 35, withdrawal, rebound	Zolpidem 10mg: -27; Zolpidem 20mg: -11; Placebo: -14; : ; : ; P-value=
Soares	Increase in Total Sleep Time over 4 weeks, mins	Eszopiclone: 56.6; Placebo: 33.6; : ; : ; : ; P-value=<0.001
	Mean no. of awakenings due to hot flashes	Eszopiclone: 0.29; Placebo: 0.37; : ; : ; : ; P-value=0.05
	Mean number of Awakenings at 4 months	Eszopiclone: 1.12; Placebo: 1.42; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=<0.01
	Reduction in sleep latency over 4 weeks (mins)	Eszopiclone: 25.8; Placebo: 10.1; : ; : ; : ; P-value=<0.001
	Reduction in sleep latency over 4 weeks, WASO, mins	Eszopiclone: 30.9; Placebo: 16.0; : ; : ; : ; P-value=<0.001
	menopause symptoms-no change at 4 weeks	Eszopiclone: 42; Placebo: 85; : ; : ; : ; P-value=<0.001
	menopause-symptoms "much imrpoved" at 4 weeks (from graph	Eszopiclone: 60; Placebo: 40; : ; : ; : ; P-value=<0.001
	menopause-symptoms "very much improved" at 4 weeks (from graph)	Eszopiclone: 35; Placebo: 15; : ; : ; : ; P-value=<0.001
Soubrane (poster)	latency to persistent sleep, mean change from baseline, night 1 and 2	Zolpidem MR: -23; Placebo: -13; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=<0.0001
	latency to persistent sleep, mean change from baseline, night 15 and 16	Zolpidem MR: -21; Placebo: -13; : ; : ; : ; P-value=0.0338
	number of awakenings, mean change from baseline, night 15 and 16	Zolpidem MR: -2.7; Placebo: -0.8; : ; : ; : ; P-value=<0.0001
	number of awakenings, mean change from baseline, night 1 and 2	Zolpidem MR: -3.0; Placebo: -0.9; : ; : ; : ; P-value=<0.0001
	patients global impression and sleep quality, day 2, 15, 22	Zolpidem MR: better; Placebo: data NR; : ; : ; : ; P-value=<0.005
		Zolpidem MR: better; Placebo: multiple data; : ; : ; : ; P-value=<0.005
	sleep efficiency, total sleep time / time in bed x100, night 1 and 2	Zolpidem MR: 13; Placebo: 5.5; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=<0.0001
		Zolpidem MR: 9.4; Placebo: 6.4; : ; : ; : ; P-value=0.0172
	wake time after sleep onset, mean change from baseline, night 1 and 2	Zolpidem MR: -33; Placebo: -10; : ; : ; : ; P-value=<0.0001
	wake time after sleep onset, mean change from baseline, night 15 and 16	Zolpidem MR: -30; Placebo: -13; : ; : ; : ; P-value=<0.0001
Terzano, 1992	sleep latency (min)	Zolpidem: 8.1; Placebo: 14.5; : ; : ; : ; P-value=NR
	total sleep time (min)	Zolpidem: 420; Placebo: 402; : ; : ; : ; P-value=NR
	wake after sleep onset (min)	Zolpidem: 16; Placebo: 41; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=NR
Walsh 2007	Ability to concentrate-change from baseline (DB avg)	Eszopiclone: 7.1; Placebo: 6.3; : ; : ; : ; P-value=<0.001
	Adjusted mean diff between two groups in change from baseline : nights 1 and 2, mins,sec	Eszopiclone: -25:42; Placebo: ; : ; : ; : ; P-value=
	Adjusted mean diff between two groups in change from baseline : nights 15 and 16 mins,sec	Eszopiclone: -11:27; Placebo: ; : ; : ; : ; P-value=
	Daytime alertness-change from baseline (DB avg)	Eszopiclone: 6.9; Placebo: 6.0; : ; : ; : ; P-value=<0.001
	LPS, adjusted mean (mins, sec) Nights 1/2 compared to baseline	Eszopiclone: -17.10; Placebo: -6.55; : ; : ; : ; P-value=0.0001
	LPS, adjusted mean (mins, sec) Nights 15/16 compared to baseline	Eszopiclone: -14.18; Placebo: -8.30; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=0.0255
	LPS,Adjusted mean diff between two groups in change from baseline Nights1/2	Eszopiclone: -10.15; Placebo: ; : ; : ; : ; P-value=
	LPS,Adjusted mean diff between two groups in change from baseline Nights15/16	Eszopiclone: -5.49; Placebo: ; : ; : ; : ; P-value=
	No. of Awakenings, mean change from baseline (DB-avg)	Eszopiclone: 1.7; Placebo: 2.2; : ; : ; : ; P-value=<0.001
	No. of awakenings:Adjusted mean change from baseline wk3	Eszopiclone: -3.18; Placebo: -2.22; : ; : ; : ; P-value=<0.0001
	Patient reported sleep quality: Adjusted mean change from baseline, wk 1	Zolpidem: -0.53; Placebo: -0.44; : ; : ; : ; P-value=0.2018
		Eszopiclone: -0.5; Placebo: -0.28; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=0.0015
	Sleep Efficiency-Nights 1/2 (mins:sec)	Eszopiclone: 0.012; Placebo: 0.030; : ; : ; : ; P-value=<0.0001
	Sleep Efficiency-Nights 15/16 (mins:sec)	Eszopiclone: 0.059; Placebo: 0.035; : ; : ; : ; P-value=0.0509
	Sleep Efficinecy-Adjusted mean diff between two groups in change from baseline Nights 15/16	Eszopiclone: 0.023; Placebo: ; : ; : ; : ; P-value=
	Sleep Efficinecy-Adjusted mean diff between two groups in change from baseline Nights1/2	Eszopiclone: 0.073; Placebo: ; : ; : ; : ; P-value=
	Sleep quality, mean change from baseline (DB-AVG)	Eszopiclone: 6.9; Placebo: 5.8; : ; : ; : ; P-value=<0.001
	Total Sleep Time, mean change from baseline (DB-avg), mins	Eszopiclone: 389.5; Placebo: 343.4; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=<0.001
	WASO 1-6 hrs, adjusted mean (mins, sec) Nights 1 and 2 compared to baseline	Eszopiclone: -32:41; Placebo: -6:59; : ; : ; : ; P-value=<0.0001
	WASO 1-6 hrs, adjusted mean (mins, sec) Nights 15 and 16 compared to baseline	Eszopiclone: -18:22; Placebo: -6:56; : ; : ; : ; P-value=0.0042
	WASO-mean change from baseline (DB avg) mins	Eszopiclone: 39.1; Placebo: 59.4; : ; : ; : ; P-value=<0.001
	WASO-mean change from baseline (DB avg), mins	Eszopiclone: 25.5; Placebo: 43.2; : ; : ; : ; P-value=<0.001
	patient reported Sleep Latency :Adjusted mean change from baseline wk1	Eszopiclone: -25.56; Placebo: -14.36; : ; : ; : ; P-value=0.02
	patient reported Sleep Latency: Adjusted mean change from baseline wk3	Eszopiclone: -26.34; Placebo: -21.58; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=0.21
Walsh, 2000a	PSG latency to persistent sleep (min)	Zaleplon 2mg: 30.4; Zaleplon 5mg: 26.0; Zaleplon 10mg: 21.8; Placebo: 47.7; : ; P-value=
	PSG no. of awakenings	Zaleplon 2mg: 21.6; Zaleplon 5mg: 21.9; Zaleplon 10mg: 22.1; Placebo: 21.6; : ; P-value=
	PSG total sleep time (min)	Zaleplon 2mg: 359.3; Zaleplon 5mg: 363.9; Zaleplon 10mg: 362.8; Placebo: 351.2; : ; P-value=
	subjective no. of awakenings	Zaleplon 2mg: 3.4; Zaleplon 5mg: 3.1; Zaleplon 10mg: 2.8; Placebo: 3.3; : ; P-value=
	subjective sleep latency (min)	Zaleplon 2mg: 55.2; Zaleplon 5mg: 42.0; Zaleplon 10mg: 34.4; Placebo: 58.3; : ; P-value=
	subjective total sleep time (min)	Zaleplon 2mg: 335.8; Zaleplon 5mg: 343.2; Zaleplon 10mg: 351.6;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		Placebo: 327.9; : ; P-value=
Walsh, 2000b, 2002	quality of life	Zolpidem: multi-data; Placebo: multi-data; : ; : ; : ; P-value=NS
	number of awakenings, with pill, 8 weeks average	Zolpidem: 1.1; Placebo: 1.8; : ; : ; : ; P-value=<0.05
	sleep latency (min), all condition, 8 weeks average	Zolpidem: 12.39; Placebo: 19.55; : ; : ; : ; P-value=NS
	sleep latency (min), with pill, 8 weeks average	Zolpidem: 36.7; Placebo: 50.4; : ; : ; : ; P-value=<0.05
	sleep quality (1=excellent; 4=poor), with pill, 8 weeks average	Zolpidem: 2.1; Placebo: 2.5; : ; : ; : ; P-value=<0.05
	total sleep time (min), with pill, 8 weeks average	Zolpidem: 415.4; Placebo: 364.1; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; : ; P-value=<0.05
Zammit, 2004	WASO (min)	Eszopiclone 2mg: 37.1; Eszopiclone 3mg: 30.2; Placebo: 45; : ; : ; P-value= 0.6884 for 2 mg vs placebo; 0.0204 for 3 mg vs placebo
	WASO (min), rebound insomnia, change vs baseline	Eszopiclone 2mg: 7; Eszopiclone 3mg: NR; : ; : ; : ; P-value<0.05 for 2 mg vs placebo; NS for 3 mg vs placebo
	daytime ability to function (higher scores indicate improved function)	Eszopiclone 2mg: 6.81; Eszopiclone 3mg: 7.15; Placebo: 6.83; : ; : ; P-value=0.901 for 2 mg vs placebo; 0.118 for 3 mg vs placebo
	daytime alertness (higher scores indicate improved function)	Eszopiclone 2mg: 6.66; Eszopiclone 3mg: 7.02; Placebo: 6.67; : ; : ; P-value=0.873 for 2 mg vs placebo; 0.059 for 3 mg vs placebo
	depth of sleep (0=poor; 100=excellent)	Eszopiclone 2mg: 58.9; Eszopiclone 3mg: 56.7; Placebo: 51.7; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=0.0.0052 for 2 mg vs placebo; 0.0457 for 3 mg vs placebo
	morning sleepiness (1=very sleepy; 100=not at all sleepy)	Eszopiclone 2mg: 51.3; Eszopiclone 3mg: 50.8; Placebo: 48.2; : ; : ; P-value=0.256 for 2 mg vs placebo; 0.344 for 3 mg vs placebo
	number of awakenings	Eszopiclone 2mg: 2.7; Eszopiclone 3mg: 2.4; Placebo: 3.0; : ; : ; P-value=0.2956 for 2 mg vs placebo; 0.1720 for 3 mg vs placebo
	number of awakenings, NAW - night 1, 15, 29 average	Eszopiclone 2mg: 6.5; Eszopiclone 3mg: 5.7; : 6.0; : ; : ; P-value=NS
	quality of sleep (0=poor; 100=excellent)	Eszopiclone 2mg: 54.5; Eszopiclone 3mg: 56.6; Placebo: 47.7; : ; : ; P-value=0.0414 for 2 mg vs placebo; 0.0072 for 3 mg vs placebo
	sleep efficiency (%) - night 1, 15, 29 average	Eszopiclone 2mg: 88.1; Eszopiclone 3mg: 90.1; : 85.7; : ; : ; P-value<0.01 for 2 mg vs placebo; <0.001 for 3 mg vs placebo

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	sleep efficiency (%), rebound insomnia, change vs baseline	Eszopiclone 2mg: -2.5; Eszopiclone 3mg: 3.7; : ; : ; : ; P-value<0.05 for 2 mg vs placebo; <0.05 for 3 mg vs placebo
	sleep latency (min)	Eszopiclone 2mg: 30; Eszopiclone 3mg: 27.7; Placebo: 46; : ; : ; P-value=<0.0001 for 2 mg vs placebo; <0.0001 for 3 mg vs placebo
	sleep latency (min), rebound insomnia, change vs baseline	Eszopiclone 2mg: NR; Eszopiclone 3mg: -8.5; : ; : ; : ; P-value=NS for 2 mg vs placebo; <0.05 for 3 mg vs placebo
	sleep latency (minute) - night 1, 15, 29 average	Eszopiclone 2mg: 15; Eszopiclone 3mg: 13.1; : 29; : ; : ; P-value=<0.001 for 2 mg vs placebo; <0.001 for 3 mg vs placebo
	total sleep time (min)	Eszopiclone 2mg: 400; Eszopiclone 3mg: 406; Placebo: 366; : ; : ; P-value=0.0207 for 2 mg vs placebo; <0.0001 for 3 mg vs placebo
	wake time after sleep onset, WASO (min) -	Eszopiclone 2mg: 37.1;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
	night 1, 15, 29 average	Eszopiclone 3mg: 33.8; : 44.1; : ; : ; P-value=NS for 2 mg vs placebo; <0.01 for 3 mg vs placebo
Zammit, 2007	Awake time (mins) at week 1	Ramelteon 8mg: 72.3; Ramelteon 16 mg: 93.4; Placebo: 86.1; : ; : ; P-value==0.026 for 8mg, =0.004 for 16mg vs placebo
	Awake time(mins) at week 5	Ramelteon 8mg: 70.3; Ramelteon 16 mg: 68.0; Placebo: 71.2; : ; : ; P-value=NS
	Sleep quality at week 5	Ramelteon 8mg: 3.6; Ramelteon 16 mg: 3.6; Placebo: 3.7; : ; : ; P-value=NS
	Sleep efficiency at week 1	Remelteon 8mg: 82.3; Remelteon 16 mg: 83.4; Placebo: 78.3; : ; : ; P-value=<0.001 vs placebo
	Sleep efficiency at wk 5	Remelteon 8mg: 81.8; Remelteon 16 mg: 82.0; Placebo: 80.4; : ; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		P-value=NS vs placebo
	Sleep quallity at week 1	Ramelteon 8mg: 3.8; Ramelteon 16 mg: 3.8; Placebo: 3.9; : ; : ; P-value=NS
	WASO at 5 week (in mins)	Remelteon 8mg: 59.9; Remelteon 16 mg: 61.1; Placebo: 56.4; : ; : ; P-value=NS
	mean LPS at week 1 (in mins)	Remelteon 8mg: 32.2; Remelteon 16 mg: 28.9; Placebo: 47.9; : ; : ; P-value=<0.001 vs placebo
	mean LPS at week 5 (in mins)	Remelteon 8mg: 31.5; Remelteon 16 mg: 29.5; Placebo: 42.5; : ; : ; P-value=0.002 for 16 mg, .007 for 8 mg vs placebo
	mean TST at week 1 (in mins)	Remelteon 8mg: 394.2; Remelteon 16 mg: 397.6; Placebo: 375.2; : ; : ; P-value=<0.001 vs placebo
	mean TST at week 5 (in mins)	Remelteon 8mg: 391.5; Remelteon 16 mg: 393.3; Placebo: 385.9; : ;

