

# **Drug Class Review on Newer Sedative Hypnotics**

**Final Report**

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

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## INTRODUCTION

Insomnia is a serious health problem that affects millions of people. Population surveys have estimated the prevalence of insomnia to be about 30% to 50% of the general population, but estimates vary depending on the methods and definitions used to define insomnia.<sup>1</sup> About three-fourths of those who have trouble sleeping say that the problem is “occasional,” averaging about six nights per month. The other 25% have frequent or chronic insomnia, averaging about 16 nights per month.<sup>2</sup> Individuals with insomnia most often report a combination of difficulty falling asleep and intermittent wakefulness during sleep.<sup>3</sup> The most common symptoms of insomnia include waking up feeling unrefreshed and being awake often during the night. The symptoms of difficulty falling asleep and waking up too early are less common, but still experienced at least a few nights a week by about one-fourth of adults with insomnia.<sup>1</sup> The risk of sleep disorders increases with age, affecting approximately 20% to 40% of older adults at least a few nights per month.<sup>2</sup>

Consequences of insomnia can include an increased risk of depression, poor memory, reduced concentration, and poor work performance. Insomnia has been associated with poor general health, greater healthcare utilization, lower quality of life, socioeconomic status and poorer social relationships, memory, mood and cognitive function.<sup>4</sup> Insomnia can occur in an acute, transient setting, and can also be a more chronic problem when associated with underlying psychiatric or medical illness.

Treatment of insomnia involves behavioral changes such as minimizing daily habits that interfere with sleep (e.g., drinking coffee or engaging in stressful activities in the evening),<sup>4</sup> and pharmacotherapy using sedating antidepressants (e.g., trazodone), antihistamines, anticholinergics, benzodiazepines, or non-benzodiazepine sedative hypnotics. While multiple drug classes can assist in improving sleep, those that act as GABA agonists are preferred. The benzodiazepines and the newer sedatives zolpidem, zaleplon, zopiclone, and eszopiclone work through these receptors.

In general, short-term use of sedative hypnotics is recommended, however it is recognized that some individuals may require longer-term treatment.

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

### Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of newer sedative hypnotics. Our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety.

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to

both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer sedative hypnotics versus each other, versus benzodiazepines, or versus trazodone in treating adults with insomnia?
2. What is the comparative tolerability and safety of newer sedative hypnotics versus each other, versus benzodiazepines, or versus trazodone when used to treat adults with insomnia?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one newer sedative hypnotic is more effective or associated with fewer adverse events?

### Included populations

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

### Included interventions

Four newer nonbenzodiazepine sedative hypnotics have been introduced since 1992 (Table 1), three are available in the US (zolpidem, zaleplon, and eszopiclone) and three in Canada and other countries (zolpidem, zaleplon, and zopiclone).

The newer sedative hypnotics differ in their pharmacokinetics, which could be expected to affect different aspects of insomnia. For example, drugs with a shorter half-life might be effective for sleep latency but less effective for sleep duration.<sup>5</sup>

The recommended starting dose in older adults is half the recommended adult dose for all of these drugs 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 sedative hypnotic drugs**

Active ingredient	Brand name	Initial dose (given at bedtime)		Half-life (hours)
		Adults	Elderly	
Eszopiclone	Lunesta	2 mg	1 mg	6
Zaleplon	Sonata	10 mg	5 mg	1
Zolpidem	Ambien	10 mg	5 mg	2.5
Zopiclone (Canada)	Imovane	5 to 7.5 mg	3.75 mg	5

## Included outcomes

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

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

These outcomes can be measured subjectively (e.g., using patient sleep diaries), or objectively, using polysomnography in a sleep laboratory. Most studies report subjective outcomes. While objective measures may give a more accurate indication of sleep duration and other outcomes, subjective outcomes may be more important to patients.

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

*Rebound insomnia* is worsening of insomnia upon discontinuation of medications. This can be measured using any of the outcomes above.

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

## METHODS

### Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (2<sup>nd</sup> Quarter 2005), Cochrane Database of Systematic Reviews, DARE, MEDLINE (1966 to April Week 4 2005), EMBASE (2<sup>nd</sup> Quarter 2004), and PsycINFO (1985 to May Week 2 2005) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). To identify additional studies, we also searched reference lists of included studies and reviews, FDA information (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>), and dossiers submitted by pharmaceutical companies. All citations were imported into an electronic database (EndNote 9.0).

### Study Selection

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

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

### Data Abstraction

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

### Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).<sup>6,7</sup> We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. We rated the quality of observational studies of adverse events based on non-biased selection of patients, low loss to followup, non-biased and accurate ascertainment of events, and control for potential confounding factors.

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

### Data Synthesis

We constructed evidence tables showing study characteristics, quality ratings and results for all included studies.

When possible, we calculated the weighted mean difference between treatments for continuous outcomes and displayed results in forest plots using RevMan (v4.2, Update Software). Meta-analysis was performed when possible (i.e., when populations

and interventions were similar and when significant heterogeneity did not exist among trials).

To assess the overall strength of evidence for a body of literature about a particular key question, we examined the consistency of study designs, patient populations, interventions, and results. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered “good-quality.”) For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm. Poor-quality studies are not considered in the assessment of the overall body of evidence.

## RESULTS

### Overview of included studies

We identified 2,040 citations from literature searches, reviews of reference lists, and citations from dossiers submitted by two pharmaceutical manufacturers: Sanofi-Aventis (zolpidem) and Sepracor (eszopiclone). After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained the full text of 255 publications. After re-applying the criteria for inclusion, we included 141 publications. The flow of study inclusion and exclusion is detailed in Figure 1.

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

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

**Table 2. Total numbers of head-to-head trials of sedative hypnotics**

	Zaleplon	Zolpidem	Zopiclone	Eszopiclone
Zaleplon	*****			
Zolpidem	4	*****		
Zopiclone	0	2	*****	
Eszopiclone	0	1	0	*****



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

We included 44 trials in 45 publications of sedative hypnotics versus benzodiazepines.<sup>16-60</sup> Most of the active-controlled studies included a placebo arm and reported efficacy and safety outcomes by comparing to placebo instead of comparing the two active drugs. Appendix D summarizes the efficacy, safety, and rebound insomnia results of these studies. Details of the populations, interventions, and outcomes are provided in Evidence Tables 4 through 12. Details of the quality assessment of all trials are provided in Evidence Table 16.

We identified two trials of a sedative hypnotic compared with trazodone; one (versus zaleplon)<sup>47</sup> was rated poor quality and the other (versus zolpidem)<sup>56</sup> was rated fair.

Thirty-one placebo-controlled trials in 32 publications were also included.<sup>61-92</sup>

Three good-quality systematic reviews of newer sedative hypnotics were included.<sup>1, 93, 94</sup> The most relevant review to this report is a comparative review conducted by the National Institute for Clinical Excellence (NICE).<sup>93</sup> The others were not designed specifically to compare the sedative hypnotics head-to-head.

We included 17 observational studies (Evidence Table 17)<sup>95-111</sup> and 29 case reports (Evidence Table 18)<sup>112-140</sup> of adverse events associated with newer sedative hypnotics.

## **Key Questions 1 and 2. What is the comparative effectiveness and safety of newer sedative hypnotics versus each other, versus benzodiazepines, or versus trazodone in treating adults with insomnia?**

### **Summary of the Evidence**

#### **Short-term Efficacy and Safety**

##### **Zolpidem vs zaleplon**

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

##### **Zolpidem vs zopiclone**

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

**Zolpidem vs eszopiclone**

- In one head-to-head trial, zolpidem and eszopiclone had similar objective sleep latency and Wake Time After Sleep Onset as measured by polysomnography after two nights of treatment.
- There was no difference between zolpidem and eszopiclone on subjective measures of next-day effects, including morning sleepiness, daytime alertness, and daytime ability to function.
- Indirect comparisons provide evidence that the drugs were similar for sleep latency and number of awakenings, but eszopiclone was more effective for increasing sleep duration. Comparisons were limited due to differences in populations across placebo-controlled studies.