Evidence Table 4. Results of placebo-controlled trials of newer insomnia drugs

Author, year	Outcome Measure	Results
		: ; P-value=

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Agnoli, 1989 (Poor)	Patients were aged 20-50 years with total score of the Hamilton Rating Scale for Anxiety less than 20. Absence of concomitant antidepressive, anxiolytic or neuroleptic medication and absence of somatic, pathophysiological or pharmacological factors related to the onset and persistence of insomnia.	Presence of concomitant general illness; renal or hepatic failure; effectiveness of placebo administration; and pregnancy.	Mean age (SD): 38.2 (2.1); 60% female; Race/ethnicity: NR	NR/ NR/ 20	0/ 0/ 20	1 days	Zopiclone; Nitrazepam; ; ;
Anderson, 1987 (Fair)	Patients were suffering from at least one of the following symptoms: unable to fall asleep within 45 minutes, more than two nocturnal awakenings with difficulty in returning to sleep without known cause, or sleeping <6 hours per night	Patients were not eligible for the trial if there was evidence for the presence (or previous history) of psychiatric disease, hepatic or renal dysfunction, heart block or cardiovascular disease with significant symptomatology, gastrointestinal disease, drug addiction or chronic alcoholism, a history of hypersensitivity to drugs or continuous use of high doses of a hypnotic for a period in excess of 6 months. Other groups excluded were pregnant women, nursing mothers, women of childbearing potential, and night shift workers.	Mean age (SD): NR ( ); 0% female; Race/ethnicity: NR	NR/ NR/ 119	5/ 15/ 99	14 days	Zopiclone; Nitrazepam; Placebo; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Ansoms, 1991 (Fair)	Only insomniac patients in their postalcoholism withdrawal period of at least ten days, who were aged between 20 and 55 years and able to participate in the trial were included, as well as those for whom it was expected they would need a hypnotic every day because of their withdrawal.	Patients with the following criteria were excluded: those being treated during the study period with psychotropic drug for the first time, or for whom the existing medication with psychotropic drugs was being changed or those using tranquilizers of the benzodiazepine type. Patients having used high doses of hypnotics or with a history of drug abuse before the study period were also excluded, as well as those suffering from myasthenia gravis, with any disease accompanies by pain, living in an unstable fluctuating condition with mental or physical stress, or patients with a severe liver or kidney disturbance. Shiftworkers were not included in the study	Mean age (SD): 43.9 ( ); 33% female; Race/ethnicity: NR	NR/ 54/ 52	0/ 0/ 52	5 days	Zopiclone; Lorazepam; ; ;
							Zopiclone; Lormetazepam; ; ;
Autret, 1987 (Poor)	Patients had suffered for more than 3 months from at least two of the following symptoms: subjective period of falling asleep greater than 2 hours; waking up more than twice at night; subjective length of night wakefulness greater than 30 minutes; waking more than 2 hours before the desired time; estimated total sleep time less than 6 hours.	NR	Mean age (SD): 46.3 (11.7); 70% female; Race/ethnicity: NR	NR/ NR/ 121	NR/ 8/ 113	7 days	Zopiclone; Temazepam; ; ;
							Zopiclone; Triazolam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Begg, 1992 (Poor)	Patients were aged 18 years or older and satisfied on or more of the following criteria: a history of taking 30 minutes or more to fall asleep; two or more awakenings during the night; total reported sleep time of less than six hours.	Patients on medications known to affect sleep or on drugs known to alter drug metabolism during and within two weeks prior to the study were excluded. Alcohol ingestion within four hours of retiring or more than one glass (10 g) alcohol in the previous 24 hours were not permitted.	Mean age (SD): NR ( ); 0% female; Race/ethnicity: NR	NR/ NR/ 88	4/ 33/ 51	11 days	Baseline; Midazolam; Zopiclone; ;
Bergener, 1989 (Fair)	Patients who have a minimum score of 14 points on the Sleep Disorder intensity Scale (SDIS) with no improvement during the initial placebo period of 4 days.	Patients with a history of a delirium or a predelirium a severe disease of the heart, liver, or kidney, seizure disorder, endogenous psychosis and treatment with drugs affecting vigilance (reserpine and sedating antihistaminics or barbiturates) were excluded	Mean age (SD): NR ( ); 86% female; Race/ethnicity: NR	NR/ NR/ 42	NR/ NR/ 42	21 days	Zopiclone; Flurazepam; ; ;
Bozin-Juracic, 1998 (Fair)	A group of workers employed in a security company were recruited to the study as subjects	NR	Mean age (SD): NR ( ); 0% female; Race/ethnicity: NR	NR/ 32/ 29	0/ 0/ 29	7 days	Zopiclone; Nitrazepam; Placebo; ;
Chaudoir, 1990 (Fair)	History of insomnia with at least one of the following symptoms present: time taken to fall asleep longer than 30 minutes, more than two nocturnal awakenings with difficulty in returning to sleep, without known cause, sleep duration of less than 6 hours.	Any serious concomitant disease, psychosis, hypersensitivity, drug addiction, or alcohol consumption that might interfere with assessment; women who were pregnant, nursing, or of child-bearing age intending to become pregnant. No patient was included if taking concomitant medication known to induce drowsiness.	Mean age (SD): 50.9 ( ); 71% female; Race/ethnicity: 100% Caucasian	NR/ NR/ 38	4/ NR/ 38	1 weeks	Zopiclone; Triazolam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Drake (1), 2001 (Fair)	Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.	Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.	Mean age (SD): 41.6 (9.5); 51% female; Race/ethnicity: NR	NR/ NR/ 47	0/ 0/ 47	2 days	Zaleplon 10mg; Zaleplon 40mg; Triazolam 0.25mg; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Drake (2), 2000 (Fair)	Age 21-60, with a recent, six-month, history or primary insomnia as defined by the DSM-III. To be eligible for polysomnographic (PSG) screening, participants must have reported at least two of the following: 6 months of sleep disturbance with a sleep latency of >30 minutes, three or more awakenings per night, or a sleep time of 4 to 6 hours. All patients had to meet the following PSG screening criteria for study eligibility: 1) latency to persistent sleep greater than 20 minutes on at least two of the screening nights, with no latency of less than 15 minutes, 2) Total sleep time between 240 and 420 on at least two of the screening nights, 3) less than five apneas per hour of sleep, 4) less than 10 leg movements per hour of sleep.	Individuals with medical or psychiatric diagnoses (including any history of alcoholism or drug abuse), abnormal laboratory results (urinalysis, hematology, and blood chemistries), an irregular sleep-wake schedule, or who regularly consumed greater than 750 mg of caffeinated beverages.	Mean age (SD): 38.1 (11.1); 39% female; Race/ethnicity: NR	NR/ NR/ 36	0/ 0/ 36	2 days	Zaleplon 20mg; Zaleplon 60mg; Triazolam 0.25mg; ;
Elie, 1990a (Fair)	Age between 60 and 90 years, living in residential homes and suffering from chronic insomnia.	Psychotic and neurotic patients, history of blood dyscrasia, neurological disorders, drug hypersensitivity, chronic alcoholism, drug abuse and coffee or tea abuse. Patients with severe medical conditions, those treated with CNS drugs and those receiving treatments which could modify drug kinetics were not accepted.	Mean age (SD): 76.0 (1.3); 75% female; Race/ethnicity: NR	NR/ NR/ 44	0/ 0/ 44	21 days	Zopiclone; Triazolam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Elie, 1990b (Fair)	Subjects had to present a history of insomnia without direct relationship to another ailment plus at least three of the following symptoms: (1) requiring longer than 30 min to fall asleep, (2) total sleep time less than 6 hours, (3) more than two nocturnal awakenings and (4) poor quality of sleep,	Patients suffering from any other psychiatric disorder including depression or presenting a history of blood dyscrasia, drug hypersensitivity, abuse of alcohol or other drugs were excluded from the study. Women of childbearing potential not following a medically recognized contraceptive program and patients receiving any treatment which could modify drug kinetics or having received enzyme inducing drugs in the previous month were also excluded.	Mean age (SD): 37.6 (1.84); 67% female; Race/ethnicity: NR	NR/ NR/ 36	0/ 0/ 36	28 days	Zopiclone; Flurazepam; Placebo; ;
Fleming, 1990 (Fair)	Ages 18 to 64 with body weight within 20% of normal for their age, with a history of insomnia of at least 3 months duration and characterized by at least 3 of the following 4 criteria: 1) a sleep latency of 45 minutes or more, 2) 2 or more nightly awakenings with difficulty in returning to sleep, 3) a total sleep time of less than 6 hours, and 4) a poor quality of sleep. Subjects previously receiving hypnotic medication were eligible provided the above criteria were met after a 7 day washout period.	Females excluded if they were pregnant, lactating, or were not using a medically recognized contraceptive method. Subjects whose sleep performance was disrupted by external factors and those taking neuroleptics, sedatives, analgesics, or antidepressants or with a history of hypersensitivity to one or more hypnotic drugs were excluded. Subjects whose insomnia was considered secondary to a psychiatric or medical disorder were also excluded as those with a history of alcoholism, drug abuse, or caffeine overuse.	Mean age (SD): 45.5 ( ); .% female; Race/ethnicity: NR	NR/ NR/ 52	4/ 0/ 48	21 days	Zopiclone; Triazolam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Fleming, 1995 (Fair)	(a) a subjective usual sleep duration of at least 4 hours but less than 6 hours per night; (b) a usual sleep latency of >= 30minutes; (c) daytime complaints associated with disturbed asleep. Each of there criteria was to be present for at least 6 months prior to study entry.	Any significant medical or psychiatric disorder or mental retardation; use of any other investigational drug within 30 days prior to the start of the study; use of flurazepam within 30 days of the first sleep laboratory night; regular use of any medication that would interfere with the assessment, absorption or metabolism of the study hypnotic; use of alcohol or short-acting central nervous system medication within 12 hours of any study night; use of triazolam within 4 nights, other short- or intermediate-acting hypnotics within 7 nights, or long-acting hypnotics within 14 nights of the first sleep laboratory night; history of exaggerated response or hypersensitivity to benzodiazepines or other CNS depressants; history of drug addiction, alcoholism, drug abuse, sleep apnoea, or nocturnal myoclonus; or a work or sleep schedule that regularly changed by at least 6 hours within 7 days of study initiation.	Mean age (SD): NR ( ); 48% female; Race/ethnicity: NR	222/ 144/ 144	7/ 1/ 141	3 days	Zolpidem 10mg; Zolpidem 20mg; Flurazepam; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Fontaine, 1990 (Fair)	Selection criteria required that: (1) patients be aged between 18 & 60 years; 92) patients have a diagnosis of generalized anxiety disorder according to the DSM-III 1978 draft (Diagnostic and Statistical Manual of Mental Disorders, 1978) which specifies that anxiety must be present for a duration of at least 6 months with its onset not associated with a psychosocial stressor (Diagnostic Criteria for GAD are different for the 1980 version); 93) patients have a total score of at least 20 on the Hamilton Anxiety Rating Scale prior to acceptance for participation in the study and; 94) patients with severe insomnia as the target symptom defined as follows. AT least three of the following criteria: sleep latency of 45 min or more, at least two nocturnal awakenings, poor quality of sleep and a total sleep time of less than 6h.	Exclusion criteria were: patients with specific sleep disorders, physical illnesses, affective or psychotic disorders, organic brain syndrome, mental deficiency (I.Q. below 70), alcoholism or drug addiction).	Mean age (SD): 42.9 (1.1); 53% female; Race/ethnicity: NR	NR/ NR/ 75	21/ 0/ 75	28 days	Zopiclone; Triazolam; ; ;
Hajak, 1998, 1995, 1994 (Fair)	Insomnia of at least 4-week duration and the presence of at least two of the following as a mean of 3 days before starting treatment (no-pill baseline): (a) sleep latency >= 45 min, (b) total sleep time <= 6 hours, and © nocturnal awakening >= 3 times.	Any patients who had taken a single daily dose of a benzodiazepine or any other hypnotic more than three times per week during the 14 days prior to admission, or any patients with psychiatric disorders (e.g., depression, schizophrenia, severe neuroses), or any patients who had contraindications for zopiclone, flunitrazepam, or triazolam were excluded from this study	Mean age (SD): 51 (11); 62% female; Race/ethnicity: 99.3% Caucasian 0.9% Others	NR/ NR/ 1507	0/ 0/ 1507	28 days	Zopiclone; Triazolam; ; ;
							Zopiclone; Triazolam;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
							Placebo; ;
Hayoun, 1989 (Fair)	Patients aged between 18 and 65 years were recruited over a one-year period by 11 general practitioners. All of them had been experiencing insomnia, for at least two weeks, with complaint of unsatisfactory quality of sleep, associated with at least two of the three following criteria for most of the last 15 nights: time to fall asleep exceeding 30 minutes, total duration of sleep less than six hours, waking up at least twice (except for voiding).	The following patients were excluded: patients having taken a sedative drug within seven days before inclusion or likely to need such drugs during study; pregnant or lactating females, or females of childbearing age without reliable contraception; patients suffering from insomnia with external causes; patients with a history of convulsive disorders, with renal or respiratory impairment, with uncontrolled and significant organic disease, with uncontrolled pain or with a psychiatric affection; patients with myasthenia or known intolerance to either study drug; shift workers, alcoholics, or drug-abusers; noncooperative patients; those unable to read and understand the self-rating scales; known resistance to hypnotics.	Mean age (SD): 47.9 ( ); 66% female; Race/ethnicity: NR	NR/ NR/ 136	9/ 0/ 127	7 days	Zopiclone; Triazolam; ; ;
Klimm, 1987 (Fair)	For the purpose of this trial, chronic insomnia was defined as the presence of two of the following criteria: hypnotics taken five times a week for the last 3 months, sleep onset latency > 1 h, total duration of sleep < 6 h, and waking more than three times during the night. The patients' mental capacity, as measured by Intellectual Quotient and memory tests (Syndrome Kurztest) was to be within normal range for their age.	Patients presenting contraindications to benzodiazepines or painful conditions, those with a history of drug allergy or chronic alcoholism, those receiving drugs liable to affect metabolism, those refusing to give their consent, those who might have been unable to complete the trial, those already involved in another trial, and those considered unlikely to cooperate were excluded.	Mean age (SD): 73.2 (1.54); 80% female; Race/ethnicity: NR	NR/ NR/ 74	2/ 2/ 72	7 days	Zopiclone; Nitrazepam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Leppik, 1997 (Fair)	Enrollment criteria included chronic insomnia of at least 3 months' duration, defined as self-reported sleep duration of 4-6 hours each night and self reported sleep latency of 30 minutes or more; some impairment of daytime functioning related to sleep deprivation; relatively stable mental and physical health; and no evidence of systemic abnormalities or other diseases that would interfere with study drug evaluation. Normal 12-lead electrocardiogram (ECG) and clinical laboratory evaluation were required.	Exclusion criteria included significant and/or unstable medical or psychiatric disorder or mental retardation, use of an investigational drug within 30 days of the start of the study, regular use of medication of a type that could interfere with assessment of a hypnotic; use of a medication that could interfere with absorption or metabolism of a benzodiazepines or other CNS depressants, and previous administration of zolpidem. In addition, patients with a recent history of drug or alcohol abuse, seizure disorder; or symptoms of sleep apnea of myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.	Mean age (SD): 69 ( ); 63% female; Race/ethnicity: 93% white	NR/ 457/ 335	40/ 0/ 335	28 days	Zolpidem; Temazepam; ; ;
							Zolpidem; Triazolam; Temazepam; Placebo;
Li Pi Shan, 2004 (Fair)	Each patient with a diagnosis of either stroke or brain injury was consecutively recruited for eligibility.	Patients were excluded if they were acutely ill, unable to communicate either in English or French, or unable to read and answer questions for any other reason (severe aphasia, blindness, severe cognitive impairment, including patients with posttraumatic amnesia). Subjects were also> 18 years of age. The patients were not excluded if they experienced any secondary causes of insomnia such as depression, sleep apnea, or restless legs syndrome.	Mean age (SD): 56.6 ( ); 44% female; Race/ethnicity: NR	44/ 27/ 18	0/ 0/ 18	As needed for 7 days	Zopiclone; Lorazepam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Liu, 1997 (Poor)	Outpatients who suffered from insomnia for more than 3 months, with at least 3 of the following symptoms: sleep onset greater than 1 hour, total sleep duration of less than 5 hours, more than 2 nocturnal awakenings, and poor subjectively reported sleep quality.	Patients with psychoses or mood disorders, history of severe physical illness, alcohol arouse or drug abuse.	Mean age (SD): 40.1 (10.9); 73% female; Race/ethnicity: NR	NR/ NR/ 15	0/ 0/ 15	14 days	Zopiclone; Triazolam; ;
Mamelak, 1987 (Fair)	Each subject had to have a history of at least 3-month's duration of any two of the following sleep disorders: sleep latency of >= 45 min, total nocturnal sleep time of <6 hours, morning awakening at least 90 min earlier than expected time, or three or more nocturnal awakenings. All subjects were required to be free of centrally acting drugs for at least 3 months before starting the study. Subjects had to be within 20% of normal body weight and only moderate users of alcohol.	Any major medical or psychiatric disorder disqualified the subject from the study. Other disqualifying cases specifically included women of child bearing potential and subjects with histories of drug abuse or allergic reactions to hypnotic-sedative drugs.	Mean age (SD): 50 ( ); 70% female; Race/ethnicity: NR	NR/ NR/ 30	0/ 0/ 30	12 days	Zopiclone; Flurazepam; Placebo; ;
Monti, 1994 (Fair)	All patients were suffering from at least 2 of the following sleep disturbances: time to fall asleep >30 minutes; total sleep time <6 hours,; total nocturnal wake time >20 minutes; number of nocturnal awakenings >3.	Pregnant women, women of child-bearing age with inadequate contraception, breastfeeding mothers, patients suffering from organic disease or severe psychiatric disorders, and patients in whom insufficient compliance was to be expected. Alcohol abuse or intake of hypnotics or anxiolytics and/or antidepressants in the seven days prior to the baseline period also led to exclusion.	Mean age (SD): 47.3 ( ); 88% female; Race/ethnicity: NR	NR/ NR/ 24	1/ 0/ 24	27 days	Zolpidem; Triazolam; Placebo; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Nair, 1990 (Fair)	(a) sleep latency of 30min or more, (b) two or more nocturnal awakenings with difficulty falling back to sleep, (c) early final morning awakening in the absence of depression, and (d) total sleep time usually less than 5 hours and always less than 6 hours.	Organic illness interfering with sleep, serious psychiatric illness, mental retardation, epilepsy, severe head trauma, significant abnormal laboratory findings, other interfering treatments or disorders, women of childbearing potential not following medically recognized contraceptive methods, pregnancy and/or breastfeeding, amphetamine use, or drug hypersensitivity.	Mean age (SD): 46.9 (1.4); 47% female; Race/ethnicity: NR	NR/ NR/ 60	/ /	7 days	Zopiclone; Flurazepam; ; ;
Ngen, 1990 (Fair)	Subjects must be between 18 and 70 years of age and must have one of the following for at least 2 weeks duration; (a) takes longer than 45 min to fall asleep, (b) more than two nocturnal awakenings each night without known cause and difficulty in returning to sleep, (c) sleep duration of less than 6 hours a night	(a) serious concomitant disease, (b) likely to require concomitant medication known to cause drowsiness, (c) psychosis, (d) a history of hypersensitivity to benzodiazepines, (e) drug and/or alcohol abuse, (f) pregnant, a nursing mother or intending to become pregnant during the study, (g) working night shifts	Mean age (SD): 38.4 ( ); 52% female; Race/ethnicity: NR	NR/ NR/ 60	16/ 0/ 44	14 days	Zopiclone; Temazepam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Pagot, 1993 (Fair)	two of the following symptoms: sleep onset latency of more than 30 minutes; more than two nocturnal awakenings; total duration of sleep of less than 6 hours; or total nocturnal wake-time of more than 20 minutes.	Patients who showed sleep disorders associated with severe psychiatric disorders, sleep apnea, sleep-related myoclonus, or insomnia that had developed during childhood, and those who showed serious medical disease or needed concomitant hypnotic medication or treatment that could have had an influence on sleep onset were excluded. Pregnant women and women of childbearing potential who were not taking adequate contraceptive precautions were also excluded, as were nursing mothers and those patients in whom adequate compliance could not be expected. Patients were excluded if they were receiving any treatment that could have an influence on sleep onset.	Mean age (SD): 48 ( ); 61% female; Race/ethnicity: NR	NR/ NR/ 95	33/ 0/ 62	86 days	Zolpidem; Triazolam; ; ;
Ponciano, 1990 (Fair)	Patients were included in the study if they were unable to sleep without medication and had at least 3 of the following symptoms: sleep onset greater than 30 min, total sleep duration of less than 6 hours, poor subjectively reported sleep quality, and/or more than 2 nocturnal awakenings. Patients had to be within normal ranges for body weight, cardiac and haematological variables.	Those patients with a clinically significant history of psychiatric illness and those with a concurrent medical condition or therapy likely to interfere with the medication to be used were excluded. Patients with a history of drug use, those with excessive alcohol consumption (<1 litre of wine/day, or equivalent) pregnant or nursing women and all females of child bearing age without adequate contraception were also excluded.	Mean age (SD): 30 (9); 46% female; Race/ethnicity: NR	NR/ NR/ 26	2/ 0/ 24	21 days	; ; ; ;
							Zopiclone; Flurazepam; Placebo; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Quadens, 1983 (Poor)	The subjects accepted for the study were aged 50-59 years and complained of insomnia for at least 2 month. To be valid the complaints were to include two or more of the following criteria: (1) sleep onset latency equal to or longer than 30 min; (2) total sleeping time during; (3) number of nocturnal awakenings equal to or higher than 3; (4) total waking time during the night equal to or longer than 30 min; (5) sleep qualified as poorly restoring, and (6) repetitiveness of the complaint if no drugs were taken	(1) weight under 45 kg or over 75 kg; (2) chronic use of drugs or alcohol; (3) admission to hospital within the 3 months preceding the recruiting for the trial; (4) mental retardation; (5) physical or psychiatric disability, and (6) treatment altering the absorption, metabolism, or excretion of the drugs and susceptible to alter the evaluation of the hypnotic effects.	Mean age (SD): NR ( ); 100% female; Race/ethnicity: NR	NR/ NR/ 12	0/ 0/ 12	13 days	Zopiclone; Flurazepam; Placebo; ;
Roger, 1993 (Fair)	Patients aged 60 to 90 years who had been hospitalized for any reason (except those listed in the exclusion criteria) and who had had insomnia requiring medication for at least 3 weeks were eligible for inclusion if they met at least two of the following criteria: time to fall asleep > 30 minutes; at least two nocturnal awakenings; total nocturnal time awake > 1 hour; total sleep time < 6 hours; or sensation of premature morning awakening.	Patients were not included if they had concomitant heart or respiratory failure, concurrent malignant or severe disease, history of cerebrovascular accident or transient ischemic accidents, or concurrent requirement for benzodiazepines.	Mean age (SD): 81.1 ( ); 74% female; Race/ethnicity: NR	NR/ NR/ 221	16/ 0/ 205	21 days	Zaleplon 5mg; Zolpidem 10mg; Triazolam; ;
							Zolpidem 5mg; Zolpidem 10mg; Triazolam; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Rosenberg, 1994 (Poor)	Patients between 18-80 years old, have had insomnia for at lease one week complying with at least two of the following criteria: 1) have more than three awakenings per night, 2) sleeping time less than six hours per night, 3) time to fall asleep more than 30 minutes, and 4) awake more than 20 minutes during the night.	General exclusion criteria were psychiatric disease requiring medication, insomnia because of well-defined illness, and treatment with hypnotics or BZDs within four weeks prior to the study. The patients was excluded from data analysis if his diary consisted of comments from less than three days, if his case record form was incompletely filled in by the doctor, or if he had taken hypnotics other than blinded drugs in the study	Mean age (SD): 54 ( ); 0% female; Race/ethnicity: NR	NR/ NR/ 178	5/ 34/ 139	14 days	Zolpidem; Triazolam; ; ;
Schwartz, 2004 (Poor)	inpatient psychiatric care	Subjects were excluded from the study if they were presently taking a hypnotic or sedating psychotropic agent in the evening, if they were using alcohol or dugs, if they were manic, or if they had a medical contraindication to the study medications.	Mean age (SD): NR ( ); 50% female; Race/ethnicity: NR	NR/ NR/ 16	0/ 0/ 16	AsN s	Zaleplon; Trazodone; ; ;
Silvestri, 1996 (Fair)	Both sexes, age between 18 and 65 years, clinical diagnosis of psychophysiological insomnia (either as a first episode or as a recurrence of short-term situational insomnia) or poor sleepers with subjective reporting of at least two out of these four complaints: time to fall asleep >30 minutes, total sleep duration <6 hours, total wake time >20 minutes, and/or number or awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.	Pregnant or lactating women; women of child-bearing age without adequate contraception; uncooperative patients; severe psychiatric diseases, also screened by means of both Hamilton Rating Scale for Anxiety (total score >16) and Hamilton Rating Scale for Depression (total score >16); neurological diseases (myoclonus, kinaesthesis disorders, restless legs syndrome, sleep obstructive apnea of >7 minutes duration); severe internal (heart, renal, liver) diseases; hemocoagulation disorders (Quick's time <70%); intake of any psychotropic drug during 2 weeks preceding the study start as well as a previous with beta blockers or corticosteroids.	Mean age (SD): 33.6 (10.4);	NR/	0/	2 weeks	Zolpidem;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
			55% female; Race/ethnicity: NR	NR/ 22	2/ 20		Triazolam; ; ;
Singh, 1990 (Fair)	NR	Psychotic and neurotic patients were excluded as well as those with a history of mental retardation, chronic alcoholism, drug abuse, coffee or tea abuse, neurological disorders, established sleep apnoea and drug hypersensitivity. Patients with any significant medical condition interfering with sleep, those treatment which could modify drug kinetics were also excluded. Finally, pregnancy, lactation, and child-bearing potential not controlled by a recognized contraceptive programme precluded entry in the study.	Mean age (SD): 39.6 (1.5); 53% female; Race/ethnicity: NR	NR/ 61/ 60	3/ 0/ 57	24 days	Zopiclone 7.5mg; Zopiclone 11.25mg; Flurazepam 30mg; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Steens, 1993 (Fair)	Males and nonpregnant females aged between 35 and 69 years with mild to moderate COPD and insomnia were recruited. Insomnia must have been present for at least 6 months and had to be associated with a sleep latency >30 minutes, sleep duration of 4-6 hours and daytime complaints associated with disturbed sleep. COPD must have been present for at least 3 years and objective inclusion criteria were, FEV1 40-80% predicted, FEV1/FVC=40-70% predicted, diffusion capacity (DL CO) >30% predicted, PaCO2=30-48mm Hg and PaO2 > 55mm Hg. Patients were required to be in stable physical health for at least 2 weeks prior to entering the study, and each gave written informed consent.	Patients were excluded if they had been hospitalized in the previous 4 weeks, if they had right ventricular hypertrophy on the ECG or right heart failure clinically, a hematocrit >55% or if they were on oxygen therapy. They were also excluded if any of the following applied: inability to be withdrawn from hypnotics for the required time (2 nights for triazolam, 7 nights for other short- or intermediate-acting hypnotics and 14 nights for long-acting hypnotics); positive screening for drugs, other than theophylline, know to alter sleep (e.g. benzodiazepines, barbiturates, opiates, amphetamines, cannabinoids and alcohol); medications interfering with the absorption or metabolism of benzodiazepines (e.g. cimetidine); a history suggestive of obstructive sleep apnea or restless legs syndrome/periodic movements during sleep, an adverse effect related to benzodiazepines or CNS depressants, alcohol or drug abuse.	Mean age (SD): 58.2 (5.5); 38% female; Race/ethnicity: NR	NR/ NR/ 24	0/ 0/ 24	1 days	Zolpidem 5mg; Zolpidem 10mg; Triazolam; ;
Stip, 1999 (Fair)	Patients with either primary insomnia or insomnia associated with mild non-psychotic psychiatric disorders (DSM III-R). Daytime fatigability, diminished power of concentration at work and at least two of the following symptoms: falling asleep time greater than 30 min, sleep duration less than 5 hours, more than two awakenings per night and early wake up in the morning.	NR	Mean age (SD): 42.6 ( ); .% female;	NR/ NR/	2/ 8/	21 days	Zopiclone; Nitrazepam;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
			Race/ethnicity: NR	60	50		Placebo; ;
							Zopiclone; Temazepam; ; ;
							Zopiclone; Temazepam; Placebo; ;
Tamminen, 1987 (Poor)	Patients aged 18 to 70 years with sleep disturbances for at least 3 months prior to entrance into the trial were included. Both untreated and preciously treated patients were included. At least two of the following criteria had to be present in untreated patients (they also had to have been present prior to treatment in treated cases): latency of sleep onset >30min, total sleep duration <6.5hours, nocturnal awakenings >2 per night, time to fall asleep after at least one nocturnal awakening >30min, awakening >2hour before scheduled time.	Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causing insomnia or likely to interfere with the assessments, known alcoholism or drug addiction, pregnant women or women who may become pregnant during the trial, frequent intakes of other medication likely to interfere with sleep.	Mean age (SD): 47 ( ); 77% female; Race/ethnicity: NR	NR/ 130/ 94	0/ 0/ 94	42 days	Zopiclone; Nitrazepam; ; ;
Venter, 1986 (Fair)	1) time taken to fall asleep longer than 45 minutes; 2) more than two awakenings each night without known cause, and difficulty in falling asleep again; 3) sleep duration less than six hours a night.	Patients were excluded if they had a psychiatric disorder necessitating treatment with antipsychotic antidepressive, or anticonvulsant drugs, with lithium, or if they received anxiolytic drugs during the day. They were also excluded if they had acute and/or severe cardiac, respiratory, hepatic, or renal disease, or had gastrointestinal disease or prior gastrointestinal surgery, if they had known tolerance to zopiclone or triazolam, or if they had hypersensitivity to drugs.	Mean age (SD): 76.8 ( ); 76% female; Race/ethnicity: NR	58/ 41/ 41	0/ 0/ 41	17 days	Zopiclone; Triazolam; ; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Voshaar, 2004 (Fair)	Patients were included in the study if they were diagnosed with primary insomnia according to DSM-III-R and were aged between 18 and 65 years.	Patients with other axis I disorders, severe somatic disorders, pregnancy, current use of psychotropic medication, complaints of a jet lag in the 2 weeks preceding the study or occupation requiring shift work	Mean age (SD): 46.1 ( ); 0% female; Race/ethnicity: NR	NR/ NR/ 221	9/ 5/ 159	28 days	Zolpidem; Temazepam; ; ;
Walsh, 1998a (Fair)	Patients had to have a minimum of a 1-month history of disturbed sleep, characterized by a self-reported sleep latency (SSL) of at least 30 min, and a self-reported sleep duration (SSD) of 4-6 hours at least three nights per week.	Any significant medical or psychiatric disorder (as determined by clinical interview by a physician), a history suggestive of sleep apnea or periodic limb movement disorder, smoking of more than 10 cigarettes per day, weight varying by more than 25% from desirable weight based on the Metro-politan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation.	Mean age (SD): NR ( ); 0% female; Race/ethnicity: NR	NR/ 589/ 306	28/ 0/ 278	14 days	Zolpidem; Trazodone; ; ;
Walsh, 1998b (Good)	Patients with a DSM-IIIR diagnosis of primary insomnia and two of the following four (including one of the first two) subjective sleep reports: a modal sleep latency >=45 minutes, mean awakenings per night >=3, a mean total sleep time of <6.5 hours/night, and daytime symptoms related to disturbed sleep (e.g. tiredness, impaired functioning, irritability).	Individuals with significant medical or psychiatric illness, as determined by history and physical examination, clinical laboratory tests, the Zung Anxiety and Depression scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplon, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.	Mean age (SD): 40.3 ( ); 58% female; Race/ethnicity: NR	673/ 456/ 132	7/ 0/ 125	14 days	Zaleplon 5mg; Zaleplon 10mg; Triazolam 0.25mg; Placebo;
						33 days	Zaleplon 5mg; Zaleplon 10mg; Triazolam 0.25mg; Placebo;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
Walsh, 2000 (Poor)	Men and women with sleep maintenance insomnia, 18 to 60 years of age.	individuals for any of the following: >120% of ideal body weight, consumption of 20 cigarettes per day or >21 ounces of ethanol per week, currently pregnant or breast-feeding, precious exposure to zaleplon, benzodiazepine sensitivity, use of another investigational drug, psychotropic medication, tryptophan, or melatoantihistamine in the past week, or use of medications that would interfere with the absorption or metabolism of the study drugs.	Mean age (SD): 42 ( ); .% female; Race/ethnicity: NR	73/ 39/ 30	2/ 0/ 22	2 days	Zaleplon; Flurazepam; Placebo; ;
Ware, 1997 (Fair)	Adults 21-55 years old with a complaint of chronic insomnia and polysomnographically disturbed sleep; minimum of a 3-month history of disturbed sleep characterized by a usual sleep time of 4 to 6 hours, a usual sleep latency of at least 30 minutes, and associated daytime complaints.	Any significant medical or psychiatric disorder, history or polysomnographically findings of sleep apnea or periodic leg movements, pregnancy or risk of becoming pregnant, and lactation. History of sensitivity to CNS depressants, regular use of any medication that would interfere with the study, a recent history of alcohol or drug abuse, use of any investigational drug within 30 days of study entry, and previous use of zolpidem also excluded patients. Finally, shift work or any other regularly changing sleep schedule excluded study participation.	Mean age (SD): NR ( ); 58% female; Race/ethnicity: 69% white	358/ NR/ 110	11/ NR/ 99	28 days	Zolpidem; Triazolam; Placebo; ;
Wheatley, 1985 (Fair)	Patients aged 18 years and over suffering from difficulty in sleeping, provided that symptoms had been present for at least one week.	NR	Mean age (SD): 61% female; Race/ethnicity: NR	NR/ NR/ 36	2/ 0/ 36	7 days	Zopiclone; Temazepam; Placebo; ;

Evidence Table 5. Characteristics of active control trials of newer insomnia drugs

Author, year (Quality)	Inclusion Criteria	Exclusion Criteria	Demographics	Screened Eligible Enrolled	Withdrawn Lost to followup Analyzed	Study Duration	Interventions
van der Kleijn, 1989 (Fair)	1. latency of sleep onset exceeding 30 min 2. waking up too early 3. waking up several times at night and difficulty in falling asleep afterwards 4. being bothered during the day by unsatisfactory sleep	1. Patients taking a non-benzodiazepine hypnotic prior to the study those who received another psychotropic drug for the first time, or patients whose psychotropic medicine was changed during the study period. 2. Patients who took benzodiazepine tranquillizers or hypnotics in doses at least twice that recommended before the study. 3. Patients suffering from painful disorder 4. Patients unable to fill in a sleep questionnaire, those with a history of alcohol and/or drug abuse, who lived in psychiatric or physical stress situations likely to fluctuate during the study, with liver or kidney disorders, myasthenia gravis, shift-workers 5. Women pregnant or likely to become pregnant	Mean age (SD): 53 ( ); 71% female; Race/ethnicity: NR	NR/ 60/ 55	2/ 0/ 53	5 days	Zopiclone; Temazepam; Placebo; ;
							Zopiclone; Temazepam; Placebo; Z and T;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
Agnoli, 1989 (Poor)	after the 1st and 2nd weeks of treatment (less score = better)	Zopiclone: lower; Nitrazepam: -; : ; : ; : ; P-value=<0.05
	number of nocturnal arousals, the quality of sleep, the duration of sleep	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	quality of daytime arousal	Zopiclone: better; Nitrazepam: -; : ; : ; : ; P-value=<0.01
	reduction of errors items on the 7th day (more reduction=better)	Zopiclone: more; Nitrazepam: -; : ; : ; : ; P-value=<0.01
	reduction of omitted items on the 14th day (more reduction=better)	Zopiclone: more; Nitrazepam: -; : ; : ; : ; P-value=<0.05
	reduction of omitted items on the 7th day (more reduction=better)	Zopiclone: more; Nitrazepam: -; : ; : ; : ; P-value=<0.01
	time of sleep induction (shorter=better)	Zopiclone: shorter; Nitrazepam: -; : ; : ; : ; P-value=<0.001
	times of execution (shorter=better)	Zopiclone: shorter; Nitrazepam: -; : ; : ; : ; P-value=<0.01
Anderson, 1987 (Fair)	all sleep parameters	Zopiclone: NR; Nitrazepam: NR;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Placebo: ; : ; : ; P-value=NS
	early morning awakenings at week 3 (in figure), higher score=worse	Zopiclone: 0.38; Nitrazepam: 0.35; Placebo: 0.78; : ; : ; P-value=
	physicians global assessment	Zopiclone: NR; Nitrazepam: NR; Placebo: ; : ; : ; P-value=NS
	sleep quality at week 3 (in figure), higher score=better	Zopiclone: 68; Nitrazepam: 66; Placebo: 49; : ; : ; P-value=
	time to fall asleep at week 3 (in figure), higher score=better	Zopiclone: 61; Nitrazepam: 63; Placebo: 44; : ; : ; P-value=
	wide-awake in the morning	Zopiclone: better; Nitrazepam: -; Placebo: ; : ; : ; P-value=0.02
Ansoms, 1991 (Fair)	Improvement from baseline to end of treatment on dreams	Zopiclone: NS; Lorazepam: NS; : ; : ; : ; P-value=
	Improvement from baseline to end of treatment on duration of sleep	Zopiclone: NS; Lorazepam: NS; : ; : ; : ; P-value=
	Improvement from baseline to end of treatment on general evaluation	Zopiclone: NS; Lorazepam: NS; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	Improvement from baseline to end of treatment on morning disposition	Zopiclone: NS; Lorazepam: NS; : ; : ; : ; P-value=
	Improvement from baseline to end of treatment on nocturnal awakenings	Zopiclone: NS; Lorazepam: NS; : ; : ; : ; P-value=
	Improvement from baseline to end of treatment on quality of sleep	Zopiclone: NS; Lorazepam: 0.065; : ; : ; : ; P-value=
	Improvement from baseline to end of treatment on time to fall asleep	Zopiclone: NS; Lorazepam: 0.013; : ; : ; : ; P-value=
	No differences between treatments on any of 18 items based on Norris mood rating scale	Zopiclone: ; Lormetazepam: ; : ; : ; : ; P-value=
	Physician's overall efficacy assessment after treatment ("excellent or good")	Zopiclone: 44; Lormetazepam: 48; : ; : ; : ; P-value=NS
Autret, 1987 (Poor)	Delay in falling asleep (higher score=better)- change from baseline	Zopiclone: 1.86; Triazolam: 1.43; : ; : ; : ; P-value=<0.01
	dream (higher score=better)- change from baseline	Zopiclone: 0.40; Triazolam: 0.32; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	global evaluation (higher score=better)- change from baseline	Zopiclone: 1.96; Triazolam: 1.43; : ; : ; : ; P-value=<0.001
	length of sleep (higher score=better)- change from baseline	Zopiclone: 1.47; Triazolam: 1.26; : ; : ; : ; P-value=NS
	morning state (higher score=better)- change from baseline	Zopiclone: 1.66; Triazolam: 1.13; : ; : ; : ; P-value=<0.001
	night waking (higher score=better)- change from baseline	Zopiclone: 1.64; Triazolam: 1.34; : ; : ; : ; P-value=<0.05
	quality of sleep (higher score=better)- change from baseline	Zopiclone: 1.98; Triazolam: 1.47; : ; : ; : ; P-value=<0.01
	therapeutic efficacy- preferences of the patients	Zopiclone: 62; Temazepam: 26; : ; : ; : ; P-value=<0.01
Begg, 1992 (Poor)	5 of 10 items	Baseline: Low; Midazolam: NR; Zopiclone: High; : ; : ; P-value=
	all 10 items	Baseline: Low; Midazolam: NR; Zopiclone: High; : ; : ; P-value=
	all 10 items (low=beneficial effect)	Baseline: High; Midazolam: Low;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Zopiclone: Low; : ; : ; P-value=p<0.01
Bergener, 1989 (Fair)	Day 33	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=<0.1
Bozin-Juracic, 1998 (Fair)	10 items of main sleep characteristics	Zopiclone: NR; Nitrazepam: NR; Placebo: NR; : ; : ; P-value=NS
	5 items of all day sleep characteristics	Zopiclone: NR; Nitrazepam: NR; Placebo: NR; : ; : ; P-value=NS
	mean sleep efficacy of all day sleep (estimate from the figure)	Zopiclone: 88; Nitrazepam: 87; Placebo: 82; : ; : ; P-value=NR
	mean sleep efficacy of main sleep (estimate from the figure)	Zopiclone: 88; Nitrazepam: 87; Placebo: 82; : ; : ; P-value=NR
	mean total length of main sleep (estimate from the figure)	Zopiclone: 295; Nitrazepam: 285; Placebo: 270; : ; : ; P-value=NR
Chaudoir, 1990 (Fair)	Mean score at week 1	Zopiclone: 57.91; Triazolam: 65.18; : ; : ; : ; P-value=NS (NR)
		Zopiclone: 58.35; Triazolam: 54.49; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS (NR)
		Zopiclone: 67.13; Triazolam: 72.13; : ; : ; : ; P-value=NS (NR)
		Zopiclone: 68.79; Triazolam: 53.03; : ; : ; : ; P-value=NS (NR)
	Patients' global assessment of efficacy	Zopiclone: NR, high; Triazolam: NR, high; : ; : ; : ; P-value=NS
	Physicians' global assessment of efficacy	Zopiclone: NR, high; Triazolam: NR, high; : ; : ; : ; P-value=NS
Drake (1), 2001 (Fair)	ease of falling asleep	Zaleplon 10mg: 65.4; Zaleplon 40mg: 74.1; Triazolam 0.25mg: 67.3; : ; : ; P-value=
	latency to persistent sleep	Zaleplon 10mg: 22.5; Zaleplon 40mg: 18.6; Triazolam 0.25mg: 27.5; : ; : ; P-value=
	latency to sleep	Zaleplon 10mg: 38.8; Zaleplon 40mg: 29.3; Triazolam 0.25mg: 36.4; : ; : ; P-value=
	sleep quality	Zaleplon 10mg: 2.5; Zaleplon 40mg: 2.7; Triazolam 0.25mg: 2.7; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	total sleep time	Zaleplon 10mg: 358.1; Zaleplon 40mg: 375.5; Triazolam 0.25mg: 386.8; : ; : ; P-value=
		Zaleplon 10mg: 386.3; Zaleplon 40mg: 392.6; Triazolam 0.25mg: 407.8; : ; : ; P-value=
Drake (2), 2000 (Fair)	ease of falling asleep (lower score=better)	Zaleplon 20mg: 58.8; Zaleplon 60mg: 64.5; Triazolam 0.25mg: 61; : ; : ; P-value=
	latency to persistent sleep	Zaleplon 20mg: 30.5; Zaleplon 60mg: 21.7; Triazolam 0.25mg: 27.6; : ; : ; P-value=
	latency to sleep	Zaleplon 20mg: 45.5; Zaleplon 60mg: 36.6; Triazolam 0.25mg: 41.9; : ; : ; P-value=
	sleep quality (higher score=better)	Zaleplon 20mg: 2.3; Zaleplon 60mg: 2.4; Triazolam 0.25mg: 2.7; : ; : ; P-value=
	total sleep time	Zaleplon 20mg: 356; Zaleplon 60mg: 376.3; Triazolam 0.25mg: 393.5; : ; : ; P-value=
		Zaleplon 20mg: 391.3; Zaleplon 60mg: 404.7; Triazolam 0.25mg: 422.8; : ; : ; P-value=
Elie, 1990a (Fair)	hangover, mean score	Zopiclone: 16.6; Triazolam: 16.7;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=NS
	morning wake-up, mean score	Zopiclone: 10.5; Triazolam: 10.5; : ; : ; : ; P-value=NS
	quality of sleep, mean score	Zopiclone: 10.8; Triazolam: 11.0; : ; : ; : ; P-value=NS
	rebound: no. of items above show withdrawal effects	Zopiclone: 0; Triazolam: 3; : ; : ; : ; P-value=
	sleep latency, mean score	Zopiclone: 6.7; Triazolam: 6.8; : ; : ; : ; P-value=
	sleep soundness, mean score	Zopiclone: 6.8; Triazolam: 6.4; : ; : ; : ; P-value=
Elie, 1990b (Fair)	duration of sleep at week 4 (higher score=better)	Zopiclone: 7.3; Flurazepam: 7.1; Placebo: 6.5; : ; : ; P-value=
	nocturnal awakenings at week 4 (higher score=worse)	Zopiclone: 3.5; Flurazepam: 3.5; Placebo: 5.5; : ; : ; P-value=
	rapidity of sleep onset at week 4 (higher score=better)	Zopiclone: 11.6; Flurazepam: 11.2; Placebo: 10.5; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	rebound: duration of sleep at day 29 (higher score=better)	Zopiclone: 3.6; Flurazepam: 6.2; Placebo: 7.3; : ; : ; P-value=
	rebound: nocturnal awakenings at day 29 (higher score=worse)	Zopiclone: 5.0; Flurazepam: 6.3; Placebo: 8.0; : ; : ; P-value=
	rebound: rapidity of sleep onset at day 29 (higher score=better)	Zopiclone: 5.8; Flurazepam: 7.3; Placebo: 10; : ; : ; P-value=
Fleming, 1990 (Fair)	rebound insomnia	Zopiclone: 73; Triazolam: 71; : ; : ; : ; P-value=NS
	rebound: sleep duration at the last withdrawal day	Zopiclone: 4.3; Triazolam: 5.9; : ; : ; : ; P-value=<0.05
	rebound: sleep induction at the last withdrawal day	Zopiclone: 4.7; Triazolam: 6.1; : ; : ; : ; P-value=NS
	rebound: sleep induction, duration and soundness at the first withdrawal nights	Zopiclone: NR; Triazolam: NR, worse; : ; : ; : ; P-value=
	rebound: sleep soundness	Zopiclone: NR; Triazolam: NR, better; : ; : ; : ; P-value=<0.05

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	rebound: sleep soundness at the last withdrawal day	Zopiclone: 7.4; Triazolam: 8.6; : ; : ; : ; P-value=NS
	rebound: withdrawal symptoms	Zopiclone: 3; Triazolam: 2; : ; : ; : ; P-value=NS
	total score	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=NS
Fleming, 1995 (Fair)	sleep efficiency	Zolpidem 10mg: NR; Zolpidem 20mg: NR; Flurazepam: NR; : ; : ; P-value=
	sleep latency	Zolpidem 10mg: -14.7; Zolpidem 20mg: -28.4; Flurazepam: -11.8; : ; : ; P-value=
	sleep quality at day 3, (higher score=better)	Zolpidem 10mg: 2.4; Zolpidem 20mg: 2.5; Flurazepam: 1.9; : ; : ; P-value=<0.05
	wake time during sleep	Zolpidem 10mg: NR; Zolpidem 20mg: NR; Flurazepam: NR; : ; : ; P-value=
Fontaine, 1990 (Fair)	daytime anxiety	Zopiclone: 5; Triazolam: 10; : ; : ; : ; P-value=0.16
	duration of sleep	Zopiclone: 2.9; Triazolam: 2.9;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=NS
	global sleep index	Zopiclone: 35.7; Triazolam: 34.6; : ; : ; : ; P-value=NS
	hangover	Zopiclone: 6.8; Triazolam: 6.3; : ; : ; : ; P-value=NS
	morning awakening	Zopiclone: 7.3; Triazolam: 6.7; : ; : ; : ; P-value=NS
	overall	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=NR
	psychic anxiety	Zopiclone: 9.3; Triazolam: 10.8; : ; : ; : ; P-value=NS
	sleep induction cluster	Zopiclone: 14.7; Triazolam: 14.1; : ; : ; : ; P-value=NS
	sleep induction time	Zopiclone: 3.5; Triazolam: 3.5; : ; : ; : ; P-value=NS
	sleep soundness	Zopiclone: 11.0; Triazolam: 10.5; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
	somatic anxiety	Zopiclone: 8.8; Triazolam: 12.0; : ; : ; : ; P-value=<0.01
	total score	Zopiclone: 18.2; Triazolam: 22.4; : ; : ; : ; P-value=<0.01
Hajak, 1998, 1995, 1994 (Fair)	Improved sleep quality and daytime well-being	Zopiclone: 37.4; Triazolam: 32.2; Placebo: 26.8; : ; : ; P-value=
	Improved sleep quality and daytime well-being- treatment period	Zopiclone: 42.3; Triazolam: 36.3; Placebo: ; : ; : ; P-value=0.1133
	Rebound: Nonresponder	Zopiclone: 36.02; Triazolam: 38.93; Placebo: ; : ; : ; P-value=<=0.01
	Rebound: Responder	Zopiclone: 9.05; Triazolam: 7.70; Placebo: 4.92; : ; : ; P-value=<=0.01
	Rebound: daytime well-being - 1 item	Zopiclone: 18.52; Triazolam: 19.04; : ; : ; : ; P-value=NS
	Rebound: daytime well-being - 2 items	Zopiclone: 14.09; Triazolam: 13.10; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	Rebound: daytime well-being - 3 items	Zopiclone: 7.89; Triazolam: 7.73; : ; : ; : ; P-value=NS
	Rebound: overall rebound	Zopiclone: 46.07; Triazolam: 46.63; Placebo: 48.56; : ; : ; P-value=
	Rebound: sleep quality - 1 item	Zopiclone: 14.33; Triazolam: 16.32; : ; : ; : ; P-value=<0.001
	Rebound: sleep quality - 2 items	Zopiclone: 6.76; Triazolam: 8.27; : ; : ; : ; P-value=<=0.05
	Rebound: sleep quality - 3 items	Zopiclone: 2.36; Triazolam: 2.39; : ; : ; : ; P-value=NS
	rebound: Improved sleep quality and daytime well-being	Zopiclone: 27.0; Triazolam: 18.8; Placebo: ; : ; : ; P-value=0.00126
Hayoun, 1989 (Fair)	Efficacy- good or excellent	Zopiclone: 73; Triazolam: 69; : ; : ; : ; P-value=NS
	awakening at night once or not at all	Zopiclone: 64; Triazolam: 89; : ; : ; : ; P-value=NS
	awakening with no concentration difficulties (with a significant investigator-by-treatment	Zopiclone: 56; Triazolam: 82;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	group interaction, p<0.01)	: ; : ; : ; P-value=0.04
	falling asleep in less than 30 minutes	Zopiclone: 63; Triazolam: 84; : ; : ; : ; P-value=NS
	feel more rest	Zopiclone: 80; Triazolam: 92; : ; : ; : ; P-value=NS
	medication aided sleep	Zopiclone: multiple data; Triazolam: multiple data; : ; : ; : ; P-value=NS
	overall	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=NS
	sleep heavily while still reporting a good awakening state	Zopiclone: 55; Triazolam: 70; : ; : ; : ; P-value=NS
	sleep more than 7 hours	Zopiclone: 50; Triazolam: 69; : ; : ; : ; P-value=NS
Klimm, 1987 (Fair)	awakenings at night	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	condition in the morning	Zopiclone: NR; Nitrazepam: NR; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
	dreams	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	duration of sleep	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	feeling on awakening- change from placebo baseline	Zopiclone: -5.7; Nitrazepam: 6.8; : ; : ; : ; P-value=NS
	feeling on awakening- on day 9 and day 11	Zopiclone: better; Nitrazepam: NR; : ; : ; : ; P-value=<0.02
	general evaluation	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	quality of sleep	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS
	quality of sleep- change from placebo baseline	Zopiclone: 24; Nitrazepam: 23.1; : ; : ; : ; P-value=NS
	sleep onset latency	Zopiclone: NR; Nitrazepam: NR; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	sleep onset latency on day 12	Zopiclone: NR; Nitrazepam: better; : ; : ; : ; P-value=<0.001
	sleep onset latency- change from placebo baseline	Zopiclone: -18.2; Nitrazepam: -15.6; : ; : ; : ; P-value=NS
Leppik, 1997 (Fair)	medication strength	Zolpidem: NR, better; Temazepam: NR, better; : ; : ; : ; P-value=
	overall feeling	Zolpidem: NR, better; Temazepam: NR, better; : ; : ; : ; P-value=
	rebound: ease of falling sleep	Zolpidem: ; Triazolam: worse; Temazepam: ; Placebo: ; : ; P-value=
	rebound: sleep quality	Zolpidem: worse; Triazolam: worse; Temazepam: worse; Placebo: ; : ; P-value=
	sleep better	Zolpidem: NR, better; Temazepam: NR, better; : ; : ; : ; P-value=
	sleep duration at week 4	Zolpidem: 362.8; Triazolam: 359.7; Temazepam: 375.3; Placebo: 363; : ; P-value=
	sleep latency	Zolpidem: NR, better; Temazepam: NR, better;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=
	sleep latency at week 1 and week 3	Zolpidem: multiple data; Triazolam: multiple data; Temazepam: ; Placebo: ; : ; P-value=NS
		Zolpidem: shorter; Triazolam: multiple data; Temazepam: ; Placebo: ; : ; P-value=<0.05
	sleep latency at week 4	Zolpidem: 40.5; Triazolam: 47.7; Temazepam: 38.0; Placebo: 57.9; : ; P-value=
	tolerance to treatment	Zolpidem: multiple data; Triazolam: multiple data; Temazepam: multiple data; Placebo: multiple data; : ; P-value=
Li Pi Shan, 2004 (Fair)	alertness (higher score=better)	Zopiclone: 4; Lorazepam: 4; : ; : ; : ; P-value=0.6
		Zopiclone: 9; Lorazepam: 9; : ; : ; : ; P-value=0.6
	depth of sleep (higher score=better)	Zopiclone: 8; Lorazepam: 8; : ; : ; : ; P-value=0.21
	feeling of being refreshed (higher score=better)	Zopiclone: 3.5; Lorazepam: 4; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=0.79
		Zopiclone: 8; Lorazepam: 8; : ; : ; : ; P-value=0.52
	quality of sleep (higher score=better)	Zopiclone: 8; Lorazepam: 8.5; : ; : ; : ; P-value=0.17
	tiredness (higher score=better)	Zopiclone: 8; Lorazepam: 7.5; : ; : ; : ; P-value=0.29
	total score	Zopiclone: 28; Lorazepam: 27; : ; : ; : ; P-value=0.054
	total time of sleep	Zopiclone: 7.23; Lorazepam: 7.49; : ; : ; : ; P-value=0.09
Liu, 1997 (Poor)	2 out of 10 items shows more effectiveness in zopiclone: quality of sleep	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=<0.05
	delay in falling asleep at day 14	Zopiclone: 3.94; Triazolam: 4.13; : ; : ; : ; P-value=NS
	dream at day 14	Zopiclone: 3.93; Triazolam: 3.73; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	global evaluation at day 14	Zopiclone: 4.13; Triazolam: 3.93; : ; : ; : ; P-value=NS
	length of sleep at day 14	Zopiclone: 3.73; Triazolam: 3.53; : ; : ; : ; P-value=NS
	morning state at day 14	Zopiclone: 3.93; Triazolam: 3.60; : ; : ; : ; P-value=NS
	night waking at day 14	Zopiclone: 4.20; Triazolam: 3.33; : ; : ; : ; P-value=<0.05
	quality of sleep at day 14	Zopiclone: 4.33; Triazolam: 3.47; : ; : ; : ; P-value=<0.05
	rebound: 6 out of 7 items shows less rebound effects in Zopiclone	Zopiclone: multiple data; Triazolam: multiple data; : ; : ; : ; P-value=<0.05
	rebound: 9/10 items show more withdrawal sleep disturbance of triazolam	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=<0.05
	therapeutic efficacy	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=NS
Mamelak, 1987 (Fair)	all sleep items at day 14, the end of treatment	Zopiclone: as below; Flurazepam: as below;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Placebo: ; : ; : ; P-value=NS
	duration of early wakefulness at day 14, the end of treatment	Zopiclone: 37.0; Flurazepam: 14.7; Placebo: 43.1; : ; : ; P-value=
	no of awakenings at day 14, the end of treatment	Zopiclone: 1.15; Flurazepam: 1.55; Placebo: 1.65; : ; : ; P-value=
	other rebounds	Zopiclone: multiple data; Flurazepam: multiple data; Placebo: ; : ; : ; P-value=NS
	rebound: duration of early wakefulness at day 15	Zopiclone: 41.5; Flurazepam: 27.8; Placebo: 46.9; : ; : ; P-value=
	rebound: no. of awakenings at day 15	Zopiclone: 2.10; Flurazepam: 2.05; Placebo: 1.70; : ; : ; P-value=
	rebound: no. of awakenings at day 17	Zopiclone: 3.15; Flurazepam: 2.05; Placebo: ; : ; : ; P-value=<0.05
	rebound: sleep latency at day 15	Zopiclone: 105.0; Flurazepam: 39.7; Placebo: ; : ; : ; P-value=<0.05
		Zopiclone: 105.0; Flurazepam: 39.7; Placebo: 75.5; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	rebound: total sleep time at day 15	Zopiclone: 313.5; Flurazepam: 356.5; Placebo: 313.5; : ; : ; P-value=
	sleep latency at day 14, the end of treatment	Zopiclone: 28.8; Flurazepam: 31.5; Placebo: 69.8; : ; : ; P-value=
	total sleep time at day 14, the end of treatment	Zopiclone: 417.5; Flurazepam: 410.5; Placebo: 328.0; : ; : ; P-value=
Monti, 1994 (Fair)	number of sleep cycles (change from baseline) - night 15-16	Zolpidem: 1.7; Triazolam: 0; Placebo: ; : ; : ; P-value=NR
	number of sleep cycles (change from baseline) - night 29-30	Zolpidem: 1.2; Triazolam: 0.3; Placebo: ; : ; : ; P-value=NR
	number of sleep cycles (change from baseline) - night 4-5	Zolpidem: 1.8; Triazolam: 0.3; Placebo: ; : ; : ; P-value=NR
	rebound: decreased sleep duration- day 32	Zolpidem: 3; Triazolam: 6; Placebo: 2; : ; : ; P-value=NR
	rebound: increased number of awakenings-day 32	Zolpidem: 3; Triazolam: 5; Placebo: 0; : ; : ; P-value=NR