**Eszopiclone vs zaleplon**

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

**Zaleplon vs zopiclone**

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

**Comparative long-term efficacy and safety**

- Evidence about long-term safety is limited; there is no comparative evidence.
- One longer-term placebo-controlled trial provides evidence that eszopiclone 3 mg is efficacious for up to 6 months.
  - Withdrawal symptoms were not observed after discontinuation.
  - Rebound insomnia was not measured.
  - This trial does not add any information about the *comparative* long-term efficacy and safety of eszopiclone versus other sedative hypnotics.
- There are case reports of dependence with both zolpidem and zopiclone.

**Newer sedative hypnotics vs benzodiazepines**

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

**Newer sedative hypnotics vs trazodone**

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

## Detailed Assessment

### Zolpidem vs Zaleplon

#### Direct comparisons

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

Sleep latency. Sleep latency (time to sleep onset) was the primary outcome in two studies in adults (Table 3).<sup>10, 11</sup> Both compared zaleplon at three fixed doses (5 mg, 10 mg, or 20 mg) to zolpidem 10 mg for 4 weeks. A placebo arm was also included, and analyses are presented for the comparison to placebo. Neither publication provided a head-to-head analysis of zolpidem versus zaleplon, but a head-to-head analysis is provided in the FDA statistical review of zaleplon<sup>5</sup> for one trial.<sup>11</sup>

At weeks 1 through 4,<sup>11</sup> there was no difference between zaleplon 5 mg or 10 mg and zolpidem 10 mg on the median number of minutes to sleep onset. The only significant difference between the drugs on this outcome was a shorter latency with zaleplon 20 mg compared to zolpidem 10 mg. There was no zolpidem 20 mg arm in this trial. There was no difference in the comparison of recommended starting doses zaleplon 10 mg and zolpidem 10 mg. These results are not intention-to-treat.

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

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

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

\*patients &gt; age 65

\*\*estimated from graph

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

Table 3 also shows results of a 2-week head-to-head trial of zaleplon 5 mg or 10 mg versus zolpidem 5 mg conducted in 549 elderly (65 years or older) patients.<sup>8</sup> Results were similar to those of the trials in younger patients: there was no difference in sleep latency for zaleplon 5 mg versus zolpidem 5 mg, but zaleplon at a higher dose (10 mg) was associated with a shorter latency than zolpidem 5 mg. Zolpidem, but not zaleplon, was associated with rebound sleep latency on the first night of discontinuation.

Sleep duration. Duration of sleep was a secondary outcome in three head-to-head trials of zaleplon versus zolpidem.<sup>8, 10, 11</sup> Table 4 shows outcomes for weeks 1 through 4 and rebound on the first day after the end of treatment. Zolpidem 5 mg and 10 mg increased sleep duration more than placebo in all three studies. In two studies in adults, zaleplon 5 mg and 10 mg were no different from placebo on this outcome at any time period. Zaleplon 20 mg was more effective than placebo at weeks 1 and 3, but not weeks 2 and 4.