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	rebound: increased time to fall sleep- day 32	Zolpidem: 3; Triazolam: 8; Placebo: 0; : ; : ; P-value=NR
	rebound: mean number of sleep cycles (change from baseline)	Zolpidem: 1.3; Triazolam: -0.7; Placebo: ; : ; : ; P-value=NR
	rebound: mean total sleep time (change from baseline)	Zolpidem: 80; Triazolam: -40; Placebo: ; : ; : ; P-value=NR
	rebound: mean wake time (change from baseline)	Zolpidem: -80; Triazolam: 43; Placebo: ; : ; : ; P-value=NR
	total sleep time (change from baseline) - night 15-16	Zolpidem: 127; Triazolam: 33; Placebo: ; : ; : ; P-value=NR
	total sleep time (change from baseline) - night 29-30	Zolpidem: 113; Triazolam: 41; Placebo: ; : ; : ; P-value=NR
	wake time (change from baseline) - night 15-16	Zolpidem: -130; Triazolam: -32; Placebo: ; : ; : ; P-value=NR
	wake time (change from baseline) - night 29-30	Zolpidem: -117; Triazolam: -39; Placebo: ; : ; : ; P-value=NR
Nair, 1990 (Fair)	Severity of illness (Zopiclone 3.75mg only)	Zopiclone: NR; Flurazepam: better;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=NR
	Severity of illness (except Zopiclone 3.75mg)	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
	global improvement, (Zopiclone at any dose)	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
	hangover effects (except zopiclone 3.75mg)	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
	hangover effects (zopiclone 3.75mg only), (higher score=better)	Zopiclone: 7; Flurazepam: 5.5; : ; : ; : ; P-value=<0.05
	quality of morning awakening	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
	quality of sleep	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
	sleep induction time	Zopiclone: NR; Flurazepam: NR; : ; : ; : ; P-value=NS
Ngen, 1990 (Fair)	efficacy- good response	Zopiclone: 10; Temazepam: 12; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
	no. of awakenings at treatment week 1	Zopiclone: 0.77; Temazepam: 1.2; : ; : ; : ; P-value=
	no. of awakenings at treatment week 2	Zopiclone: 0.62; Temazepam: 1.28; : ; : ; : ; P-value=
	sleep latency at treatment week 1	Zopiclone: 84; Temazepam: 25.9; : ; : ; : ; P-value=
	sleep latency at treatment week 2	Zopiclone: 64.5; Temazepam: 26.1; : ; : ; : ; P-value=
	total duration of sleep at treatment week 1	Zopiclone: 5.97; Temazepam: 5.90; : ; : ; : ; P-value=
	total duration of sleep at treatment week 2	Zopiclone: 6.03; Temazepam: 5.62; : ; : ; : ; P-value=
Pagot, 1993 (Fair)	mean sleep time at day 90, change from baseline	Zolpidem: 2.72; Triazolam: 2.26; : ; : ; : ; P-value=NS
	duration of nocturnal awakenings at day 60	Zolpidem: 18; Triazolam: 14; : ; : ; : ; P-value=<0.05

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	number of nocturnal awakenings at day 60, change from baseline	Zolpidem: -1.7; Triazolam: -1; : ; : ; : ; P-value=<0.05
	overall rating	Zolpidem: 38.4; Triazolam: 36.3; : ; : ; : ; P-value=NR
	quality of sleep at day 60	Zolpidem: 74; Triazolam: 65; : ; : ; : ; P-value=NR
	quality of sleep at day 90	Zolpidem: 81; Triazolam: 73; : ; : ; : ; P-value=NR
	rebound: therapeutic effects at day 120- good and excellent	Zolpidem: 33; Triazolam: 34; : ; : ; : ; P-value=NS
	sleep latency at day 90, change from baseline	Zolpidem: -1.9; Triazolam: -1.9; : ; : ; : ; P-value=NS
	status on awakening and alertness, number of patients	Zolpidem: 28; Triazolam: 40; : ; : ; : ; P-value=NR
	therapeutic effects at day 30- good and excellent	Zolpidem: 32; Triazolam: 32; : ; : ; : ; P-value=NS
	therapeutic effects at day 60- good and excellent	Zolpidem: 33; Triazolam: 31;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=NS
	therapeutic effects at day 90- good and excellent	Zolpidem: 32; Triazolam: 29; : ; : ; : ; P-value=NS
	total score	Zolpidem: multiple data; Triazolam: multiple data; : ; : ; : ; P-value=NS
Ponciano, 1990 (Fair)	mood changes	: NR; : NR; : NR; : ; : ; P-value=NS
	sleep duration	Zopiclone: 393; Flurazepam: 425; Placebo: 410; : ; : ; P-value=
	sleep onset latency at day 21	Zopiclone: 30; Flurazepam: 28; Placebo: 60; : ; : ; P-value=
Quadens, 1983 (Poor)	All sleep items comparing two treatment	Zopiclone: as below; Flurazepam: as below; Placebo: ; : ; : ; P-value=NS
	no. of awakenings	Zopiclone: 3.2; Flurazepam: 1.9; Placebo: 6; : ; : ; P-value=
	rebound: no. of awakenings	Zopiclone: 5.5; Flurazepam: 6.1; Placebo: ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	rebound: sleep efficiency index	Zopiclone: 86.9; Flurazepam: 84.9; Placebo: ; : ; : ; P-value=
	rebound: sleep onset latency	Zopiclone: 1255; Flurazepam: 1042; Placebo: ; : ; : ; P-value=
	rebound: total sleep time	Zopiclone: 23490; Flurazepam: 23184; Placebo: ; : ; : ; P-value=
	sleep efficiency index	Zopiclone: 91.4; Flurazepam: 92.2; Placebo: 83.6; : ; : ; P-value=
	sleep onset latency	Zopiclone: 1117; Flurazepam: 1174; Placebo: 1452; : ; : ; P-value=
	total sleep time	Zopiclone: 24903; Flurazepam: 25129; Placebo: 23225; : ; : ; P-value=
Roger, 1993 (Fair)	% of patients falling asleep in <30 minutes at day 24, change from baseline	Zaleplon 5mg: 35; Zolpidem 10mg: 35; Triazolam: 35; : ; : ; P-value=
	% of patients falling asleep well at day 24, change from baseline	Zaleplon 5mg: 55.9; Zolpidem 10mg: 47.9; Triazolam: 51.9; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	% of patients falling asleep well at day 31, change from baseline	Zaleplon 5mg: 34.6; Zolpidem 10mg: 19.8; Triazolam: 18.6; : ; : ; P-value=
	% of patients who reported too early awakening at day 24, change from baseline	Zaleplon 5mg: -35; Zolpidem 10mg: -38; Triazolam: -35; : ; : ; P-value=
	% of patients with >2 awakenings per night at day 24, change from baseline	Zaleplon 5mg: -36.8; Zolpidem 10mg: -28.8; Triazolam: -29.8; : ; : ; P-value=
	% of patients with a total nocturnal waking time >1 hours	Zaleplon 5mg: 55.9; Zolpidem 10mg: 47.9; Triazolam: 55.8; : ; : ; P-value=
	mean total sleep time at day 24, change from baseline	Zaleplon 5mg: 1.6; Zolpidem 10mg: 1.9; Triazolam: 1.9; : ; : ; P-value=
	overall sleep quality at day 24, change from baseline (higher score=better)	Zaleplon 5mg: 35.5; Zolpidem 10mg: 34.4; Triazolam: 33.6; : ; : ; P-value=
	rebound: % of patients falling asleep in <30 minutes at day 31, change from baseline	Zaleplon 5mg: 18; Zolpidem 10mg: 28; Triazolam: 9; : ; : ; P-value=
	rebound: % of patients with a total nocturnal waking time >1 hours	Zaleplon 5mg: 55.9; Zolpidem 10mg: 47.9; Triazolam: 55.8; : ; : ; P-value=
	rebound: feel well rested in the morning, change from baseline (higher score=better)	Zaleplon 5mg: 17.2; Zolpidem 10mg: 23.9;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Triazolam: 10.5; : ; : ; P-value=
	total mean score- safety and efficacy	Zolpidem 5mg: 2.54; Zolpidem 10mg: 2.43; Triazolam: 2.51; : ; : ; P-value=NS
Rosenberg, 1994 (Poor)	No. of awakenings	Zolpidem: 1; Triazolam: 1; : ; : ; : ; P-value=NS
	daytime alertness. unalert-alert	Zolpidem: 65; Triazolam: 63; : ; : ; : ; P-value=NS
	morning feeling, bad-good	Zolpidem: 64; Triazolam: 56; : ; : ; : ; P-value=NS
	sleep quality, bad-good	Zolpidem: 69; Triazolam: 69; : ; : ; : ; P-value=NS
	subjective day feeling	Zolpidem: 64; Triazolam: 60; : ; : ; : ; P-value=NS
	total sleep times	Zolpidem: 6.9; Triazolam: 7.1; : ; : ; : ; P-value=NS
Schwartz, 2004 (Poor)	media change from baseline efficacy and tolerability	Zaleplon: -1; Trazodone: 1; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=0.23
	median at study entry-matching	Zaleplon: 7; Trazodone: 9; : ; : ; : ; P-value=0.885
	sleep- median at study entry-matching	Zaleplon: 3; Trazodone: 3; : ; : ; : ; P-value=0.894
	sleep- median change from baseline efficacy and tolerability	Zaleplon: 0; Trazodone: 3; : ; : ; : ; P-value=0.181
Silvestri, 1996 (Fair)	awakening quality- change from baseline- night 14	Zolpidem: -16.3; Triazolam: -26.9; : ; : ; : ; P-value=NS
	no. of awakenings- change from baseline- night 14	Zolpidem: -2.2; Triazolam: -3.5; : ; : ; : ; P-value=NS
	no. of nocturnal awakenings- change from baseline- night 14	Zolpidem: -1.4; Triazolam: -1.2; : ; : ; : ; P-value=NS
	rebound: awakening quality- change from baseline- night 15	Zolpidem: -12.9; Triazolam: -1.5; : ; : ; : ; P-value=NS
	rebound: no. nocturnal awakenings- change from baseline- night 15	Zolpidem: -0.3; Triazolam: 0.4; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	rebound: no. of awakenings- change from baseline- night 15	Zolpidem: -1.9; Triazolam: -1.2; : ; : ; : ; P-value=NS
	rebound: sleep efficiency- change from baseline- night 15	Zolpidem: 9.9; Triazolam: -6.3; : ; : ; : ; P-value=<0.01
	rebound: sleep onset latency- change from baseline- night 15	Zolpidem: -11.6; Triazolam: 7.1; : ; : ; : ; P-value=NS
	rebound: sleep quality- change from baseline night 15	Zolpidem: -12.9; Triazolam: 0.8; : ; : ; : ; P-value=NS
	rebound: time to fall asleep- change from baseline- night 15	Zolpidem: -20.8; Triazolam: 8.6; : ; : ; : ; P-value=<0.05
	rebound: total sleep time- change from baseline- night 15	Zolpidem: 43.8; Triazolam: -34.5; : ; : ; : ; P-value=<0.01
		Zolpidem: 51.9; Triazolam: -35.6; : ; : ; : ; P-value=<0.01
	rebound: total wake time- change from baseline- night 15	Zolpidem: -2.2; Triazolam: 13.2; : ; : ; : ; P-value=NS
	rebound: wake time after sleep onset- change from baseline- night 15	Zolpidem: 9.9-37.5; Triazolam: 17.3;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=<0.01
	sleep efficiency- change from baseline- night 14	Zolpidem: 14.3; Triazolam: 10.7; : ; : ; : ; P-value=NS
	sleep onset latency- change from baseline- night 14	Zolpidem: -23; Triazolam: -14.8; : ; : ; : ; P-value=NS
	sleep quality- change from baseline- night 14	Zolpidem: -22.8; Triazolam: -31.8; : ; : ; : ; P-value=NS
	time to fall asleep- change from baseline- night 14	Zolpidem: -41.8; Triazolam: -19.9; : ; : ; : ; P-value=NS
	total sleep time- change from baseline- night 14	Zolpidem: 61.1; Triazolam: 54.4; : ; : ; : ; P-value=NS
		Zolpidem: 66.9; Triazolam: 81.4; : ; : ; : ; P-value=NS
	total wake time- change from baseline- night 14	Zolpidem: -12.1; Triazolam: -11.4; : ; : ; : ; P-value=NS
	wake time after sleep onset- change from baseline- night 14	Zolpidem: -44.9; Triazolam: -37; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
Singh, 1990 (Fair)	duration of sleep onset at week 4	Zopiclone 7.5mg: 6.7; Zopiclone 11.25mg: 6.9; Flurazepam 30mg: 7.5; : ; : ; P-value=
	duration of sleep onset, sleep soundness, quality of sleep at week 4	Zopiclone 7.5mg: as above; Zopiclone 11.25mg: as above; Flurazepam 30mg: as above; : ; : ; P-value=
	quality of sleep at week 4	Zopiclone 7.5mg: 11.2; Zopiclone 11.25mg: 11.0; Flurazepam 30mg: 12.2; : ; : ; P-value=
	sleep soundness at week 4	Zopiclone 7.5mg: 6.7; Zopiclone 11.25mg: 6.6; Flurazepam 30mg: 7.5; : ; : ; P-value=
	therapeutic index (less score=worse) at week 4	Zopiclone 7.5mg: 3.2; Zopiclone 11.25mg: 3; Flurazepam 30mg: 2.5; : ; : ; P-value=<0.05
Steens, 1993 (Fair)	Arousals/total sleep time (no./hour)	Zolpidem 5mg: 18.69; Zolpidem 10mg: 16.46; Triazolam: 16.72; : ; : ; P-value=
	awakenings (no./hours of sleep)	Zolpidem 5mg: 4.70; Zolpidem 10mg: 4.07; Triazolam: 3.68; : ; : ; P-value=
	concentration in the morning (1=excellent, 4=poor)	Zolpidem 5mg: 2.30; Zolpidem 10mg: 2.26; Triazolam: 2.13; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	duration of night waking	Zolpidem 5mg: 103.04; Zolpidem 10mg: 16.78; Triazolam: 43.83; : ; : ; P-value=
	ease of falling sleep (lower score=better)	Zolpidem 5mg: 46.48; Zolpidem 10mg: 30.09; Triazolam: 20.96; : ; : ; P-value=
	feeling of sleep (1=excellent, 4=poor)	Zolpidem 5mg: 2.61; Zolpidem 10mg: 2.13; Triazolam: 1.87; : ; : ; P-value=
	microarousals (no./hour of sleep)	Zolpidem 5mg: 14.08; Zolpidem 10mg: 12.57; Triazolam: 13.23; : ; : ; P-value=
	no. of awakenings	Zolpidem 5mg: 2.74; Zolpidem 10mg: 2.17; Triazolam: 1.61; : ; : ; P-value=
	sleep duration	Zolpidem 5mg: 333.26; Zolpidem 10mg: 388.22; Triazolam: 411.17; : ; : ; P-value=
	sleep efficacy	Zolpidem 5mg: 79.74; Zolpidem 10mg: 82.35; Triazolam: 85.83; : ; : ; P-value=
	sleep latency	Zolpidem 5mg: 38.7; Zolpidem 10mg: 30.22; Triazolam: 25.52; : ; : ; P-value=
	sleepy in the morning (higher score=better)	Zolpidem 5mg: 55.04; Zolpidem 10mg: 65.44;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Triazolam: 66.52; : ; : ; P-value=
	total sleep time	Zolpidem 5mg: 384.82; Zolpidem 10mg: 397.12; Triazolam: 413.79; : ; : ; P-value=
	total wake time	Zolpidem 5mg: 93.09; Zolpidem 10mg: 82.37; Triazolam: 66.10; : ; : ; P-value=
	wake time during sleep	Zolpidem 5mg: 55.57; Zolpidem 10mg: 50.69; Triazolam: 40.47; : ; : ; P-value=
Stip, 1999 (Fair)	alertness over all 5 weeks	Zopiclone: multiple data; Nitrazepam: multiple data; Placebo: multiple data; : ; : ; P-value=NS
	anxiety	Zopiclone: NR; Temazepam: NR; Placebo: NR; : ; : ; P-value=NS
	sleep depth after discontinuation- rebound	Zopiclone: NR, worse; Temazepam: NR, worse; : ; : ; : ; P-value=
	sleep depth at treatment week 1	Zopiclone: NR; Temazepam: NR; : ; : ; : ; P-value=
	sleep onset after discontinuation - rebound	Zopiclone: NR; Temazepam: NR, worse; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	sleep onset at treatment week 1	Zopiclone: NR; Temazepam: NR; : ; : ; : ; P-value=
Tamminen, 1987 (Poor)	>2 night awakenings	Zopiclone: 18.4; Nitrazepam: 24.4; : ; : ; : ; P-value=NS
	awakening at least 2 hours before expected time	Zopiclone: 20.4; Nitrazepam: 20; : ; : ; : ; P-value=NS
	duration of sleep <6.5 hours	Zopiclone: 37.5; Nitrazepam: 37.7; : ; : ; : ; P-value=NS
	efficacy (1=poor; 5=excellent)	Zopiclone: 3.2; Nitrazepam: 3.1; : ; : ; : ; P-value=NS
	latency of sleep onset >30 min	Zopiclone: 38; Nitrazepam: 44.4; : ; : ; : ; P-value=0.07
	overall	Zopiclone: -; Nitrazepam: better; : ; : ; : ; P-value=<0.05
	quality of sleep, mean score	Zopiclone: 34; Nitrazepam: 30.2; : ; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	sleep onset latency, mean score	Zopiclone: 32.6; Nitrazepam: 33.1; : ; : ; : ; P-value=NS
	time to fall asleep after a night awakenings >30 min	Zopiclone: 14.6; Nitrazepam: 22.2; : ; : ; : ; P-value=NS
Venter, 1986 (Fair)	Daytime sleep - day 17 (no. of patients)	Zopiclone: 2; Triazolam: 5; : ; : ; : ; P-value=NR
	Daytime sleep - day 17, compare to mean	Zopiclone: -8; Triazolam: 4; : ; : ; : ; P-value=NS
	Daytime sleep - day 7, compare to mean	Zopiclone: -8; Triazolam: 9; : ; : ; : ; P-value=0.07
	Difficulty in falling sleep - day 7 (1=none/very little; 2=some; 3=a lot)	Zopiclone: 1.21; Triazolam: 1.62; : ; : ; : ; P-value=0.03
	Night awakenings - day 17	Zopiclone: NR; Triazolam: 1; : ; : ; : ; P-value=0.06
	Night awakenings - day 7	Zopiclone: 1; Triazolam: 1.7; : ; : ; : ; P-value=0.06
	Sleep duration (hr) - day 7	Zopiclone: 7.4; Triazolam: 7.5;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; : ; : ; P-value=0.05
	Sleep quality, Early morning awakenings, Mental alertness on rising, Sleep satisfaction-day 7	Zopiclone: NR; Triazolam: NR; : ; : ; : ; P-value=NS
Voshaar, 2004 (Fair)	STAI-DY-1 sum score	Zolpidem: 41.6; Temazepam: 39; : ; : ; : ; P-value=NS
	SWEL total score	Zolpidem: 35.7; Temazepam: 35.8; : ; : ; : ; P-value=NS
	rebound- mean total sleep time	Zolpidem: 370; Temazepam: 352; : ; : ; : ; P-value=NS
	rebound- prevalence rebound insomnia (SOL)	Zolpidem: 53.4; Temazepam: 58.3; : ; : ; : ; P-value=NS
	rebound- prevalence rebound insomnia (TST)	Zolpidem: 27; Temazepam: 25.9; : ; : ; : ; P-value=NS
	rebound- sleep onset latency	Zolpidem: 60; Temazepam: 73; : ; : ; : ; P-value=NS
	sleep onset latency	Zolpidem: 46; Temazepam: 46; : ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
	time in bed	Zolpidem: 530; Temazepam: 508; : ; : ; : ; P-value=NS
	total sleep time	Zolpidem: 413; Temazepam: 386; : ; : ; : ; P-value=NS
	wake time after sleep	Zolpidem: 40; Temazepam: 39; : ; : ; : ; P-value=NS
Walsh, 1998a (Fair)	ease of falling asleep at week 2	Zolpidem: 44.3; Trazodone: 44.0; : ; : ; : ; P-value=NS
	number of awakenings at week 2	Zolpidem: 1.5; Trazodone: 1.4; : ; : ; : ; P-value=NS
	overall	Zolpidem: NR; Trazodone: NR; : ; : ; : ; P-value=NS
	sleep duration at week 1	Zolpidem: 378.8; Trazodone: 366.4; : ; : ; : ; P-value=NR
	sleep duration at week 2	Zolpidem: NR; Trazodone: NR; : ; : ; : ; P-value=NS

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	sleep improvement (a lot and somewhat) at week 2	Zolpidem: 60; Trazodone: 62; : ; : ; : ; P-value=NS
	sleep latency at week 1	Zolpidem: 48.2; Trazodone: 57.7; : ; : ; : ; P-value=<0.037
	sleep latency at week 2	Zolpidem: 48.1; Trazodone: 54.5; : ; : ; : ; P-value=NS
	sleep quality at week 2	Zolpidem: 2.45; Trazodone: 2.43; : ; : ; : ; P-value=NS
	sleep status (excellent and good) at week 2	Zolpidem: 49; Trazodone: 47; : ; : ; : ; P-value=NS
	sleep time (increased a lot and increased somewhat) at week 2	Zolpidem: 56; Trazodone: 61; : ; : ; : ; P-value=NS
	subjective waking time after sleep onset at week 2	Zolpidem: 39.5; Trazodone: 42.1; : ; : ; : ; P-value=NS
	time to fall asleep (shortened a lot and shortened somewhat) at week 2	Zolpidem: 56; Trazodone: 50; : ; : ; : ; P-value=NS
Walsh, 1998b (Good)	% of total sleep time spent in each sleep stage- day 4-5 and day 16-17	Zaleplon 5mg: NR; Zaleplon 10mg: NR;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Triazolam 0.25mg: NR; Placebo: NR; : ; P-value=NS
	Latency to persistent sleep- day 16-17	Zaleplon 5mg: 18; Zaleplon 10mg: 16.75; Triazolam 0.25mg: 23.75; Placebo: 20.5; : ; P-value=
		Zaleplon 5mg: 416.5; Zaleplon 10mg: 400; Triazolam 0.25mg: 406.75; Placebo: 408.5; : ; P-value=NS
	Latency to persistent sleep- day 4-5	Zaleplon 5mg: 17; Zaleplon 10mg: 19.25; Triazolam 0.25mg: 18.5; Placebo: 25.38; : ; P-value=
	No. of awakenings- day 4-5 and day 16-17	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: NR; Placebo: NR; : ; P-value=NS
	Subjective no. of awakenings- day 6-14, number	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: NR; Placebo: NR; : ; P-value=
	Subjective sleep latency after discontinuation night, score	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: longer; Placebo: NR; : ; P-value=
	Subjective sleep latency- day 4-5, score	Zaleplon 5mg: shorter; Zaleplon 10mg: shorter; Triazolam 0.25mg: shorter; Placebo: NR; : ; P-value=
	Subjective sleep latency- day 6-14, score	Zaleplon 5mg: shorter; Zaleplon 10mg: shorter; Triazolam 0.25mg: shorter; Placebo: NR;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=
	Subjective total sleep time after discontinuation night, score	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: shorter; Placebo: NR; : ; P-value=
	Subjective total sleep time- day 1-2, score	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: NR; Placebo: NR; : ; P-value=
	Subjective total sleep time- day 3-19, score	Zaleplon 5mg: NR; Zaleplon 10mg: NR; Triazolam 0.25mg: NR; Placebo: NR; : ; P-value=
	Total sleep time day 4-5 and day 16-17, minutes	Zaleplon 5mg: 413.6; Zaleplon 10mg: 402; Triazolam 0.25mg: NR; Placebo: 400; : ; P-value=NS
	Total sleep time- day 16-17	Zaleplon 5mg: 418; Zaleplon 10mg: 396.8; Triazolam 0.25mg: 420; Placebo: 411.3; : ; P-value=
	Total sleep time- day 4-5	Zaleplon 5mg: 413.6; Zaleplon 10mg: 402; Triazolam 0.25mg: 431; Placebo: 400; : ; P-value=
Walsh, 2000 (Poor)	5 hours after drug administration, score	Zaleplon: 16.6; Flurazepam: 6.8; Placebo: 14.4; : ; : ; P-value=
	6.5 hours after drug administration, score	Zaleplon: 14.7; Flurazepam: 5.6; Placebo: 12.1; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	number of minutes sleep	Zaleplon: 195; Flurazepam: 206.3; Placebo: 180; : ; : ; P-value=NR
	time to sleep (minute)	Zaleplon: 27.5; Flurazepam: 22.5; Placebo: 27.5; : ; : ; P-value=NR
Ware, 1997 (Fair)	latency to persistent sleep- night 27 & 28	Zolpidem: -7; Triazolam: 0; Placebo: -15; : ; : ; P-value=
	no. of awakenings- night 27 & 28	Zolpidem: 1; Triazolam: -2; Placebo: -1; : ; : ; P-value=
	rebound: ability to concentrate	Zolpidem: 0.2; Triazolam: 0.1; Placebo: -0.1; : ; : ; P-value=
	rebound: latency to persistent sleep-discontinuation night 1	Zolpidem: 6; Triazolam: 47; Placebo: -11; : ; : ; P-value=
	rebound: morning sleepiness	Zolpidem: -5; Triazolam: -6.7; Placebo: 4.5; : ; : ; P-value=
	rebound: no. of awakenings	Zolpidem: 1; Triazolam: 1; Placebo: -1; : ; : ; P-value=
	rebound: over all rebounds	Zolpidem: 15; Triazolam: 43;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		Placebo: 11; : ; : ; P-value=
	rebound: quality latency	Zolpidem: 0.3; Triazolam: 0.8; Placebo: -0.4; : ; : ; P-value=
	rebound: sleep efficiency- discontinuation night 1	Zolpidem: -3; Triazolam: -15; Placebo: 5; : ; : ; P-value=
	rebound: sleep latency	Zolpidem: 14; Triazolam: 72; Placebo: -16; : ; : ; P-value=
	rebound: total sleep time	Zolpidem: -4; Triazolam: -63; Placebo: 49; : ; : ; P-value=
	rebound: wake min during sleep	Zolpidem: -4; Triazolam: 48; Placebo: -29; : ; : ; P-value=
	sleep efficiency- night 27 & 28	Zolpidem: 1; Triazolam: 3; Placebo: 5; : ; : ; P-value=
	waking time during sleep	Zolpidem: 0; Triazolam: -20; Placebo: 2; : ; : ; P-value=
Wheatley, 1985 (Fair)	All measures	Zopiclone: as above; Temazepam: as above; Placebo: ; : ;

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
		: ; P-value=NS
	At work (0-3)	Zopiclone: 0.51; Temazepam: 0.54; Placebo: ; : ; : ; P-value=
	Dreaming (0-4)	Zopiclone: 0.46; Temazepam: 0.46; Placebo: ; : ; : ; P-value=
	Driving (0-3)	Zopiclone: 0.35; Temazepam: 0.57; Placebo: ; : ; : ; P-value=
	Duration of sleep	Zopiclone: 6.6; Temazepam: 6.6; Placebo: ; : ; : ; P-value=
	No. time waking	Zopiclone: 0.75; Temazepam: 0.66; Placebo: ; : ; : ; P-value=
	Quality of sleep (0-4)	Zopiclone: 0.93; Temazepam: 0.87; Placebo: ; : ; : ; P-value=
	Sleep latency	Zopiclone: 30.8; Temazepam: NR; Placebo: 29.1; : ; : ; P-value=
	State on waking (0-3)	Zopiclone: 0.39; Temazepam: 0.38; Placebo: ; : ; : ; P-value=

Evidence Table 6. Results of active control trials of newer insomnia drugs

Author, year (Quality)	Outcome Measure	Results
	With others (0-3)	Zopiclone: 0.63; Temazepam: 0.67; Placebo: ; : ; : ; P-value=
van der Kleijn, 1989 (Fair)	Better status during the day	Zopiclone: 29; Temazepam: 23; Placebo: 0; Z and T: 0; : ; P-value=NR
	Latency of sleep onset - average score	Zopiclone: 3.8; Temazepam: 3.7; Placebo: 3.1; : ; : ; P-value=
	Preferred drug to continue	Zopiclone: 8; Temazepam: 3; Placebo: 5; Z and T: 2; : ; P-value=NR
	Sleep better	Zopiclone: 16; Temazepam: 10; Placebo: 6; Z and T: 2; : ; P-value=NR
	Sleep quality - average score	Zopiclone: 3.9; Temazepam: 3.9; Placebo: 3.4; : ; : ; P-value=
	Status after awaking - average score	Zopiclone: 3.5; Temazepam: 3.4; Placebo: 3.2; : ; : ; P-value=

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
Allain, 1998	Placebo	bitter taste (Number)	Zopiclone:1; Nitrazepam:0; : ; : ; : ; P-value:
		complaints in answer to the standarized question on tolerance (Number)	Zopiclone:less; Nitrazepam:more; : ; : ; : ; P-value:
		confusion (Number)	Zopiclone:0; Nitrazepam:1; : ; : ; : ; P-value:
		dizziness (Number)	Zopiclone:1; Nitrazepam:0; : ; : ; : ; P-value:
		fatigue (Number)	Zopiclone:0; Nitrazepam:1; : ; : ; : ; P-value:
Allain, 2001	Placebo	excessive sedation (Number)	Zopiclone:2; Temazepam:0; Placebo:1; : ; : ; P-value:
Allain, 2003	H2H	( )	: ; : ; : ; : ; : ; P-value:
Ancoli-Israel, 1999	H2H	( )	: ; : ; : ; : ; : ; P-value:
Anderson, 1987	Active	total withdrawals (Number)	Zopiclone:2; Temazepam:0; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:2; Temazepam:0; : ; : ; : ; P-value:
Ansoms, 1991	Active	Daytime drowsiness (Number)	Zopiclone:3; Temazepam:2; : ; : ; : ; P-value: NR
		Overall AEs, no. of patients (Number)	Zopiclone:10; Temazepam:9; : ; : ; :2; P-value: NR
Asnis, 1999	Placebo	no. of patients experiencing AEs (Number)	Zaleplon 20mg:6; Zaleplon 60mg:17; Triazolam:8; : ; : ; P-value:
Autret, 1987	Active	Depressive (%)	Zopiclone:3; Temazepam:1; Placebo:2; : ; : ; P-value:
		Difficulties to concentrate (Number)	Zopiclone:2; Temazepam:0; Placebo:0; : ; : ; P-value: NR

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		Headache (Number)	Zopiclone:3; Temazepam:3; Placebo:1; : ; : ; P-value: NR
		Irritable/unstable (Number)	Zopiclone:4; Temazepam:4; Placebo:6; : ; : ; P-value: NR
		Sleepy/dull/tired (Number)	Zopiclone:7; Temazepam:6; Placebo:12; : ; : ; P-value: NR
		Trembling/palpitation (Number)	Zopiclone:2; Temazepam:4; Placebo:2; : ; : ; P-value: NR
		Unknown (%)	Zopiclone:2; Temazepam:0; Placebo:3; : ; : ; P-value:
		Well/normal (Number)	Zopiclone:30; Temazepam:35; Placebo:27; : ; : ; P-value: NR
Begg, 1992	Active	Total withdrawals (Number)	Zopiclone:1; Temazepam:1; : ; : ; : ; P-value: NR
		withdrawals due to AEs (Number)	Zopiclone:1; Temazepam:1; : ; : ; : ; P-value: NR
Bergener, 1989	Active	Bad headache (%)	Zopiclone:8; Temazepam:12; Placebo:14; : ; : ; P-value: NR
		Very severe perspiration (%)	Zopiclone:8; Temazepam:18; Placebo:10; : ; : ; P-value: NR
Berry, 2006	Placebo	backache (Number)	Zolpidem:5; Placebo:0; : ; : ; : ; P-value: 0.02
		dizziness (Number)	Zolpidem:6; Placebo:0; : ; : ; : ; P-value: 0.01
		drowsiness (Number)	Zolpidem:7; Placebo:1; : ; : ; : ; P-value: 0.03
		headache (Number)	Zolpidem:36; Placebo:24; : ; : ; : ; P-value: 0.08

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		irritability (Number)	Zolpidem:5; Placebo:2; : ; : ; : ; P-value: 0.02
		upper respiratory tract infection (Number)	Zolpidem:11; Placebo:5; : ; : ; : ; P-value: 0.11
Bozin-Juracic, 1998	Active	due to AEs (Number)	Zopiclone 7.5mg:0; Zopiclone 11.25mg:1; Flurazepam 30mg:0; : ; : ; P-value:
		total (Number)	Zopiclone 7.5mg:0; Zopiclone 11.25mg:2; Flurazepam 30mg:1; : ; : ; P-value:
Chaudoir, 1983	Placebo	arthralgia (Number)	Zolpidem:4; Triazolam:5; Temazepam:0; Placebo:3; : ; P-value:
		drowsiness (Number)	Zolpidem:4; Triazolam:7; Temazepam:8; Placebo:3; : ; P-value:
		dyspepsia (Number)	Zolpidem:5; Triazolam:3; Temazepam:5; Placebo:7; : ; P-value:
		fatigue (Number)	Zolpidem:1; Triazolam:2; Temazepam:5; Placebo:1; : ; P-value:
		headache (Number)	Zolpidem:15; Triazolam:22; Temazepam:18; Placebo:16; : ; P-value:
		myalgia (Number)	Zolpidem:8; Triazolam:7; Temazepam:8; Placebo:9; : ; P-value:
		nausea (Number)	Zolpidem:6; Triazolam:6; Temazepam:4; Placebo:6; : ; P-value:
		nervousness (Number)	Zolpidem:2; Triazolam:7; Temazepam:3; Placebo:4; : ; P-value:
		overall incidence rates (Number)	Zolpidem:52; Triazolam:54; Temazepam:56; Placebo:47; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		upper resp infection (Number)	Zolpidem:6; Triazolam:2; Temazepam:7; Placebo:7; : ; P-value:
Chaudoir, 1990	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
Declerck, 1999	Placebo	moderate or severe adverse effects reported (%)	Zopiclone:18; Triazolam:42; : ; : ; : ; P-value: <0.05
		no. of patients experiencing adverse effect (Number)	Zopiclone:18; Triazolam:20; : ; : ; : ; P-value: NS
		taste perception (Number)	Zopiclone:NR; Triazolam:NR, more; : ; : ; : ; P-value: <0.05
Dockhorn, 1996	Placebo	bitter taste (Number)	Zopiclone:5; Triazolam:0; : ; : ; : ; P-value:
		reduction of dreams (Number)	Zopiclone:5; Triazolam:3; : ; : ; : ; P-value:
Dorsey, 2004	Placebo	headache (highest incidence) (%)	Zolpidem:24; Trazodone:30; Placebo:19; : ; : ; P-value:
		somnolence (highest incidence) (%)	Zolpidem:16; Trazodone:23; Placebo:8; : ; : ; P-value:
		total number of events (Number)	Zolpidem:78; Trazodone:75; : ; : ; : ; P-value: NS
Drake (1), 2001	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
Drake (2), 2000	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
Drewes, 1991	Placebo	total withdrawals (Number)	Zolpidem:6; Triazolam:14; Temazepam:10; Placebo:10; : ; P-value:
		withdrawals due to AEs (Number)	Zolpidem:2; Triazolam:5; Temazepam:5; Placebo:6; : ; P-value:

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
Drewes, 1998	Placebo	total withdrawals (Number)	Zaleplon 10mg:NR; Zaleplon 40mg:NR; Triazolam 0.25mg:NR; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zaleplon 10mg:0; Zaleplon 40mg:0; Triazolam 0.25mg:0; : ; : ; P-value:
Elie, 1990a	Active	( )	: ; : ; : ; : ; : ; P-value:
Elie, 1990b	Active	( )	: ; : ; : ; : ; : ; P-value:
Elie, 1999	H2H	Any adverse event (%)	Zolpidem:5.7; Zaleplon:7.5; : ; : ; : ; P-value: NR
Erman, 2006	Placebo	total withdrawals (Number)	Zopiclone:1; Triazolam:3; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Triazolam:1; : ; : ; : ; P-value:
Fava	Placebo	amnesia (Number)	Zolpidem 10mg:1; Zolpidem 15mg:2; Placebo:0; : ; : ; P-value:
		arthralgia (Number)	Zolpidem 10mg:1; Zolpidem 15mg:0; Placebo:2; : ; : ; P-value:
		confusion (Number)	Zolpidem 10mg:0; Zolpidem 15mg:2; Placebo:0; : ; : ; P-value:
		dizziness (Number)	Zolpidem 10mg:3; Zolpidem 15mg:4; Placebo:0; : ; : ; P-value:
		drowsiness (Number)	Zolpidem 10mg:3; Zolpidem 15mg:5; Placebo:2; : ; : ; P-value:
		drugged (Number)	Zolpidem 10mg:2; Zolpidem 15mg:1; Placebo:0; : ; : ; P-value:
		dry mouth (Number)	Zolpidem 10mg:0; Zolpidem 15mg:2; Placebo:0; : ; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		dyspepsia (Number)	Zolpidem 10mg:2; Zolpidem 15mg:2; Placebo:0; : ; : ; P-value:
		headache (Number)	Zolpidem 10mg:2; Zolpidem 15mg:4; Placebo:7; : ; : ; P-value:
		lethargy (Number)	Zolpidem 10mg:2; Zolpidem 15mg:1; Placebo:1; : ; : ; P-value:
		nausea (Number)	Zolpidem 10mg:1; Zolpidem 15mg:3; Placebo:1; : ; : ; P-value:
		rhinitis (Number)	Zolpidem 10mg:0; Zolpidem 15mg:0; Placebo:2; : ; : ; P-value:
Fava, 2006	Placebo	total withdrawals, (placebo = 2) (Number)	Zopiclone 3.75mg:0; Zopiclone 7.5mg:0; Zopiclone 11.5mg:1; Zopiclone 15mg:1; Flurazepam:0; P-value:
		withdrawals due to AEs, (placebo = 1) (Number)	Zopiclone 3.75mg:0; Zopiclone 7.5mg:0; Zopiclone 11.5mg:1; Zopiclone 15mg:1; Flurazepam:0; P-value:
Fleming, 1990	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
Fleming, 1995	Active	Withdrawals due to adverse events (%)	Zolpidem:6.1; Zopiclone:8.1; : ; : ; : ; P-value: NR
Fontaine, 1990	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
Fry, 2000	H2H	Nausea (Number)	Placebo:0; Zaleplon 5mg:0; Zaleplon 10mg:1; Triazolam:4; : ; P-value:
		Overall number of reports (Number)	Placebo:13; Zaleplon 5mg:12; Zaleplon 10mg:14; Triazolam:17; : ; P-value: NS

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		headache- the most common adverse event (Number)	Placebo:5; Zaleplon 5mg:5; Zaleplon 10mg:6; Triazolam:7; : ; P-value:
Goldenberg, 1994	Placebo	( )	: ; : ; : ; : ; : ; P-value:
Gronblad, 1993	Placebo	total withdrawals (Number)	Zolpidem 10mg:0; Zolpidem 20mg:7; Flurazepam 30mg:1; Placebo:0; : ; P-value: NR
		withdrawal due to AEs (Number)	Zolpidem 10mg:0; Zolpidem 20mg:6; Flurazepam 30mg:0; Placebo:0; : ; P-value: NR
Hajak, 1998, 1995, 1994	Active	number of patient reporting AEs on day 7 and day 9 (Number)	Zopiclone:more; Triazolam:NR; : ; : ; : ; P-value: 0.013
		total number of patient (Number)	Zopiclone:7; Triazolam:8; : ; : ; : ; P-value: NR
Hayoun, 1989	Active	Patients experiencing adverse events "related", "possibly related" or "probably related" to study medication (%)	Zolpidem:31; Zopiclone:45; : ; : ; : ; P-value: 0.004
Hedner, 2000	Placebo	Overall AEs (%)	Zopiclone:26; Lormetazepam:28; : ; : ; : ; P-value: NS
Herrmann, 1993	Placebo	overall side effects (%)	Zopiclone:NR; Zaleplon:NR; : ; : ; : ; P-value: NS
Hindmarch, 1995	Placebo	total withdrawals (Number)	Zolpidem 5mg:7; Zolpidem 10mg:1; Triazolam:5; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zolpidem 5mg:0; Zolpidem 10mg:0; Triazolam:2; : ; : ; P-value:
Klimm, 1987	Active	total withdrawals (Number)	Zolpidem:0; Triazolam:2; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zolpidem:0; Triazolam:0; : ; : ; : ; P-value:
Krystal	Placebo	CNS related (Number)	Zolpidem 10mg:19; Zolpidem 15mg:15; Placebo:15; : ; : ; P-value:

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		dizziness (%)	Zolpidem 10mg:5; Zolpidem 15mg:7; Placebo:4; : ; : ; P-value:
		drowsiness (%)	Zolpidem 10mg:11; Zolpidem 15mg:12; Placebo:6; : ; : ; P-value:
		lethargy (%)	Zolpidem 10mg:7; Zolpidem 15mg:2; Placebo:0; : ; : ; P-value:
		overall (Number)	Zolpidem 10mg:25; Zolpidem 15mg:30; Placebo:56; : ; : ; P-value:
		pharyngitis (%)	Zolpidem 10mg:2; Zolpidem 15mg:9; Placebo:2; : ; : ; P-value:
		rhinitis (%)	Zolpidem 10mg:0; Zolpidem 15mg:7; Placebo:2; : ; : ; P-value:
Krystal (poster)	Placebo	total withdrawals (Number)	Zopiclone:0; Flurazepam:0; Placebo:2; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Flurazepam:0; Placebo:1; : ; : ; P-value:
Krystal, 2003	Placebo	( )	: ; : ; : ; : ; : ; : ; P-value:
Lahmeyer, 1997	Placebo	no, of patients (Number)	Zopiclone:9; Nitrazepam:NR; : ; : ; : ; P-value:
Lemoine, 1995	H2H	Patients with treatment-emergent adverse events (%)	Zaleplon 5 mg:59; Zaleplon 10 mg:73; Zaleplon 20 mg:61; Zolpidem 10 mg:64; : ; P-value:
Leppik, 1997	Active	( )	: ; : ; : ; : ; : ; P-value:
Li Pi Shan, 2004	Active	number of patients (Number)	Zopiclone:8; Flurazepam:8; : ; : ; : ; P-value: NS

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		withdrawals due to AEs (Number)	Zopiclone:2; Flurazepam:5; : ; : ; : ; : ; P-value: NS
Liu, 1997	Active	Total withdrawals (%)	Zaleplon 5 mg:16.9; Zaleplon 10 mg:15.0; Zaleplon 20 mg:14.5; Zolpidem 10 mg:17.2; : ; P-value:
Lofaso, 1997	Placebo	total withdrawals (Number)	Zaleplon 20mg:NR; Zaleplon 60mg:NR; Triazolam:NR; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zaleplon 20mg:0; Zaleplon 60mg:1; Triazolam:0; : ; : ; P-value:
Mamelak, 1987	Active	( )	: ; : ; : ; : ; : ; : ; P-value:
McCall	Placebo	diarrhea (%)	Zolpidem:4.3; Placebo:0; : ; : ; : ; : P-value:
		dizziness (%)	Zolpidem:4.3; Placebo:0; : ; : ; : ; : P-value:
		drowsiness (%)	Zolpidem:5.8; Placebo:1.4; : ; : ; : ; : P-value:
		headache (%)	Zolpidem:31.9; Placebo:24.6; : ; : ; : ; : P-value:
		myalgia (%)	Zolpidem:1.4; Placebo:4.3; : ; : ; : ; : P-value:
		nausea (%)	Zolpidem:1.4; Placebo:4.3; : ; : ; : ; : P-value:
Moldofsky, 1996	Placebo	total withdrawals (Number)	Zolpidem:NR; Temazepam:NR; : ; : ; : ; : P-value:
		withdrawals due to Aes (Number)	Zolpidem:NR; Temazepam:NR; : ; : ; : ; : P-value:
Monchesky, 1986	Placebo	total withdrawals (Number)	Zopiclone:NR; Lorazepam:NR; : ; : ; : ; : P-value:
		withdrawals due to Aes (Number)	Zopiclone:NR; Lorazepam:NR; : ; : ; : ; : P-value:
Monchesky, 1989	Placebo	total withdrawals (Number)	Zolpidem:11; Trazodone:10; Placebo:7; : ; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		withdrawals due to AEs (Number)	Zolpidem:5; Trazodone:5; Placebo:2; : ; : ; P-value:
Monti, 1994	Active	Emergent adverse events (Number)	Zolpidem:13; Triazolam:16; Placebo:10; : ; : ; P-value: NR
Monti, 1996	Placebo	anxiety (Score)	Zopiclone:3.8; Nitrazepam:-6.8; : ; : ; : ; P-value: <0.05
		dizziness (Score)	Zopiclone:3.5; Nitrazepam:-7.8; : ; : ; : ; P-value: <0.05
		indigestion (Score)	Zopiclone:8.8; Nitrazepam:-10; : ; : ; : ; P-value: <0.05
		loss of appetite (Score)	Zopiclone:0; Nitrazepam:-6.5; : ; : ; : ; P-value: NS
		nausea (Score)	Zopiclone:4.3; Nitrazepam:-3.2; : ; : ; : ; P-value: <0.05
		physical tiredness (Score)	Zopiclone:-3.5; Nitrazepam:-10.3; : ; : ; : ; P-value: NS
		restlessness (Score)	Zopiclone:2.2; Nitrazepam:-5.9; : ; : ; : ; P-value: NS
		sweating (Score)	Zopiclone:5.7; Nitrazepam:-7.1; : ; : ; : ; P-value: NS
Monti, 2000	Placebo	apnea-hypopnea (Number)	Zolpidem 5mg:1; Zolpidem 10mg:2; Triazolam:1; : ; : ; P-value:
		reduction of SaO2 (Number)	Zolpidem 5mg:0; Zolpidem 10mg:2; Triazolam:2; : ; : ; P-value:
Nair, 1990	Active	( )	: ; : ; : ; : ; : ; P-value:
Ngen, 1990	Active	Withdrawals due to adverse effects (%)	Zaleplon 5mg:3; Zaleplon 10mg:4; Zaleplon 20mg:9; Zolpidem 10mg:6; : ; P-value:
Pagot, 1993	Active	due to AEs (Number)	Zopiclone:0; Flurazepam:0; : ; : ; : ; P-value: NR

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		total (Number)	Zopiclone:0; Flurazepam:0; : ; : ; : ; P-value: NR
Parrino	Placebo	anxiety (Number)	Zolpidem:1; Placebo:1; : ; : ; : ; P-value: NR
		palpitations (Number)	Zaleplon:1; Placebo:2; : ; : ; : ; P-value: NR
		transpiration (Number)	Zolpidem:1; Placebo:2; : ; : ; : ; P-value: NR
Perlis, 2004	Placebo	safety score (1=poor; 5=excellent) (Score)	Zopiclone:3.4; Nitrazepam:3.5; : ; : ; : ; P-value: NS
Ponciano, 1990	Active	( )	: ; : ; : ; : ; : ; P-value:
Quadens, 1983	Active	( )	: ; : ; : ; : ; : ; P-value:
Roehrs (poster)	Placebo	total withdrawals (Number)	Zopiclone:7; Temazepam:7; Placebo:10; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:2; Temazepam:0; Placebo:1; : ; : ; P-value:
Roger, 1993	Active	total withdrawals (Number)	Zolpidem:NR; Triazolam:NR; Placebo:NR; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zolpidem:3; Triazolam:4; Placebo:0; : ; : ; P-value:
Rosenberg	Placebo	apraxia (Number)	Zolpidem 10mg:2; Zolpidem 20mg:1; Placebo:2; : ; : ; P-value:
		daytime sedation (Number)	Zolpidem 10mg:3; Zolpidem 20mg:1; Placebo:0; : ; : ; P-value:
		infection (Number)	Zolpidem 10mg:2; Zolpidem 20mg:0; Placebo:0; : ; : ; P-value:
		overall (Number)	Zolpidem 10mg:4; Zolpidem 20mg:7; Placebo:3; : ; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		post-treatment adverse event (pneumonia and daytime aggression) (Number)	Zolpidem 10mg:1; Zolpidem 20mg:1; Placebo:2; : ; : ; P-value:
		rash (Number)	Zolpidem 10mg:0; Zolpidem 20mg:1; Placebo:0; : ; : ; P-value:
Rosenberg, 1994	Active	rebound: pessimist (Number)	Zolpidem:lower; Triazolam:higher; : ; : ; : ; P-value: 0.040
			Zolpidem:lower; Triazolam:higher; : ; : ; : ; P-value: 0.096
		rebound: tense (Number)	Zolpidem:lower; Triazolam:higher; : ; : ; : ; P-value: 0.061
Roth	Placebo	headache - during treatment (Number)	Zolpidem:3; Placebo:4; : ; : ; : ; P-value:
		headache - withdrawal (Number)	Zolpidem:2; Placebo:1; : ; : ; : ; P-value:
		rebound insomnia (Total)	Zolpidem:0; Placebo:15; : ; : ; : ; P-value:
Roth 2006	Placebo	total withdrawals (Number)	Zopiclone:0; Temazepam:1; Placebo:1; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Temazepam:0; Placebo:0; : ; : ; P-value:
Sabbatini, 2003	Placebe	total withdrawals (Number)	Zaleplon 5mg:3; Zaleplon 10mg:1; Triazolam:0; Placebo:3; : ; P-value:
		withdrawals due to AEs (Number)	Zaleplon 5mg:1; Zaleplon 10mg:0; Triazolam:0; Placebo:0; : ; P-value:
Scharf, 1994	Placebo	12 out of 18 items shows favour Zopiclone (Score)	Zopiclone:NR, better; Triazolam:NR; : ; : ; : ; P-value: <0.05
Scharf, 2005	Placebo	abnormal vision (Number)	Zolpidem 10mg:0; Zolpidem 20mg:2; Flurazepam 30mg:0; Placebo:0; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		amnesia (Number)	Zolpidem 10mg:1; Zolpidem 20mg:3; Flurazepam 30mg:1; Placebo:0; : ; P-value:
		any event (Number)	Zolpidem 10mg:14; Zolpidem 20mg:23; Flurazepam 30mg:15; Placebo:15; : ; P-value: <0.05
		ataxia (Number)	Zolpidem 10mg:1; Zolpidem 20mg:3; Flurazepam 30mg:0; Placebo:1; : ; P-value:
		back pain (Number)	Zolpidem 10mg:0; Zolpidem 20mg:2; Flurazepam 30mg:0; Placebo:0; : ; P-value:
		confusion (Number)	Zolpidem 10mg:0; Zolpidem 20mg:2; Flurazepam 30mg:0; Placebo:0; : ; P-value:
		difficulty concentrating (Number)	Zolpidem 10mg:0; Zolpidem 20mg:0; Flurazepam 30mg:1; Placebo:2; : ; P-value:
		dizziness (Number)	Zolpidem 10mg:0; Zolpidem 20mg:3; Flurazepam 30mg:1; Placebo:0; : ; P-value:
		drugged feeling (Number)	Zolpidem 10mg:0; Zolpidem 20mg:2; Flurazepam 30mg:1; Placebo:0; : ; P-value:
		dry mouth (Number)	Zolpidem 10mg:0; Zolpidem 20mg:1; Flurazepam 30mg:2; Placebo:0; : ; P-value:
		dysarthria (Number)	Zolpidem 10mg:1; Zolpidem 20mg:3; Flurazepam 30mg:0; Placebo:0; : ; P-value:
		fatigue (Number)	Zolpidem 10mg:3; Zolpidem 20mg:2; Flurazepam 30mg:0; Placebo:1; : ; P-value:
		headache (Number)	Zolpidem 10mg:4; Zolpidem 20mg:2; Flurazepam 30mg:4; Placebo:3; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value:
		light-headedness (Number)	Zolpidem 10mg:0; Zolpidem 20mg:0; Flurazepam 30mg:2; Placebo:0; : ; P-value:
		myalgia (Number)	Zolpidem 10mg:0; Zolpidem 20mg:2; Flurazepam 30mg:1; Placebo:1; : ; P-value:
		nervousness (Number)	Zolpidem 10mg:1; Zolpidem 20mg:2; Flurazepam 30mg:1; Placebo:0; : ; P-value:
		pharyngitis (Number)	Zolpidem 10mg:2; Zolpidem 20mg:0; Flurazepam 30mg:1; Placebo:0; : ; P-value:
		vomiting (Number)	Zolpidem 10mg:0; Zolpidem 20mg:3; Flurazepam 30mg:0; Placebo:0; : ; P-value:
Schnitzer (poster)	Placebo	total withdrawals (Number)	Zopiclone:1; Nitrazepam:1; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Nitrazepam:1; : ; : ; : ; P-value:
Schwartz, 2004	Active	( )	: ; : ; : ; : ; : ; P-value:
Sepracor Study #190-045	H2H	total withdrawals (Number)	Zopiclone:0; Flurazepam:0; Placebo:0; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Flurazepam:0; Placebo:0; : ; : ; P-value:
Shaw, 1992	Placebo	( )	: ; : ; : ; : ; : ; P-value:
Silvestri, 1996	Active	( )	: ; : ; : ; : ; : ; P-value:
Singh, 1990	Active	1st week (Number)	Zopiclone:1; Nitrazepam:1; : ; : ; : ; P-value: NR
Soares	Placebo	abnormal coordination (Number)	Zopiclone:2; Placebo:0; : ; : ; : ; P-value: NS