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

Study	Week 1	Week 2	Week 3	Week 4	Withdrawal day +1 (rebound)
Fry (not ITT) <sup>5</sup>	<u>Zaleplon</u> (p vs placebo) 5 mg: +13 (NS) 10 mg: +14 (NS) 20 mg: +22 <b>(&lt;0.05)</b>	<u>Zaleplon</u> (p vs placebo) 5 mg: +6 (NS) 10 mg: +4 (NS) 20 mg: +9 (NS)	<u>Zaleplon</u> (p vs placebo) 5 mg: -5 (NS) 10 mg: +11 (NS) 20 mg: +20 <b>(&lt;0.05)</b>	<u>Zaleplon</u> (p vs placebo) 5 mg: -4 (NS) 10 mg: +12 (NS) 20 mg: +13 (NS)	<u>Zaleplon</u> (p vs placebo) 5 mg: 0 (NS) 10 mg: 0 (NS) 20 mg: 0 (NS)
	<u>Zolpidem</u> (p vs placebo) 10 mg: +30 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +24 <b>(&lt;0.05)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +26 <b>(&lt;0.01)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +29 <b>(&lt;0.05)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: -30 <b>(P&lt;0.05)</b>
Elie (LOCF analyses) <sup>5</sup>	<u>Zaleplon</u> (p vs placebo) 5 mg: 0 (0.92) 10 mg: +19 (0.11) 20 mg: +19 (0.04)	<u>Zaleplon</u> (p vs placebo) 5 mg: 0 (0.28) 10 mg: +8 (0.24) 20 mg: +13 <b>(0.01)</b>	<u>Zaleplon</u> (p vs placebo) 5 mg: +10 (0.26) 10 mg: +10 (0.43) 20 mg: +9 (0.07)	<u>Zaleplon</u> (p vs placebo) 5 mg: +13 (0.47) 10 mg: +15 (0.10) 20 mg: +23 <b>(0.02)</b>	<u>Zaleplon</u> (p vs placebo) 5 mg: 0 (NS) 10 mg: 0 (NS) 20 mg: 0 (NS)
	<u>Zolpidem</u> (p vs placebo) 10 mg: +28 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +29 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +21 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: +39 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 10 mg: 0 <b>(&lt;0.05 using F test)</b>
Ancoli-Israel 1999 <sup>*96</sup>	<u>Zaleplon</u> (p vs placebo) 5 mg: NR (NS) 10 mg: +27 <b>(0.05)</b>	<u>Zaleplon</u> (p vs placebo) 5 mg: NR (NS) 10 mg: NR (NS)	--	--	<u>Zaleplon</u> (p vs placebo) 5 mg: +12.5 (NS) 10 mg: -2.5 <b>(&lt;0.05)</b>
	<u>Zolpidem</u> (p vs placebo) 5 mg: +42 <b>(&lt;0.001)</b>	<u>Zolpidem</u> (p vs placebo) 5 mg: +34 <b>(&lt;0.01)</b>			<u>Zolpidem</u> (p vs placebo) 5 mg: -17.5 <b>(&lt;0.001)</b>

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

Number of awakenings. The difference from placebo in the median number of awakenings during the night was another secondary outcome in head-to-head trials (Table 5). In one trial,<sup>10</sup> there was no difference from placebo for any dose of either zaleplon or zolpidem at any time period. The other trial in adults,<sup>11</sup> had mixed results. Zaleplon 5 mg and 10 mg was no different from placebo, zaleplon 20mg was more effective than placebo at weeks 2, 3, and 4, and zolpidem 10 mg was better than placebo

at weeks 1, 2, and 3. In older adults, only zolpidem 5 mg was more effective than placebo.<sup>8</sup>

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

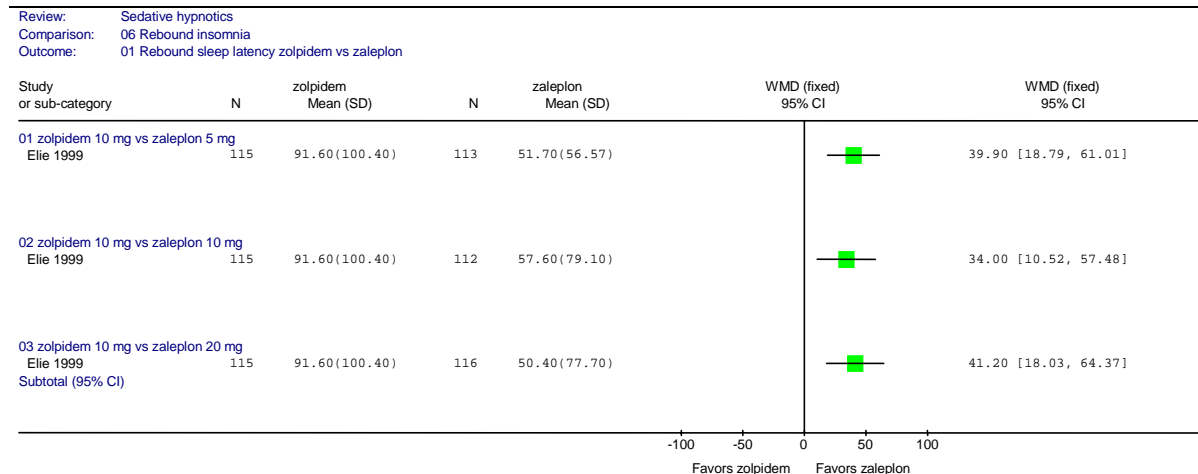
Study	Week 1	Week 2	Week 3	Week 4	Withdrawal day +1 (rebound)
Fry (not ITT) <sup>11</sup>	<u>Zaleplon</u> (p vs placebo) placebo: 1.71 5 mg: 1.93 (NS) 10 mg: 1.69 (NS) 20 mg: 1.75 (NS)	<u>Zaleplon</u> (p vs placebo) placebo: 2.00 5 mg: +6 (NS) 10 mg: +4 (NS) 20 mg: +9 <b>(&lt;0.001)</b>	<u>Zaleplon</u>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