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		balance disorder (Number)	Zopiclone:3; Placebo:0; : ; : ; : ; P-value: NS
		drowsiness (Number)	Zopiclone:7; Placebo:1; : ; : ; : ; P-value: NS
		dry mouth (Number)	Zopiclone:2; Placebo:2; : ; : ; : ; P-value: NS
		headache (Number)	Zopiclone:3; Placebo:5; : ; : ; : ; P-value: NS
		taste disturbance (Number)	Zopiclone:20; Placebo:6; : ; : ; : ; P-value: <0.05
Soares (poster)	Placebo	total withdrawals (Number)	Zopiclone:0; Lorazepam:0; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Lorazepam:0; : ; : ; : ; P-value:
Soubrane (poster)	Placebo	total withdrawals (Number)	Zopiclone:0; Triazolam:0; : ; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:0; Triazolam:0; : ; : ; : ; P-value:
Staner, 2005	H2H	total withdrawals (Number)	Zopiclone:190; Triazolam:187; Placebo:193; : ; : ; P-value:
		withdrawals due to AEs (Number)	Zopiclone:26; Triazolam:11; Placebo:25; : ; : ; P-value:
Steens, 1993	Active	no. of adverse events reported by patients (Number)	Zolpidem:1; Triazolam:1; : ; : ; : ; P-value: NR
Stip, 1999	Active	1st week (Number)	Zopiclone:0; Nitrazepam:6; : ; : ; : ; P-value: NR
		2dn week (Number)	Zopiclone:0; Nitrazepam:14; : ; : ; : ; P-value: NR
		prolonged into the wash-out period between treatment (Number)	Zopiclone:0; Nitrazepam:3; : ; : ; : ; P-value: NR
Tamminen, 1987	Active	No. of AEs (Number)	Zopiclone:21; Midazolam:28; : ; : ; : ; P-value: >0.05
		No. of patients experiencing AEs (overall) (Number)	Zopiclone:15; Midazolam:16; : ; : ; : ; P-value: >0.05

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
		No. of patients experiencing AEs - Clumsiness (Number)	Zopiclone:0; Midazolam:4; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Daytime tiredness (Number)	Zopiclone:6; Midazolam:6; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Disturbed sleep pattern (Number)	Zopiclone:2; Midazolam:5; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Dry mouth (Number)	Zopiclone:2; Midazolam:3; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Indigestion/nausea/vomiting (Number)	Zopiclone:1; Midazolam:5; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Others (Number)	Zopiclone:4; Midazolam:5; : ; : ; : ; P-value: NR
		No. of patients experiencing AEs - Taste disturbance (Number)	Zopiclone:6; Midazolam:0; : ; : ; : ; P-value: NR
Terzano, 1992	Placebo	ataxia (Number)	Zopiclone:2; Triazolam:3; Placebo:1; : ; : ; P-value: NS
		drowsiness (Number)	Zopiclone:3; Triazolam:5; Placebo:4; : ; : ; P-value: NS
		dry mouth (Number)	Zopiclone:7; Triazolam:1; Placebo:1; : ; : ; P-value: <0.05
		headache (Number)	Zopiclone:6; Triazolam:3; Placebo:3; : ; : ; P-value: NS
		nausea (Number)	Zopiclone:2; Triazolam:3; Placebo:4; : ; : ; P-value: NS
		taste perversion (Number)	Zopiclone:17; Triazolam:3; Placebo:1; : ; : ; P-value: <0.001
Tsutsui, 2001	H2H	Incidence of 3 or more new withdrawal symptoms after discontinuation of treatment (NR)	Zolpidem 10 mg:NR; Zaleplon 10 mg:NR; : ; : ; : ; P-value:
Venter, 1986	Active	depression, tearfulness, drowsiness, dizziness, agitation, nightmares, confusion, and disturbed sleep (Number)	Zopiclone:3; Triazolam:7; : ; : ; : ;

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
			P-value: NR
Voshaar, 2004	Active	Withdrawals due to adverse events (%)	Zaleplon 5 mg:2; Zaleplon 10 mg:6; Zaleplon 20 mg:2; Zolpidem 10 mg:6; : ; P-value:
Walsh	Placebo	anxiety (%)	Zolpidem:4; Placebo:0; : ; : ; : ; P-value: NR
		bitter taste (Number)	Zolpidem:11; Placebo:0; : ; : ; : ; P-value:
		dry mouth (Number)	Zaleplon:10; Placebo:5; : ; : ; : ; P-value:
		headache (%)	Zolpidem:3.2; Placebo:0; : ; : ; : ; P-value: NR
		overall (Number)	Zolpidem:23; Placebo:18; : ; : ; : ; P-value: NS
		overall drop out (Number)	Zolpidem:30; Placebo:54; : ; : ; : ; P-value: NS
		rhinitis (%)	Zolpidem:0; Placebo:3.3; : ; : ; : ; P-value: NR
Walsh, 1998a	Active	Total withdrawals (%)	Zolpidem:13.9; Zopiclone:18.1; : ; : ; : ; P-value: NS
Walsh, 1998b	Active	CNS-related adverse events (Number)	Zolpidem:8; Triazolam:10; : ; : ; : ; P-value: NS
		GI-related adverse events (Number)	Zolpidem:2; Triazolam:3; : ; : ; : ; P-value: NS
		other adverse events (Number)	Zolpidem:5; Triazolam:2; : ; : ; : ; P-value: NS
		total (Number)	Zolpidem:15; Triazolam:15; : ; : ; : ; P-value: NS
Walsh, 2000	Active	1st week (Number)	Zopiclone:0; Nitrazepam:1; : ; : ; : ; P-value: NR
Walsh, 2000a	Placebo	nightmares- the most common adverse effect (Number)	Zolpidem 5mg:2; Zolpidem 10mg:3; Triazolam:2; : ; : ; P-value:
		no. patients experiencing adverse events (Number)	Zolpidem 5mg:11; Zolpidem 10mg:8; Triazolam:16; : ; : ; P-value:

Evidence Table 7. Adverse events reported in trials of newer insomnia drugs

Author, year	Type of trial	Outcome	Results
Walsh, 2000b, 2002	Placebo	no. of patients experiencing severe side effect (Number)	Zopiclone:1; Triazolam:1; : ; : ; : ; P-value:
Ware, 1997	Active	( )	: ; : ; : ; : ; : ; P-value:
Wheatley, 1985	Active	muscular pain, angina pectoris episodes, and shortness of breath (Number)	Zopiclone:3; Triazolam:1; : ; : ; : ; P-value: NR
Zammit, 2004	Placebo	Total number of patients, (Placebo=5) (Number)	Zopiclone 3.75:4; Zopiclone 7.5mg:4; Zopiclone 11.25mg:11; Zopiclone 15mg:5; Flurazepam:10; P-value:
Zammit, 2007	Placebo	bitter taste (data NR) (Number)	Zopiclone:more; Placebo:less; : ; : ; : ; P-value: NR
		drowsiness/dizziness (Number)	Zopiclone:2; Placebo:1; : ; : ; : ; P-value: NR
		overall adverse event (Number)	Zopiclone:5; Placebo:2; : ; : ; : ; P-value: NR
van der Kleijn, 1989	Active	Bad taste (Number)	Zopiclone:6; Triazolam:2; : ; : ; : ; P-value: NR

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Agnoli, 1989	Active	NR	NR	NR	Yes	Yes	NR	Yes	No	No
Allain, 1998	Placebo	NR	NR	Yes	Yes	Yes	Yes	Yes	No	No
Allain, 2001	Placebo	NR	NR	Placebo group lower sleepiness scale and > WASO	Yes	Yes	NR	Yes	Yes	No
Allain, 2003	H2H	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes
Ancoli-Israel, 1999	H2H	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No
Anderson, 1987	Active	NR	NR	Yes	Yes	No	NR	Yes	Yes	No
Ansoms, 1991	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes, but not described	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Asnis, 1999	Placebo									
Autret, 1987	Active	Not randomized	NR	NR	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Begg, 1992	Active	Yes	NR	No	Yes	Yes	NR	Yes	Yes	No
Bergener, 1989	Active	NR	NR	NR	Yes	Yes, but not described	Yes, but not described	Yes	Yes	No
Bozin-Juracic, 1998	Active	NR	NR	Yes	No	Yes	NR	Yes	No	No
Chaudoir, 1983	Placebo	NR	NR	Yes	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Chaudoir, 1990	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Declerck, 1999	Placebo									
Dockhorn, 1996	Placebo	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No
Dorsey, 2004	Placebo	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Drake (1), 2001	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	0
Drake (2), 2000	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No
Drewes, 1991	Placebo									
Drewes, 1998	Placebo									
Elie, 1990a	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	No	No
Elie, 1990b	Active	NR	NR	NR	Yes	Yes	NR	Yes	No	No
Elie, 1999	H2H	NR	NR	NR	Yes	Yes	NR	Yes	Yes	No
Erman, 2006	Placebo	Yes	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes	Yes	No
Fava, 2006	Placebo									0
Fleming, 1990	Active	Yes	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Fleming, 1995	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	Yes
Fontaine, 1990	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Fry, 2000	H2H	NR	NR	NR	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Goldenberg, 1994	Placebo	NR	NR	Yes (for analyzed population)	Yes	Yes, but not described	NR	Yes	Yes	No
Gronblad, 1993	Placebo									
Hajak, 1998, 1995, 1994	Active	Yes	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Hayoun, 1989	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Hedner, 2000	Placebo	NR	NR	Yes for analyzed population, randomized NR	Yes	Yes	NR	Yes	No	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Herrmann, 1993	Placebo	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No
Hindmarch, 1995	Placebo	NR	NR	global QOL score higher in placebo group	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Klimm, 1987	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Krystal (poster)	Placebo									0
Krystal, 2003	Placebo	NR	NR	weight and BMI > in eszopiclone group	Yes	Yes	NR	Yes	Yes	No
Lahmeyer, 1997	Placebo	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No
Lemoine, 1995	H2H	NR	NR	Yes		Yes	NR	Yes	Yes	No
Leppik, 1997	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Li Pi Shan, 2004	Active	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	No
Liu, 1997	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes, but not described	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Lofaso, 1997	Placebo									
Mamelak, 1987	Active	NR	NR	NR	Yes	Yes	NR	Yes	No	No
Moldofsky, 1996	Placebo									
Monchesky, 1986	Placebo	Yes	NR	Yes (for 91/99 analyzed)	Yes	Yes, but not described	NR	Yes	Yes	No
Monchesky, 1989	Placebo									
Monti, 1994	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	Yes
Monti, 1996	Placebo	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	No	No
Monti, 2000	Placebo	No (sequential order)	No (randomized in sequential order)	Lower weight in zolpidem group	Yes	Yes	NR	Yes	No	No
Nair, 1990	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	0
Ngen, 1990	Active	Yes	Yes			Yes	NR	Yes		0

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Pagot, 1993	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Perlis, 2004	Placebo	Yes	Yes	More women in placebo group (81% vs 61%)	Yes	Yes	NR	Yes	Yes	No
Ponciano, 1990	Active	NR	NR	NR	Yes	Yes	NR	Yes	Yes	No
Quadens, 1983	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	No	No
Roehrs (poster)	Placebo	NR	NR	Some differences (adjusted)	Yes	Yes, but not described	Yes, but not described	Yes, but not described	Yes	No
Roger, 1993	Active	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes	Yes	No
Rosenberg, 1994	Active	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Roth 2006	Placebo	NR	NR	Yes (but data NR)	Yes	Yes, but not described	Yes, but not described	Yes, but not described	Yes	No
Sabbatini, 2003	Placebe									
Scharf, 1994	Placebo	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No
Scharf, 2005	Placebo	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No
Schnitzer (poster)	Placebo									
Schwartz, 2004	Active	NR	No- open	NR	No	No	No	No	Yes	No
Sepracor Study #190-045	H2H	NR	NR	NR	Yes	Yes (but concern re. unpleasant taste)	NR	Yes (but concern re. unpleasant taste)	No	No
Shaw, 1992	Placebo									
Silvestri, 1996	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Singh, 1990	Active	NR	NR	NR	No	Yes, but not described	NR	Yes	Yes	No
Soares (poster)	Placebo									0

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Soubrane (poster)	Placebo	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes, but not described	Yes	No
Staner, 2005	H2H	Method NR	NR	NR	Yes	Yes, but not described	Yes, but not described	Yes	No	No
Steens, 1993	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	No	No
Stip, 1999	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No
Tamminen, 1987	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No
Terzano, 1992	Placebo	NR	NR	NR	Yes	Yes, but not described	NR	Yes, but not described	No	No
Tsutsui, 2001	H2H	NR	NR	NR	Yes	Yes	NR	Yes	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
van der Kleijn, 1989	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes	Yes	No
Venter, 1986	Active	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes, but not described	No	No
Voshaar, 2004	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	0
Walsh, 1998a	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Walsh, 1998b	Active	Yes	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Walsh, 2000	Active	NR	NR	NR	Yes	Yes, but not described	NR	Yes, but not described	Yes	0
Walsh, 2000a	Placebo	Not clear (allocation schedule provided by sponsor	Not clear (allocation schedule provided by sponsor	NR	Yes	Yes, but not described	NR	Yes, but not described	Yes	No

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Trial type	Randomization method reported?	Allocation concealment method reported?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?	Crossover reported
Walsh, 2000b, 2002	Placebo	Yes	NR	Yes	Yes	Yes, but not described	NR	Yes	Yes	No
Ware, 1997	Active	NR	NR	Yes	Yes	Yes, but not described	NR	Yes, but not described	Yes	No
Wheatley, 1985	Active	NR	NR	No	No	Yes, but not described	NR	Yes	Yes	No
Zammit, 2004	Placebo	NR	NR	Differences in gener and BMI (controlled for)	Yes	Yes	NR	Yes	Yes	No
Zammit, 2007	Placebo	Yes								0

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Agnoli, 1989	No	No	No		Unable to determine	Unable to determine	Poor	Not reported
Allain, 1998	No	No	NR		Unable to determine	NR	Fair	NR
Allain, 2001	Yes	No	Yes	7 placebo and 3 zolpidem withdrew, but report ITT results	Yes	No	Fair	Sanofi-Synthelabo
Allain, 2003	Yes	No	No		Yes	No	Fair	Sanofi-Synthelabo
Ancoli-Israel, 1999	No	No	No		No	Yes	Fair	Wyeth-Ayerst
Anderson, 1987	Yes	No	Yes	17% who withdrew before taking medication or did not comply excluded from analysis.	No	Yes	Fair	Not reported
Ansoms, 1991	No	No	Yes	54 enrolled, 27 zopiclone and 25 lormetazepam evaluable, but numbers randomized not reported.	No	Yes	Fair	Not reported

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Asnis, 1999							?	
Autret, 1987	Yes	No	No		Unable to determine	Unable to determine	Poor	
Begg, 1992	Yes	No	Yes	42% withdrew, but not differential.	No	Yes	Poor	Roche Products (NZ) Ltd.
Bergener, 1989	No	No	Yes	16 of 42 patients (38%) dropped out, but not differential (8 in each group) and information provided on reasons for dropout.	Unable to determine	No	Fair	Not reported
Bozin-Juracic, 1998	No	No	No		Unable to determine	Yes	Fair	May and Becker and Rhone Poulenc Sante
Chaudoir, 1983	No	No	Yes	High (16.7%, 2 zopiclone, 3 placebo)	No (25/30 analyzed)	No	Poor	NR (May & Baker provided medications and placebo)
Chaudoir, 1990	No	No	No		Not clear	Unable to determine	Fair	Not reported

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Declerck, 1999							?	
Dockhorn, 1996	No	No	No		No (136/139 analyzed)	Yes (1 patient)	Fair	Lorex Pharmaceuticals
Dorsey, 2004	No	No	No		Yes	No	Fair	Sanofi-Synthelabo
Drake (1), 2001	No	No	No		Unable to determine	No	Fair	Wyeth-Ayerst Research
Drake (2), 2000	No	No	No		Unable to determine	No	Fair	Wyeth-Ayerst Research
Drewes, 1991							?	
Drewes, 1998							?	
Elie, 1990a	No	No	NR		Yes	Unable to determine	Fair	Not reported
Elie, 1990b	No	No	NR		Unable to determine	Unable to determine	Fair	Not reported
Elie, 1999	Yes	No	No		No	Yes	Fair	Wyeth-Ayerst
Erman, 2006	No	No	No		No (103/107 analyzed)	Unable to determine	Fair	Takeda
Fava, 2006							?	
Fleming, 1990	No	No	No		No (48/52 analyzed)	Yes	Fair	Not reported

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Fleming, 1995	No	Yes	Yes	7 (10%) zolpidem vs 1 (3%) flurazepam discontinued	No	Yes	Fair	Not reported
Fontaine, 1990	No	No	No		Yes	No	Fair	Rhone-Poulenc Pharma
Fry, 2000	No	No	No		No	Yes	Fair	Wyeth-Ayerst
Goldenberg, 1994	No	No	Yes	High: 36.8% dropped out; groups not specified	No	Unable to determine	Poor	NR
Gronblad, 1993							?	
Hajak, 1998, 1995, 1994	Yes	No	No		Yes	No	Fair	Not reported
Hayoun, 1989	No	Yes	Yes	2 of 68 (3%) triazolam vs 5 of 66 (8%) zopiclone patients discontinued and not included in analysis.	No	Yes	Fair	Not reported (corresponding author from Upjohn)
Hedner, 2000	No	No	NR		No (422/437 analyzed)	NR	Fair	

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Herrmann, 1993	No	No	Yes	16% not analyzed	No (21/25 analyzed)	Yes (1/25)	Poor	NR
Hindmarch, 1995	No	No	Yes	High- 36.8%; groups not specified	No	Unable to determine	Fair	
Klimm, 1987	Yes	No	No		No	No	Fair	Not reported
Krystal (poster)							?	
Krystal, 2003	No	No	No		Yes	3 patients discontinued before taking study drug	Fair	Sepracor
Lahmeyer, 1997	Yes	No	Yes	High- 19% discontinued; not differential	No	No	Fair	?orex Pharmaceuticals
Lemoine, 1995	No	No	No		No	No	Fair	Not reported
Leppik, 1997	No	No	No		Yes	No	Fair	Lornex Pharmaceuticals
Li Pi Shan, 2004	No	No	No		No	No	Fair	Not reported
Liu, 1997	Yes	No	Yes	8 patients did not finish the trial due to lack of compliance.	Unable to determine	Unable to determine	Poor	

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Lofaso, 1997							?	
Mamelak, 1987	No	No	No		Unable to determine	Unable to determine	Fair	Not reported
Moldofsky, 1996							?	
Monchesky, 1986	No	No	Unable to determine		No (91/99 analyzed)	1/99	Fair	NR
Monchesky, 1989							?	
Monti, 1994	Yes	Yes	No		Yes	No	Fair	Not reported
Monti, 1996	No	No	No		Yes	No	Fair	NR
Monti, 2000	No	No	NR		Unable to determine	Unable to determine	Poor	NR
Nair, 1990	Yes	No	No		No	No	Fair	Rhone-Poulenc Pharma
Ngen, 1990			Yes	27% discontinued, but not differential (7 placebo, 5 zopiclone, 4 temazepam)	No	No	Fair	Rhone-Poulenc Pharma

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Pagot, 1993	No	No	Yes	32% zolpidem and 38% triazolam dropped out	No	No	Fair	Not reported
Perlis, 2004	Yes	Yes	No		No	No	Fair	Lorex Pharmaceuticals
Ponciano, 1990	No	No	No		Yes	No	Fair	Not reported
Quadens, 1983	No	No	NR		Unable to determine	Unable to determine	Poor	Not reported
Roehrs (poster)	No	No	No		No	Unable to determine	Fair	Sanofi-Aventis
Roger, 1993	No	No	No		Unable to determine	No	Fair	Not reported
Rosenberg, 1994	No	No	Yes	19% excluded due to lack of data or protocol violations (16 zolpidem, 23 triazolam, number randomized not reported by group)	No	Yes	Poor	Synthelabo Scandinavia A/S

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Roth 2006	No	No	NR		Unable to determine	No	Fair	Takeda Pharmaceuticals
Sabbatini, 2003							?	
Scharf, 1994	No	Yes	No		Unable to determine	No	Fair	NR
Scharf, 2005	No	No	No		Yes	Unable to determine	Fair	
Schnitzer (poster)							?	
Schwartz, 2004	No	No	No		Yes	No	Poor	Not reported
Sepracor Study #190-045	No	No	NR		Pts who rec'd at least one dose of medication	Unable to determine	Fair	Sepracor
Shaw, 1992							?	
Silvestri, 1996	No	No	Yes	2/12 triazolam (10%) patients vs 0/10 zolpidem patients lost to f/u	No	Yes	Fair	Not reported
Singh, 1990	No	No	No		Yes	Yes (1 patient)	Fair	Rhone-Poulenc Pharma Inc.
Soares (poster)							?	