Sleep Quality. In a pooled analysis of three trials of zaleplon versus zolpidem<sup>8, 10, 11</sup>, the NICE review<sup>93</sup> found that patients on zaleplon were less likely to experience improvement in sleep quality at the end of treatment than patients taking zolpidem (OR 0.66; 95% CI 0.51 to 0.87).

Rebound insomnia. Two head-to-head trials found zolpidem 10 mg to be associated with more rebound insomnia than zaleplon as measured by median sleep latency on the first night after discontinuation.<sup>10, 11</sup> Zolpidem 10 mg was associated with

a 20- to 22-minute increase in sleep latency versus placebo on the first night of discontinuation. Rebound sleep latency was not seen with zaleplon at any dose. Figure 2 shows the mean difference between zolpidem and zaleplon for rebound sleep latency, measured on the first day after withdrawal after 4 weeks of treatment in one of these studies.<sup>10</sup> Zaleplon at all doses (5 mg, 10 mg, and 20 mg) was less likely to cause rebound sleep latency than zolpidem 10 mg. The mean difference for zolpidem 10 mg versus zaleplon 10 mg was 34 minutes (95% CI, 10.5 to 57.5 minutes).

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



Head-to-head studies also found zolpidem to be associated with rebound decrease in sleep duration on the first night of discontinuation. Zaleplon was not associated with rebound on this outcome, except at the 10 mg dose in older adults.

In two studies in adults,<sup>10,11</sup> 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.<sup>8</sup>

**Other Outcomes.** A small (N=53) single-dose crossover study of zolpidem 10 mg versus zaleplon 10 mg was designed to measure patient preference for a drug as a primary outcome.<sup>13</sup> This was measured by a questionnaire filled in by the patient the evening following administration of the drug. More patients preferred zolpidem, but the difference was not statistically significant (62% vs 32%; p=0.81).

Secondary outcomes were mean scores on the Leeds sleep evaluation questionnaire (LSEQ), and “day quality,” a visual analogue scale (0-100, higher is better) measuring 7 factors on the day following the administration of the drug. Zolpidem patients improved more on two of four factors on the LSEQ (Getting to Sleep and Quality of Sleep); there was no difference between drugs on the other two factors (Ease of Waking Up and Behavior Following Wakefulness). Only one of 7 factors on the “day quality” measure was significantly different between drugs. Zolpidem patients reported better quality of sleep (mean score 68.8 vs 50.2, p<0.0001), but there were no differences on other factors.

**Short-term adverse events.** Table 6 shows the total withdrawals and withdrawals due to adverse events reported in short-term head-to-head trials of zaleplon versus

zolpidem. Rates of overall adverse events and withdrawals due to adverse events were similar for both drugs and increased with longer duration of the trials.

The most common treatment-emergent adverse events were headache and dizziness. In a 2-week trial in older adults,<sup>8</sup> 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,<sup>11</sup> dizziness was significantly more frequent in 10 mg and 20 mg treatment groups than placebo ( $p<0.001$ ), occurring in 8% of patients in the placebo group, 3% in the zaleplon 5 mg group, 9% in the zaleplon 10 mg group, 14% in the zaleplon 20 mg group, and 14% in the zolpidem 10 mg group.

In the single-dose study conducted in 53 general practice patients,<sup>13</sup> 3 adverse events occurred in the zolpidem 10 mg group (sluggish tongue, impaired concentration, leg complaints), and 4 in the zaleplon 10 mg group (cephalgia requiring analgesic treatment, headache, abdominal fullness, vertigo).

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

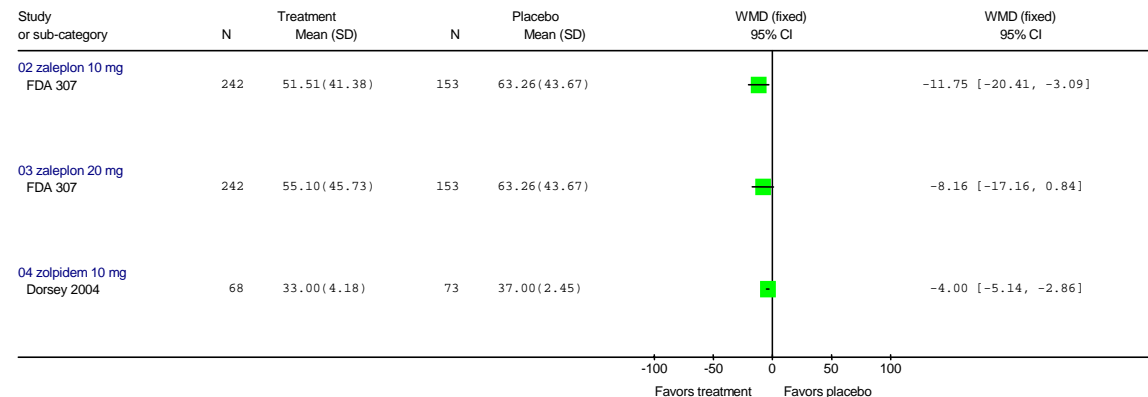
Comparison (duration)	N	Incidence of adverse events		Withdrawals due to adverse events	
		Percent	Risk difference (95% CI)	Percent	Risk difference (95% CI)
Zaleplon 5 mg vs zolpidem 10 mg <sup>10, 11</sup> (4 weeks)	476	67% vs 73%	-6% (-14% to 2%)	2% vs 6%	-4% (-7% to 0%)
Zaleplon 10 mg vs zolpidem 10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

### Indirect comparisons

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



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



## Zolpidem vs zopiclone

### Direct comparisons

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

A two-week, double-blind trial in 479 patients at multiple centers in Japan<sup>12</sup> is the only head-to-head trial of zolpidem versus zopiclone designed to measure efficacy. The funding source is not reported.

**Global assessment of improvement.** The primary outcome was the investigator's global assessment of improvement, based on patient sleep diaries and reported as the proportion of patients who were "moderately improved" or "markedly improved." At the end of treatment, there were no significant differences between treatment groups in the number of patients "markedly improved" (18.7% zolpidem vs 16.4% zopiclone) or "moderately improved" (49.3% zolpidem vs 45.2% zopiclone). Patients' ratings of treatment efficacy were similar and did not differ between treatment groups. Sleep outcomes (sleep onset latency, frequency of awakening, sleep duration, daytime mood, and daytime physical condition) were improved from placebo to a similar extent in both treatment groups, but data are not reported.