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Soubrane (poster)	No	No	No		No	Unable to determine	Fair	Sanofi-Aventis
Staner, 2005	No	No	NR		Unable to determine	Unable to determine	Poor	Sanofi-Aventis
Steens, 1993	No	No	No		Yes	No	Fair	Lorex Pharmaceuticals
Stip, 1999	No	No	Yes	17% excluded from analysis	No	Yes	Fair	Not reported
Tamminen, 1987	No	No	Yes	28% not included n the analysis (10 zopiclone, 16 nitrazepam excluded)	No	Yes	Poor	Not reported
Terzano, 1992	No	No	NR		NR	NR	Poor	Partially supported by Italian Ministry of University and Scientific Research
Tsutsui, 2001	Yes	No	Yes	13.9% zolpidem vs 18.1% zopiclone withdrew (p=NS)	No	Yes	Fair	Not reported

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
van der Kleijn, 1989	No	No	No		No	Unable to determine	Fair	Rhone-Poulenc Pharma
Venter, 1986	No	No	No		Yes	No	Fair	Not reported
Voshaar, 2004	No	No	Yes	More zolpidem patients dropped out (24 vs 12, p<0.05)	No	Yes	Fair	Sanfi-Synthelabo
Walsh, 1998a	No	No	No		No	Yes	Fair	Lorex Pharmaceuticals
Walsh, 1998b	No	No	No		Yes	No	Good	Wyeth Ayerst
Walsh, 2000	Yes	No	Yes	8 of 30 (27%) randomized were excluded from analysis; groups not specified.	No	Yes	Poor	Wyeth-Ayerst Research
Walsh, 2000a	No	No	No- unclear if differential		No (48/54 analyzed)	Yes	Poor	

Evidence Table 8a. Quality assessment of randomized controlled trials of newer drugs for insomnia

Author, year	Adherence reported	Contamination	Loss to fu reported?	Loss to fu comments	ITT analysis?	Post-randomization exclusions?	Quality rating	Funding
Walsh, 2000b, 2002	Yes	Yes	Yes	18% withdrew:12.3% placebo, 30% zolpidem	No	Yes	Fair	Lorex Pharmaceuticals
Ware, 1997	No	No	No		No	No	Fair	Lorex Pharmaceuticals
Wheatley, 1985	No	No	No		Unable to determine	Unable to determine	Fair	Not reported
Zammit, 2004	No	No	No		No (303/308 at night 1; 293/308 at 1 month)	No	Fair	Sepracor
Zammit, 2007								

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Year	Randomization method described?	Allocation concealment method described?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?
Berry	2006	Method not described	Method not described	Yes		Yes		NR	NR	NR	Yes
Fava	2006	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	
Kryger	2007	Method not described	Method not described	NR	Not reported by order of randomization	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes
Krystal 2008	2008	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes	Yes
McCall	2006	Method not described	Method not described	Yes		Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Rosenberg	2007	Method not described	Method not described	NR	Not reported by order of randomization	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Roth 2007	2007	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Year	Randomization method described?	Allocation concealment method described?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?
Soares	2006	Method not described	Method not described	Yes		Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind	Yes
Walsh	2008	Method not described	Yes	No	Number of awakenings and sleep quality higher in placebo group (different directions)	Yes	Yes	Yes	Unclear, reported as double blind	Yes	Yes
Walsh (eszopiclone)	2007	Method not described	Method not described	Yes		Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Year	Randomization method described?	Allocation concealment method described?	Groups similar at baseline?	Comments	Inclusion criteria specified?	Exclusion criteria specified?	Outcome assessors masked?	Care provider masked?	Patients masked?	Attrition reported?
Zammit (ramelteon)	2007	Method not described	Yes	No	Differences in weight and sex at baseline	Yes	Yes	Yes	Yes	Yes	

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Loss to fu differential or high?	Comments	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Withdrawal rate differential or high?	Comment	Handling of carryover effects (for crossover studies only)	Funding
Berry	No		Unable to determine		No		No			
Fava	Yes	50/545 (9.2%), not differential	Yes	543/545 analyzed (99.6%)	Yes	40 for protocol violation, did not meet entry criteria, or "other"	Yes	172/545 (31.6%)		Sepracor
Kryger	No		Yes		No		No	no dropouts	washout	Takeda
Krystal 2008	Yes	77/1018 (7.6%)	Yes	1016/1025 analyzed (99.1%)	Yes	43 for poor compliance	Yes	405/1018 (39.8%)		Sanofi-Aventis
McCall	No		Unable to determine		No		No	9/264 (3.4%)		Sepracor
Rosenberg	No		Yes		Yes	1 excluded for protocol violation	No	1/22 (4.5%)	washout	Sepracor
Roth 2007	No		Yes		No		No	No dropouts	washout	Takeda

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Loss to fu differential or high?	Comments	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Withdrawal rate differential or high?	Comment	Handling of carryover effects (for crossover studies only)	Funding
Soares	No	4/410 (1%)	Yes		Yes	13 for protocol violation, did not meet entry criteria, or other	No	51/410 (12.4%)		Sepracor
Walsh	No		Yes	199/205 analyzed (97.1%)	Yes	1 for poor compliance	No	7/205 (3.4%)		Sanofi-Aventis
Walsh (eszopiclone)	No	9.6%	Yes	548/550 analyzed	Yes	35 discontinued for protocol violation; 20 for other reasons	Yes	More placebo patients discontinued (52% vs 37%) 80/830 discontinued overall (9.6%)		Sepracor

Evidence Table 8b. Quality assessment of randomized controlled trials (new for Update #2)

Author	Loss to fu differential or high?	Comments	ITT analysis?	Comment	Post-randomization exclusions?	Comment	Withdrawal rate differential or high?	Comment	Handling of carryover effects (for crossover studies only)	Funding
Zammit (ramelteon)	No	1/405	No		Yes	6 for protocol deviation, 1 for noncompliance	No	34/405 withdrew (8.4%); not reported by group		Takeda

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Allain, 1991 France; Delahaye, France	20,513	Zopiclone 7.5 mg for adults 18-69 years, 3.75 mg to older patients.	3 weeks	Men and women 18 years or older who complained of poor sleep for at least 2 weeks and who were followed as outpatients by general practitioners.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Allain, 1991 France; Delahaye, France	62.6% women, mean age 52.3 (range 15-99), 58% had concomitant diseases (29% had cardiovascular disorders, 12.3% had anxiety and/or depression	Postmarketing surveillance survey	Case report forms completed by general practitioners	6 months	Reported by the patient

Evidence Table 9. Observational studies

Author Year Country	Results		Funding
Allain, 1991 France; Delahaye, France	Neuropsychiatric adverse events, no. of AEs (%)/ no. of drop-outs Difficulty arising in the morning: 267(1.3%)/ 85 Sleepiness: 107(0.52%)/ 44 Hypersomnia: 6(0.03%)/ 2 Increased frequency of dreams: 38(0.19%)/ 6 Nightmares: 101(0.49%)/ 59 Headache: 61(0.30%)/ 27 Light headedness/heavy headedness: 11(0.05%)/ 3 Ebrious feeling: 53(0.26%)/ 32 Dizziness: 57(0.28%)/ 24 Fall: 8(0.04%)/ 5 Anxiety: 10(0.05%)/ 5 Agitation/ excitation: 56(0.27%)/ 41 Irritability: 17(0.07%)/ 8 Aggressiveness: 4(0.02%)/ 2 Tremor: 12(0.06%)/ 9 Hallucinations: 7(0.03%)/ 7 Confusion: 7(0.03%)/ 5 Difficulty concentrating: 6(0.03%)/ 1 Memory complaints: 15(0.07%)/ 2 Reduced libido: 4(0.02%)/ 2 Various neuropsychiatric disorders: 15(0.07%)/ 12	Gastrointestinal adverse events, no. of AEs (%)/ no. of drop-outs Bitter taste: 746(3.64%)/ 181 Dysgeusia: 20(0.10%)/ 6 Dry mouth: 325(1.58%)/ 53 Gastric pain: 61(0.30%)/ 33 Nausea: 101(0.49%)/ 49 Vomiting: 101(0.05%)/ 8 Diarrhea: 3(0.01%)/ 2 Constipation: 6(0.03%)/ 1 Various GI disorders: 46(0.22%)/ 23 Somatic adverse events, no. of AEs (%)/ no. of drop-outs Asthenia: 38(0.19%)/ 6 Malaise: 14(0.07%)/ 8 Dyspnea: 8(0.02%)/ 5 Palpitation: 4(0.02%)/ 4 Rash: 8(0.04%)/ 8 Pruritus: 3(0.16%)/ 3 Other: 15(0.07%)/ 7	Not reported

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Ancoli-Israel, 2005 US and Europe	260	Zaleplon 5 mg, increased to 10 mg if needed.	1 year	Primary insomnia defined by DSM-IV criteria. Admission to randomized phase was restricted to those whose symptoms lasted at least 3 months. Inclusion in the extension phase required completion of the double-blind phase and a run-out period of 7 days followed by 7 to 28 treatment-free days without adverse effects, and return to the clinic after the treatment free interval with a minimum of five daily sleep questionnaires to confirm the need for continued sleep therapy.
Bain, 2003 US	4,752 (687 zolpidem, 4,065 temazepam)	Zolpidem or temazepam	Not reported	Patients prescribed zolpidem or temazepam in one hospice practice setting.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Ancoli-Israel, 2005 US and Europe	Mean age 73.3 years (SD 5.3, range 65-86 years) in the US and 71.8 years (SD 6.8, range 59-95 years) in Europe	Prospective cohort study; open label continuation phase of RCT	Monthly safety assessments which included routine physical exams, laboratory determinations, vital signs including blood pressure, and electrocardiograms.	7 days	Treatment emergent adverse events were defined as any adverse event that first appeared or that intensified after the initiation of open-label treatment. Discontinuation effects.
Bain, 2003 US	Hospice patients	Retrospective database analysis of prescribing patterns	Database from one practice. ICD-9 codes associated with each treatment modality.	6 months	Number of times therapy was discontinued, reasons for discontinuation

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Ancoli-Israel, 2005 US and Europe	Frequency of common Treatment-emergent adverse events (TEAEs) during open-label run-out phase, number(%): Headache- 155(27%) Infection- 73(13%) Backache- 58(10%) Bronchitis/pharyngitis- 65(11%) Rhinitis- 53(9%) Dizziness- 43(7%) The TEAEs most frequently associated with discontinuation, number(%): Pain- 29(5%) Somnolence or dizziness- 23(4%) Gastrointestinal changes- 11(2%) Cardiovascular changes- 8(1%)	Wyeth Research and the Research Service of Veteran Affairs Diego Healthcare System.
Bain, 2003 US	Use temazepam or zolpidem, discontinuation due to adverse events: zolpidem(n=89) vs. temazepam(n=401), (%) adverse drug reaction- 2.2% vs. 4.2% Discontinuation due to adverse events: [use temazepam and then switch to zolpidem] vs. [use zolpidem and then switch to temazepam], (%) adverse drug reaction or others- 10.6% vs. 7.5% Discontinuation due to adverse events after filtering out "change in dose" as a reason for discontinuation. Among discontinuation except "change in dose": adverse drug reaction- 4.3% vs.10.1%	Not reported

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Buckley, 2004 UK	12,063 (10,763 zopiclone, 1,300 zolpidem)	Zolpidem, zopiclone, other sedative hypnotics.	Not reported	Fatal toxicity of anxiolytic and sedative drugs for the years 1983-1999.
Devins, 1995 Canada	274	Zopiclone	Not reported	Women who received zopiclone during pregnancy and consulted the Toronto Motherisk Program Teratogen Information Service).

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Buckley, 2004 UK	Not reported.	Retrospective database analysis	Office for National Statistics (England, Wales), and General Registrar's Office (Scotland)	1983-1999	Total number of deaths/number of prescriptions Zolpidem: 3/1300 Zopiclone: 23/10,763
Devins, 1995 Canada	Indications for drug use: depression (n=10), insomnia (n=3), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Mailed patient questionnaire	Not reported	Daytime sleepiness, anxiousness, bad taste, weakness, drowsiness/fatigue, dry mouth, poor memory, poor concentration, Rage/aggression/irritability, illness intrusiveness, depressive symptoms

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Buckley, 2004 UK	Fatal toxicity index: total no. of deaths zolpidem vs. zopiclone= 3 vs. 23 Fatal toxicity index: no. of prescriptions (thousands) zolpidem vs. zopiclone= 1300 vs. 10763 Fatal toxicity index: deaths/million prescriptions (95%CI) zolpidem vs. zopiclone= 2.3(0.5-6.7) vs. 2.1 (1.4-3.2)	None
Devins, 1995 Canada	Adverse events: [zopiclone] vs. [lorazepam] vs. [triazolan] vs. [nitrazepam or flurazepam] vs. [temazepam], no.(%) Daytime sleepiness: 5.6(4.71) vs. 6.1(3.91) vs. 6.6(4.28) vs. 6.4(4.3) vs. 5.5(4.7), p<0.001 Side-effects anxiousness: 45(16.4) vs. 52(19.8) vs. 33(23.15) vs. 22(18.2) vs. 39(21.7) Bad taste: 111(40.5) vs. 35(13.3) vs. 18(12.6) vs. 22(18.2) vs. 37(20.6), p<0.0001 Weakness: 24(8.8) vs. 24(9.1) vs. 10(7.0) vs. 12(9.9) vs. 16(8.9) Drowsiness/fatigue: 82(29.9) vs. 80(30.4) vs. 42(29.4) vs. 37(30.6) vs. 60(33.3) Dry mouth: 93(33.9) vs. 85(32.3) vs. 34(23.8) vs. 26(21.5) vs. 60(33.3), p<0.0001 Poor memory: 90(32.8) vs. 90(34.2) vs. 43(30.1) vs. 47(38.8) vs. 67(37.2) Poor concentration: 77(28.1) vs. 75(28.5) vs. 39(27.3) vs. 43(35.5) vs. 57(31.70) Rage/aggression/irritability: 29(10.6) vs. 39(14.8) vs. 31(21.7) vs. 30(24.8) vs. 39(21.7), p<0.02 Illness intrusiveness: 34.7(17.64) vs. 33.7(17.14) vs. 29.6(16.11) vs. 34.4(20.11) vs. 36.1(20.10) Depressive symptoms: 21.8(9.73) vs. 22.2(10.58) vs. 20.3(9.18) vs. 20.7(9.4) vs. 21.81(10.76)	Rhone-Poulenc Rorer and Health Canada.

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Diav-Citrin, 1999 Canada	40	Zopiclone	Not reported	Women who received zopiclone during pregnancy and consulted the Toronto Motherisk Program Teratogen Information Service).

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Diav-Citrin, 1999 Canada	Indications for drug use: depression (n=10), insomnia (n=3), anxiety depressive disorder (n=3), anxiety (n=2), bipolar disorder (n=2), and schizophrenia (n=2). 16 did not specify and 2 did not know indication.	Prospective cohort study	Followup by telephone interview after the expected date of delivery, using a structured questionnaire.	1993-1997	Pregnancy outcome.

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Diav-Citrin, 1999 Canada	Pregnancy outcome, zopiclone vs. control: Pregnancy outcome: NS Birth defects: NS Delivery methods: NS Mean GA (wk): 38.3±2.7 vs. 40.0±1.6, p=0.002 Preterm delivery of <37 wks: NS Mean birth weight (g): 3245.9±676 vs. 3624.2±536, p=0.01 Birth weight by GA: NS Meconium: NS Fetal distress: NS NICU admission: NS	

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Ganzoni, 1994 Switzerland	1,972	Zolpidem 10 mg (5-10 mg in patients over age 65)	Median duration of treatment 29.5 days; range 1-1,095 days	Men and women aged 15 and above, complaining of insomnia and for whom a hypnotic drug treatment was prescribed by a general practitioner, internist, psychiatrist, or gerontologist.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Ganzoni, 1994 Switzerland	64.8% male 31.6% elderly mean age=54.6±16.5	Postmarketing surveillance survey	Safety data recorded by the prescribing physician on a monitoring form. Codification of adverse events was reviewed by two physicians of the Drug Monitoring Unit.	September 1990-December 1993	CNS-related symptoms Non-CNS-related symptoms.

Evidence Table 9. Observational studies

Author Year Country	Results		Funding
Ganzoni, 1994 Switzerland	CNS-related adverse events, n=1972: no. of Aes(%)/ no. drop-outs(%) Residual daytime sedation: 73(3.7)/ 28(1.4) Lack of efficacy: 31(1.6)/ 19(1.0) Confusion, disorientation, obsessive ideas, delirium, psychosis: 19(1.0)/ 15(0.8) Nervousness, internal trembling, nervous feet, restlessness, excitation feeling: 16(0.8)/ 14(0.7) Nightmares: 15(0.8)/ 11(0.6) Amnesia, memory impaired: 15(0.8)/ 7(0.4) Concentration impaired: 11(0.6)/ 4(0.2) Anxiety: 11(0.6)/ 8(0.4) Somnambulism, sleep walking, nocturnal activity, walking activity: 9(0.5)/ 5(0.3) Hallucunation: 6(0.3)/ 4(0.2) Dreaming increased: 6(0.3)/ 3(0.2) Blurred vision, diplopia, crying, reading impaired, vision abnormal: 5(0.3)/ 3(0.2) Agitation, aggressivity: 3(0.2)/ 2(0.1) Speech disorder: 3(0.2)/ 2(0.1) Tremor: 2(0.1)/ 0(0.0) Benzodiazepine withdrawal: 1(0.1)/ 1(0.1) Suspicion of drug dependence: 1(0.1)/ 0(0.0) Drug misuse: 1(0.1)/ 0(0.0) Total: 228(11.6)/ 126(6.4)	Non-CNS-related adverse events, n=1972: no. of Aes(%)/ no. drop-outs(%) Gastrointestinal: 33(1.7)/ 25(1.3) Headache, head pressure: 21(1.1)/ 8(0.4) Pruritus, eczema, rash, rash, urticaria, skin papules: 10(0.5)/ 5(0.3) Fall, gait abnormal, coordination impaired, muscle weakness: 9(0.5)/ 4(0.2) Dyspnoea, tachypnoea, respiration regulation impaired: 7(0.4)/ 6(0.3) Palpitation, tachycardia, precordialgia: 6(0.3)/ 4(0.2) Malaise, weakness: 5(0.3)/ 5(0.3) Eating activity, bulimia: 4(0.2)/ 2(0.1) Dry mouth: 3(0.2)/ 0(0.0) Bone/head contusion, skin wound: 3(0.2)/ 1(0.1) Hypotension: 2(0.1)/ 1(0.1) Polyuria: 2(0.1)/ 2(0.1) Loss of appetite: 1(0.1)/ 0(0.0) Myocardial infarction: 1(0.1)/ 0(0.0) Nasal congestion: 1(0.1)/ 1(0.1) Retching: 1(0.1)/ 1(0.1) Total: 115(5.8)/ 69(3.5)	Not Reported

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Hajak, 1998 Germany	16,944	Zolpidem 10 mg-20 mg (5 mg-10 mg in patients over age 65 years)	3 to 4 weeks.	Patients in outpatient practice with difficulties in initiating and/or maintaining sleep.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Hajak, 1998 Germany	64% women, mean age 58.5 (SD 14.9)	Before-after.	Questionnaire	3-4 weeks	Discontinuation, adverse events.

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Hajak, 1998 Germany	Tolerance: moderate-1.4%, poor- 0.6% Adverse events: no. patients /% of 268 AEs/ % of 16944 treated patients/ no. drop-outs Total: 268/ 100/ 1.5/ 118 Nausea: 36/ 13.4/ 0.2/ 27 Dizziness: 35/ 13.1/ 0.2/ 20 Malaise: 23/ 8.6/ 0.1/ 10 Nightmares: 20/ 7.5/ 0.1/ 15 Agitation: 19/ 7.1/ 0.1/ 15 Headache: 18/ 6.7/ 0.1/ 13 Vomiting: 13/ 4.9/ 0.08/ 11 Somnolence: 9/ 3.4/ 0.05/ 4 Confusion: 8/ 3.0/ 0.05/ 7 Fatigue: 7/ 2.6/ 0.04/ 4 Dyspepsia: 7/ 2.6/ 0.04/ 5 Abnormal gait: 6/ 2.2/ 0.04/ 4 Hallucination: 5/ 1.9/ 0.03/ 4 Tremor: 4/ 1.5/ 0.02/ 2 Anxiety: 4/ 1.5/ 0.02/ 4 Insomnia: 4/ 1.5/ 0.02/ 4 Amnesia: 3/ 1.1/ 0.02/ 2 Asthenia: 3/ 1.1/ 0.02/ 2 Dry mouth: 3/ 1.1/ 0.02/ 3	Synthelabo Arzeimittel GmbH, Germany

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Jaffe, 2003 UK	297	Zolpidem, zopiclone, other sedative hypnotics.	Not reported	Patients admitted to addiction treatment centers.
Maarek, 1992 France	96	Zolpidem 10 mg	1 year (360 days)	Patients were known to be suffering from disorders involving the initiation and/or maintenance of sleep, included in the trial had to be over 40 years of age and show clear evidence of insomnia defined by at least one of the following symptoms: sleep onset latency of more than 30 min; more than two nocturnal awakenings; and total duration of sleep of less than 6 hours.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Jaffe, 2003 UK	78% male	Before-after.	survey	Not reported	Abuse liability
Maarek, 1992 France	Not reported.	Before-after.	The general practitioner assessed patient compliance by questioning the patients at each visit	6 months-12 months	Any adverse events detected by clinical examination or reported spontaneously by the patient were recorded at each visit.

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Jaffe, 2003 UK	Drug use pattern: zolpidem vs. zopiclone (n=297) % subjects use: 5.8 vs. 53.7 % street purchase: 23.5 vs. 42.0 % doctor prescribed: 76.5 vs. 79.0 % not recommend by doctor: 23.5 vs. 30.6 % took to sleep: 82.3 vs. 88.5 % took to get high: 23.5 vs. 22.9 % took to make feel better: 64.7 vs. 56.7 % like the effects: 41.2 vs. 48.4 % think they need: 11.8 vs. 28 % addicted: 0 vs. 5.1 % might become addicted: 11.8 vs. 19.8	Sepracor
Maarek, 1992 France	7(7.3%) of all patients withdrew because of adverse events: 1(1%) feeling of strangeness 1(1%) feeling of drunkenness 2(2.1%) anterograde amnesia 1(1%) nausea 1(1%) confusional episode 1(1%) nightmares 1(1%) malaise 4(4.2%) vertigo 2(2.1%) daytime drowsiness 1(1%) unpleasant awakening	

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Morishita, 2000 Japan	31 (13 zopiclone, 18 brotizolam)	Zopiclone 7.5 mg to 10 mg (mean 9.42 mg);	Mean 4.5 years	Elderly patients who had received brotizolam or zopiclone for insomnia in the department of psychiatry at one hospital.
Peeters, 1997 Belgium	1,219	Zolpidem	1 month	Men or women age 50 years or older, suffering from insomnia.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Morishita, 2000 Japan	Mean age 74.4 years (range 70-86 years). Psychiatric diagnoses: depression (n=23), hypomania (n=1), hypochondriacal neurosis (n=2), paraphrenia (n=1), dementia (n=1), nonorganic insomnia (n=3).	Retrospective chart review.	Medical record review.	Not clear-appears to be 1999-2000	Ataxia, hyperexcitability, daytime anxiety, agitation and confusion, amnesia, affective disturbance, somnambulism, or morning drowsiness.
Peeters, 1997 Belgium	461 males, 751 females, not recorded.	Multicenter, open label postmarketing surveillance study; before-after.	sleep parameters assessed on entry and at the follow-up visit by the investigator.	January 1st to May 31st, 1994	Reported by the patient at the followup visit.

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Morishita, 2000 Japan	All patients reported no adverse events, such as ataxia, hyperexcitability, daytime anxiety, agitation and confusion, amnesia, affective disturbance, somnambulism or morning drowsiness.	Not reported
Peeters, 1997 Belgium	Adverse events reported: All patients (n=1219)/ Patients <65 (n=720)/ Patients >=65 (n=495) Autonomic nervous system: 5/ 4/ 1 Central/ peripheral nervous system: 27/ 14/ 13 Gastro-intestinal system: 4/ 2/ 2 Heart rate and rhythm: 3/ 0/ 3 Musculoskeletal system: 1/ 0/ 1 Neoplasms: 2/ 1/ 1 Psychiatric system: 48/ 25/ 23 Special senses: 2/ 2/ 0 Vision: 1/ 0/ 1 Unknown: 5/ 5/ 0 Patients with at least one adverse events: 87/ 46/ 41	

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Reith, 2003	946,013	Zopiclone	Not reported	Deaths from sedative and anxiolytic poisonings for New Zealand (NZ) in 2001 were identified from chemical injury cases that are routinely collected for surveillance purposes by Institute of Environmental Science and Research (ESR) from the Coronial Services Office (CSO) in Wellington.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Reith, 2003	Not reported.	surveillance	The PharmHouse database	January 1, 2001 to December 31, 2001.	Fatal toxicity

Evidence Table 9. Observational studies

Author Year Country	Results		Funding
Reith, 2003	Zopiclone involved in poisoning deaths no. of patients <60 vs >=60 years: 8 vs. 4 Zopiclone No. of dreath:12 Deaths/100,000 prescriptions: 5.4(2.8-9.4) Deaths/1,000,000 defined daily doses: 1.9(1.0-3.3) No. of primary agent death: 3 Primary agent deaths/100,000 prescription: 1.4(0.3-4.0) Primary agent deaths/1,000,000 defined daily doses: 0.5(0.1-1.4) Lorazepam No. of dreath: 2 Deaths/100,000 prescriptions: 2.9(0.3-10.3) Deaths/1,000,000 defined daily doses: 1.5(0.2-5.5) No. of primary agent death: 0 Primary agent deaths/100,000 prescription: 0(0-5.3) Primary agent deaths/1,000,000 defined daily doses: 0(0-2.8) Lormetazepam No. of dreath: 0 Deaths/100,000 prescriptions: 0(0-138.0) Deaths/1,000,000 defined daily doses: 0(0-1379.6) No. of primary agent death: 0 Primary agent deaths/100,000 prescription: 0(0-138.0) Primary agent deaths/1,000,000 defined daily doses: 0(0-39.9) Midazolam No. of dreath: 0 Deaths/100,000 prescriptions: 0(0-35) Deaths/1,000,000 defined daily doses: 0(0-22.2) No. of primary agent death: 0 Primary agent deaths/100,000 prescription: 0(0-35) Primary agent deaths/1,000,000 defined daily doses: 0(0-22.2)	Nitrazepam No. of death: 3 Deaths/100,000 prescriptions: 10.1(2.1-29.4) Deaths/1,000,000 defined daily doses: 2.8(0.6-8.2) No. of primary agent death: 0 Primary agent deaths/100,000 prescription: 0(0-12.4) Primary agent deaths/1,000,000 defined daily doses: 0(0-3.4) Temazepam No. of death: 5 Deaths/100,000 prescriptions: 4.4(1.4-10.3) Deaths/1,000,000 defined daily doses: 2.1(0.7-4.8) No. of primary agent death: 1 Primary agent deaths/100,000 prescription: 0.9(0-4.9) Primary agent deaths/1,000,000 defined daily doses: 0.4(0-2.2) Triazolam No. of death: 3 Deaths/100,000 prescriptions: 2.7(0.6-8.0) Deaths/1,000,000 defined daily doses: 1.0(0.2-2.8) No. of primary agent death: 1 Primary agent deaths/100,000 prescription: 0.9(0-5.1) Primary agent deaths/1,000,000 defined daily doses: 0.3(0-1.8)	Not reported

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Schneeweiss, 2005 US	8,785	Zolpidem benzodiazepine	NR	The study population was restricted to persons living in communities. Of these, the study population was further restricted to Medicare Current Beneficiary Survey respondents aged 65 and older and beneficiaries with at least one medication use in 1999.
Scharf, 1994	233	Zolpidem 15 mg. If adverse events occurred, the investigator could reduce the nightly dose to 10 mg. Patients unable to tolerate 10-mg doses were withdrawn from the study.	3 months	Men and women ages 18 to 60 years, with a history of insomnia of at least 3 months' duration. Patients had to satisfy one or more of the following criteria: usual duration of sleep less than 6 hours, sleep latency of at least 45 minutes on most nights, and the use of a hypnotic drug on most nights.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Schneeweiss, 2005 US	Mean age = NR 41.7% 65-74 years old 58.2% >=75 years old 41.6% male	Cross-sectional survey data	Medicare Current Beneficiary Survey	1 year	NR
Scharf, 1994	Not reported.	Before-after.	Patient reports Physician assessments	13 weeks	Treatment emergent adverse events.

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Schneeweiss, 2005 US	Zolpidem (n=62) vs benzodiazepine (n=567) vs none (n=6434) Patients characteristics: ADL score >=1 point: 54.8% vs 41.3% vs 27.3% Cognitive impairment: 16.1% vs 15.2% vs 10.2% Rosow-Breslau, impairments: 75.8% vs 69.5% vs 55.9% Z vs B; Z vs None; B vs none: Quantitative assessment of confounding bias in risk estimates ADL score (>1 points): 10.00; 21.48; 9.96 Cognitive impairment (yes vs no): 1.19; 7.00; 5.78 Rosow-Breslau (>=1 impairments): 3.43; 10.58; 6.54	NR
Scharf, 1994	Adverse events: zolpidem 10mg (n=33) vs. zolpidem 15mg (n=229), no.(%) Dry mouth: 2(6.1) vs. 14(6.1) Fatigue: 6(18.2) vs. 38(16.6) Ataxia: 2(6.1) vs. 7(3.1) Confusion: 2(6.1) vs. 5(2.2) Dizziness: 2(3.1) vs. 32(14.0) Drowsiness: 5(15.2) vs. 60(26.2) Drugged: 0(0) vs. 12(5.2) Headache: 7(21.2) vs. 65(28.4) Lethargy: 1(3.0) vs. 14(6.1) Light-headedness: 1(3.0) vs. 24(10.5) Abdominal pain: 0(0) vs. 13(5.7) Dyspepsia: 1(3.0) vs. 20(8.7) Nausea: 1(3.0) vs. 28(12.2) Arthralgia: 2(3.1) vs. 7(3.1) Amnesia: 1(3.0) vs. 15(6.6) Nervousness: 3(9.1) vs. 11(4.8) Herpes simplex: 2(6.1) vs. 0(0) Pharyngitis: 2(6.1) vs. 6(2.6) URI: 4(12.1) vs. 38(16.6)	

Evidence Table 9. Observational studies

Author Year Country	N	Drugs (mean dose); duration of treatment	Duration of treatment	Eligibility Criteria
Schlich, 1991 France	107	Zolpidem	6 months	Over age 40, clear evidence of insomnia defined as sleep onset latency of more than 30 minutes, number of nocturnal awakenings each night greater than two, and /or total duration of sleep each night less than 6 hours.
Wang, 2001 US	1,222 cases, 4,888 controls	Zolpidem, benzodiazepines, other	6 months	subjects aged >= 65 on July 1, 1993, and have filled one or more claims for a nonprescription service between January 1, 1994 and December 31, 1994 and have filled at least one prescription for any medication through the Medicaid or PAAD programs of New Jersey in each of four consecutive 6-month periods beginning January 1, 1993.

Evidence Table 9. Observational studies

Author Year Country	Other population characteristics	Design	Data sources	Time period of assessment	Adverse events assessment
Schlich, 1991 France	74 females; mean age=63.15+1.10 years 65(60.7%) patients enrolled were aged 60 years or over and only 17(15.9%) were under 50 years of age.	Before-after	clinical examinations	6 months	malaise vertigo anterograde amnesia confusion
Wang, 2001 US	Not reported.	Case Control	New Jersey Medicaid Program New Jersey Pharmaceutical Assistance to the Aged and Disable (PAAD) Program New Jersey Medicare	6 months	NR

Evidence Table 9. Observational studies

Author Year Country	Results	Funding
Schlich, 1991 France	Tolerance: no evidence Adverse events: zolpidem vs. placebo no. of patients- 24 vs.7 no. adverse events- 42 vs. 10 Adverse events list: 5 malaise 5 vertigo (all elderly) 5 anterograde amnesia 2 confusion (all elderly) Withdrawal effects: 5(7.2%) withdrawal due to adverse events.	
Wang, 2001 US	Hip Fracture: Adjusted OR (95% CI)- adjusted for age and gender zolpidem: 1.95 (1.09-3.51) benzodiazepine: 1.46 (1.21-1.76) antipsychotic medication: 1.61 (1.29-2.01) antidepression: 1.46 (1.22-1.75) other psychoactive medication: 1.23 (0.90-1.68) thiazide diuretic: 0.85 (0.71-1.02)	National Institute on drug Abuse and the National Institute on Aging.

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Eszopiclone	Adult	visual and auditory hallucinations	(Duggal, 2007)	1	45-year old male night shift worker, had to wake up only a few hours after taking medication and falling asleep no history of psychiatric illness negative drug screen taking several other medications (doses unchanged)	difficulty sleeping erratic sleep pattern visual and auditory hallucinations after waking up a few hours after taking medication (lasting several minutes)	Hallucinations subsided after taking medication and sleeping for the recommended 8 hours
Zaleplon	Adult	CNS side effect	(Stillwell, 2003)	1	drug abuse concurrent use of other drugs	CNS depression including slow movements and reactions, poor coordination, lack of balance, and poor attention	not reported
Zaleplon	Adult	hallucination illusions depersonalization	(Bhatia, Arora, & Bhatia, 2001)	1	healthy female nonsmoker, occasional drinker	lightheaded illusion visual hallucinations	not reported
Zaleplon	Pediatrics	somnambulism	(Liskow & Pikalov, 2004)	1	major depressive disorder, moderate no history of sleep deprivation	somnambulism with complex behavior	not reported
Zolpidem	Adult	anterograde amnesia compulsive repetitive behaviors	(Tsai, 2007)	3	adult women	compulsive repetitive behaviors (eating, shopping, and cleaning) combined with anterograde amnesia (no recollection of behaviors)	adverse events stopped after discontinuation of zolpidem
Zolpidem	Adult	CNS side effect	(Canaday, 1996)	2	not reported	amnesia	not reported
Zolpidem	Adult	CNS side effect	(Markowitz & Brewerton, 1996)	2	depression no history of drug abuse concurrent use of antidepressants, serotonin-reuptake inhibitors	visual hallucination auditory hallucination confusion difficulties at work and marital	hallucination ceased
Zolpidem	Adult	CNS side effect	(Toner, 1999)	3	motor vehicle accident or psychiatric history	nightmare hallucination visual illusion difficulty in concentration	nightmares, hallucination and visual illusion ceased
Zolpidem	Adult	CNS side effect	(Tripodinakis, 2003)	1	no epileptic seizure nor drug abuse history	the patients increased the dose to 600mg per day epigastric pain, nausea, epileptic seizures and depression	not reported
Zolpidem	Adult	delirium hallucination	(Freudenreich & Menza, 2000)	1	depression	agitated and confused disorganized visual hallucinations	not reported

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	dependence	(Aragona, 2000)	1	history of drug abuse seizure history after benzodiazepine discontinuation	the patient increased the dose up to 450-600mg per day for anxiolytic effect. dependence and tolerance	epileptic seizure
Zolpidem	Adult	dependence	(Bottlender, 1996)	1	history of drug abuse	the patient increased the dose up to 140mg per day for well-being and reduction of tremor caused by parkinsonism, and also took five other drugs for Parkinson disease delusion disorder at the same time. dependence and tolerance	disturbed sleep, restlessness, sweating, tachycardia and hypertension.
Zolpidem	Adult	dependence	(Liappas et al., 2002)	1	history of abuse and dependence on cocaine	consumed up to 200-300 mg/day for progressive reduction of his cocaine craving. more excited, hyperactive and euphoric, often exhibiting childish behavior, logorrhea and memory blanks.	not reported
Zolpidem	Adult	dependence	(Liappas, 2003)	3	history of drug abuse	patients increased the dose up to 300-600mg for sedation, reduction of cocaine craving, stimulation, or euphoria. dependence and tolerance childish behavior, confusion, memory blank or amnesia	confusion, amnesia or epileptic seizure
Zolpidem	Adult	dependence	(Ravishankar 1998)	2	depression	the patient increased the dose up to 200mg per day	tachycardia, confusion, anxiety, panic attacks and fear of ongoing outside
Zolpidem	Adult	dependence	(Sakkas 1999)	1	depression history of drug abuse	the patient increased the dose up to 300mg per day for stimulation dependence and tolerance depression mood disorders suicidality visual hallucinations	not reported
Zolpidem	Adult	dependence	(Vartzopoulos, Bozikas, Phocas, Karavatos, & Kaprinis, 2000)	4	history of drug abuse patients with borderline personality disorder	patients increased the dose up to 500mg daily to enhance the experienced relieving effect on their dysphoric states. dependence and tolerance Mild to severe withdrawal syndrome after discontinuation.	confusion, anxiety, irritability, nausea, vomiting or psychomotor agitation.

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult Elderly	dependence delirium	(Sharan, 2007)	5	history of drug/alcohol dependence and/or mental illness (depression, bipolar disorder, late-onset psychosis) elderly patients (3) all taking 10mg zolpidem (recommended dose for the elderly is 5 mg)	dependence (including symptoms of withdrawal, cravings, apprehension/anxiety, restlessness, irritability, insomnia, palpitations) delirium (agitation, talking irrelevantly, unable to recognize relatives, disorientation, auditory/visual/tactile hallucinations, restlessness, violent behavior)	2 patients diagnosed with zolpidem dependence: both successfully detoxified with clonazepam (8 mg/day), with one of the two relapsing after 3 months 3 patients diagnosed with delirium induced by zolpidem: symptoms subsided after zolpidem was discontinued
Zolpidem	Adult	dependence tolerance	(Kao, 2004)	1	history of substance abuse	IV administration for stimulant effect and euphoria and increased up to 300-400 mg/day	yawning, rhinorrhea and lacrimation
Zolpidem	Adult	dependence tolerance	(Quaglio et al., 2005)	2	no common characteristics	increasing tolerance	no withdrawal disturbances during detoxification with flumazenil infusion
Zolpidem	Adult	generalized seizure	(Cubala, 2007)	1	female history of psychiatric hospitalization for organic dissociative disorder history of depression Zolpidem dependence	Zolpidem tolerance, abuse and dependence major depression	generalized tonic clonic seizures and a prolonged post convulsion period following sudden zolpidem withdrawal subsequent to drug dependence
Zolpidem	Adult	hallucination	(Elko, Burgess, & Robertson, 1998)	5	concurrent use of serotonin-reuptake inhibition depression	hallucination	not reported
Zolpidem	Adult	hallucination	(Ginsberg, 2003), (Huang, 2003)	1	concurrent use of other drugs for hormone replacement, osteoporosis and insomnia	headache spotty memory hallucination visual perception distortion	not reported
Zolpidem	Adult	hallucination	(Tsai, 2003)	1	not reported	visual illusions, confusion and hallucination especially reusing after rapid withdrawals.	insomnia
Zolpidem	Adult	hallucination amnesia	(Van Puijenbroek, Egberts, & Krom, 1996)	2	one without history of psychiatric disorders, the other with major depressive disorder for 6 month	hallucination amnesia	not reported

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	hallucination CNS side effect	(Hoyler, Tekell, & Silva, 1996)	1	history of pothyroidism, mild vascular dementia, and auditory hallucinations	agitated and disoriented to time and place hallucination and increased psychomotor activity	regained her orientation, responded to redirection, was able to communicate at her usual level of efficiency, and her bizarre behavior was resolved
Zolpidem	Adult	Hepatic problem	(Clark, 1999)	1	liver transplantation	decline in mentality hepatic encephalopathy abdominal pain awoke in a stupor and was disoriented to place and time	not reported
Zolpidem	Adult	hepatic problem	(Karsenti, Blanc, Bacq, & Melman, 1999)	1	cholecystectomy	abdominal pain hepatotoxicity	not reported
Zolpidem	Adult	others- drug interaction	(Ortega 1996)	1	long term benzodiazepine user no psychiatric history	nervousness, irritability, fainting, asthenia, muscular cramps, excessive hear and sweating occasional febrile episodes, weight loss, and a surprising sweet taste in the mouth	all symptoms disappeared
Zolpidem	Adult	seizure dependence tolerance	(Gericke & Ludolph, 1994)	1	depression no seizure history	consumed 150-280 mg/day for stimulant effect	recurrence of depressive mood with apathy and drug carving
Zolpidem	Adult	sensory distortions tolerance	(Pies, 1995)	1	no history of psychosis or substance abuse	sensory distortions	not reported
Zolpidem	Adult	sleep related eating disorder	(Najjar, 2007)	1	46-year old female history of depression, hypothyroidism, hypertension and insomnia	sleep related eating disorder starting 3 weeks after starting zolpidem, resulting in weight gain (50 pounds over a one-year period) and the development of obstructive sleep apnea	complete recovery after zolpidem was discontinued
Zolpidem	Adult	somnambulism	(Harazin & Berigan, 1999)	1	depression	somnambulism	somnambulism stopped
Zolpidem	Adult	somnambulism	(Sattar, Ramaswamy, Bhatia, & Petty, 2003)	1	bipolar disorder history of drug abuse history of alcohol dependence mania taking valproic at the same time	somnambulism difficulty in concentration	insomnia

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Adult	somnambulism	(Yang, 2005)	1	Heavy alcohol consumption with questionable delitium tremens but had stopped drinking alcohol 20 years ago Traumatic head injury	somnambulism agitated and confused but had no psychotic experiences	no additional episodes of sleepwalking
Zolpidem	Adult	tolerance	(Cavallaro, 1993)	2	psychiatric disorders	increase dosage because of tolerance with awakening after 2-3 h. abstinence phenomena during the day and increased dosage again to control those symptoms.	not reported
Zolpidem	Adult	abruption vaginal spotting periorbital headache abdominal pain respiratory problems trouble sleeping withdrawal-like symptoms (nervousness, anxiety)	(Askew, 2007)	1	pregnant female history of zolpidem abuse (10–15 tablets/night)	cord blood testing resulted in measurable zolpidem levels (possibly as high as peak plasma concentrations after a 5-mg dose of the drug), but no withdrawal symptoms noted in the neonate	withdrawal-like symptoms (nervousness, anxiety), complained of headaches and inability to sleep after treatment reduction
Zolpidem	Adult	visual hallucinations sleepiness nausea dizziness diplopia	(de Haas, 2007)	1	32-year old male negative psychiatric personal or family history no concomitant medication or illicit drugs	visual hallucinations starting 20 minutes after drug intake and lasting 2 hours sleepiness, nausea, dizziness, diplopia, and dysphasia (present for 3.5 hours)	adverse events subsided after a few hours of taking the medication
Zolpidem	Adult Elderly	CNS side effect	(Logan & Couper, 2001)	29	no common characteristics	driving impairment because of slow movements and reactions visual distortions	not reported
Zolpidem	Adult Elderly	dependence	(Liappas, 2003)	8	minor psychiatric disorders	patients increased the dose up to 150-600mg for stimulation, sedation, improving mood, relax, coping or sleep better. dependence and tolerance several traffic accidents memory impairment confusion	4 without withdrawal symptoms 1 with discomfort, irritability, and agitation 1 with epileptic seizure 1 with instability, dizziness and a craving for other psychotropic substances 1 not reported
Zolpidem	Adult Elderly	others	(Morgenthaler & Silber, 2002)	5	no history of eating disorders concurrent use of other drugs	amnestic sleep-related eating disorder restless legs syndrome	no nocturnal eating

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Elderly	CNS side effect	(Brodeur & Stirling, 2001)	1	Extensive medical history	delirium psychosis restless amnesia	not reported
Zolpidem	Elderly	delirium mania	(Hill, Oberstar, & Dunn, 2004)	1	no significant psychiatric history family history of mild depression	no hallucination no suicidal or homicidal ideation mania	not reported
Zolpidem	Elderly	dependence	(Madrak & Rosenberg , 2001)	1	history of alcohol and drug abuse	use up to 100mg/day for the last 1.5 years psychomotor agitation; tremor; facial flushing; anxiety	not reported
Zolpidem	Elderly	hallucination	(Markowitz , Rames, Reeves, & Thomas, 1997)	1	no substance abuse depression	hallucination	no further episodes after discontinuation
Zolpidem	Elderly	hallucination	(Pitner, Gardner, Neville, & Mintzer, 1997)	1	no psychiatric history	hallucination delusion psychomotor agitation irritable and difficult to redirect	not reported
Zolpidem	Elderly	palpitations Torsades de Pointes (TdP) ventricular tachycardia degenerated to ventricular fibrillation QTc interval prolongation	(Letsas, 2006)	1	67-year-old woman history of prosthetic mitral valve and congestive heart failure (NYHA II)	3 weeks after starting zolpidem, complained of palpitations Potential drug interaction with amiodarone, causing TdP ventricular tachycardia degenerated to ventricular fibrillation and a QTc interval prolongation	after zolpidem and amiodarone were withdrawn, patient's QTc interval gradually decreased to its initial value
Zolpidem	Elderly	visual hallucinations amnesia	(Kito, 2006)	1	82-year-old Asian woman being treated with fluvoxamine an d zolpidem for major depressive disorder and insomnia no prior psychiatric treatment and no history of alcohol or substance abuse	visual hallucinations (lasting several minutes to half an hour) and amnesia 30 minutes after taking zolpidem starting on the third day of being given an increased dose of fluvoxamine – researchers postulated a possible fluvoxamine–zolpidem interaction	nightly visual hallucinations and amnesia disappeared after discontinuing zolpidem
Zolpidem	Pediatrics	hallucination	(Andrade, 2002)	1	history of vascular headache	drowsiness, confusion, unsteadiness and hallucination vascular headache and the use of zolpidem in children may increase the hallucination	not reported

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zolpidem	Pediatrics	somnambulism	(Lange, 2005)	1	depressive disorder history of somnambulism family history of somnambulism no epileptiform activity	somnambulism	change to citalopram without incident
Zopiclone	Adult	dependence	(Aranko, Henriksson, Hublin, & Seppalainen, 1991)	1	depression compulsive personality disorder history of drug abuse concurrent use of antidepressants	the patient increase the dose up to 90mg per day for uninterrupted sleep. Memory difficulties cognitive impairments dependence	grand-mal-type convulsion
Zopiclone	Adult	dependence	(Haasen, Mueller-Thomsen, Fink, Bussopulos, & Reimer, 2005)	1	no history of benzodiazepine or other psychotropic substance use and only very in frequently drank a glass of wine	dependence daily dosage of 37.5mg	Remain symptom: dystonia symptoms peaked 8 days after initiating the reduction and 3 days after discontinuation, and then gradually remitted: torticollis such as tremulousness, sympathetic autonomic hyperactivity, including anxiety, arousal, sweating, tachycardia, facial flushing and mild hypertension Reappeared insomnia
Zopiclone	Adult	dependence	(Jones, 2005)	4	no common characteristics	dependence	severe anxiety with tachycardia, tremor, sweating, rebound insomnia, flushes, palpitations, and derealization.
Zopiclone	Adult	dependence	(Thakore & Dinan, 1992)	1	depression history of alcohol dependency history of flurazepam addiction take zopiclone more due to anxiety and agoraphobia	dependence	tachycardia hand tremor weakness panic attack

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zopiclone	Adult	extreme agitation	(Moloney, 2007)	2	3-month history of depression concomitant alprazolam and antidepressant medication	one patient developed insomnia, restlessness, agitation, and a complete inability to relax 3 weeks after starting zopiclone Another patient became extremely agitated, developed forgetfulness, inability to sit still, insomnia, nocturnal wandering, and racing thoughts one week after starting zopiclone	after zopiclone was withdrawn, adverse events resolved within 24-48 hours
Zopiclone	Adult	global amnesia	(Fava, 1996)	1	no current psychiatric symptomatology no drinking history no other medication	global amnesia	no further episodes of global amnesia were observed during a 6-month period
Zopiclone	Adult	incidence of cancer	(Stebbing et al., 2005)	32	not reported	2 weeks of zopiclone. 32 (5.3%) patients have subsequently been diagnosed with cancer at least 3 months after exposure to zopiclone The label for eszopiclone contains significant warnings regarding carcinogenicity and mutagenesis	not reported
Zopiclone	Elderly	dependence	(Bramness, Arnestad, Karinen, & Hilberg, 2001)	1	smoker respiratory problems anxiety	difficulty in breathing death caused by 337.5mg overdose	not reported
Zopiclone	Elderly	dependence	(Kuntze, Bullinger, & Mueller-Spahn, 2002)	1	depressive disorder no use of psychotropic	tolerance to 337.5mg/day dependence	not reported
Zopiclone	Elderly	dependence delirium	(Wong, 2005)	1	74-year old woman with congestive heart failure taking several concomitant medications habit of using high-dose zopiclone (112.5 mg) daily for 20+ years	dependence delirium (including confusion, disorientation) caused by abrupt zopiclone withdrawal	after zopiclone was resumed at a lower dose, delirium resolved completely after a few days
Zopiclone	Elderly	others- drug interaction	(Alderman, Gebauer, Gilbert, & Condon, 2001)	1	depression concurrent use of antidepressants	morning drowsiness increased plasma concentrations	zopiclone plasma concentrations back to normal after nefazodone discontinuation

Evidence Table 10. Case Reports

Drug	Sub-group	Adverse Events	Study	# of cases	Case Characteristics	Effects during treatment	Effects during treatment reduction or discontinuation
Zopiclone	Elderly	respiratory depression	(Vogal, 1998)	1	COPD ex-smoker with a history of ethanol abuse	drowsy respiratory acidosis	not reported
Zopiclone	Pediatrics	others	(Sullivan, McBride, & Clee, 1995)	3	history of drug abuse alcohol abuse	no evidence of dependence	not reported

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