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

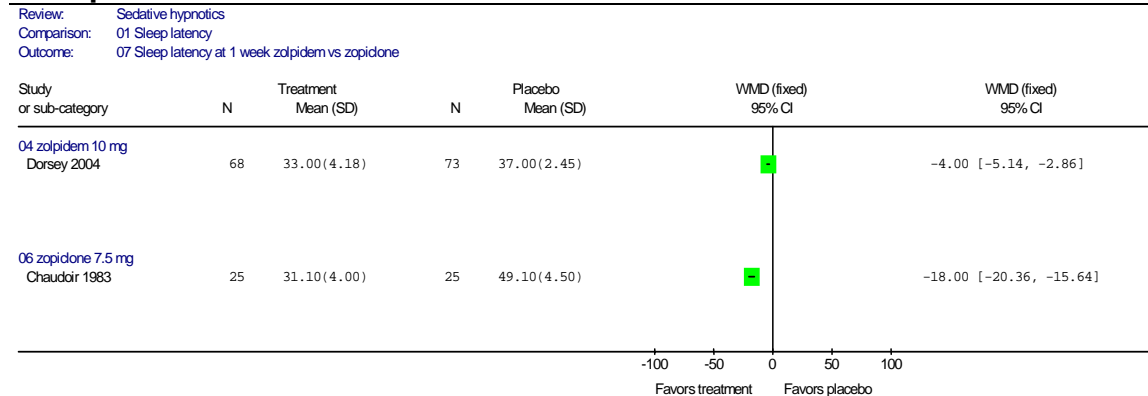
**Short-term adverse events.** More patients in the zopiclone group than the zolpidem group had an adverse event "related", "probably related", or "possibly related" to treatment (31.3% vs 45.3%;  $p = 0.004$ ). There were no significant differences in the proportion of patients who withdrew due to any adverse event (8.5% zolpidem vs 10.2% zopiclone) or due to a drug-related adverse event (6.6% vs 8.9%). The frequency of specific adverse events was similar between groups, with the exception of bitter taste, which occurred in 3% of patients in the zolpidem group, and 31% of those in the zopiclone group.

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

### Indirect comparisons

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

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



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

### Zolpidem vs Eszopiclone

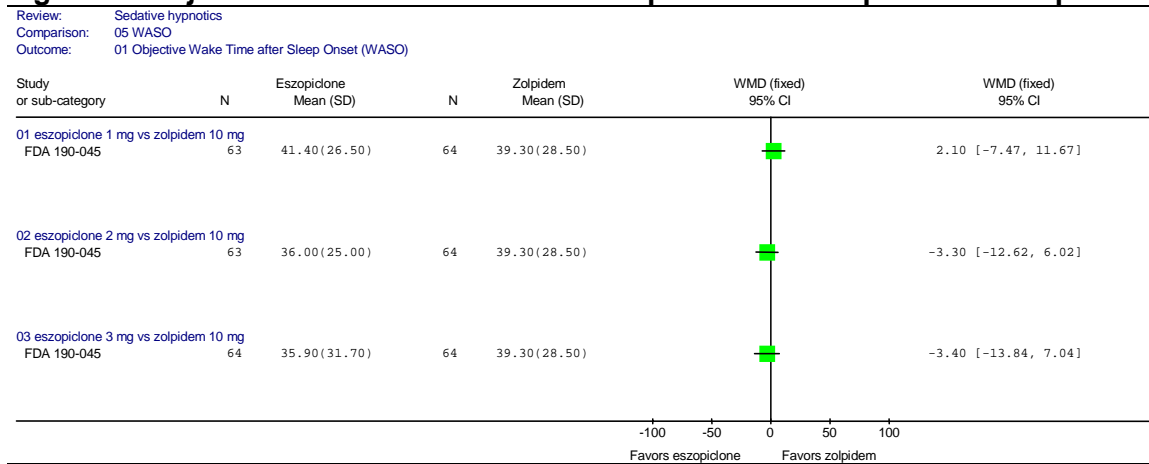
#### Direct comparisons

There is one head-to-head trial of eszopiclone versus zolpidem. This study has not yet been fully published. It has been reported in a poster presentation,<sup>14</sup> and additional information is provided in the FDA statistical review of eszopiclone.<sup>15</sup> The primary efficacy outcome was latency to persistent sleep as measured by polysomnography. Comparative information on subjective sleep outcomes is not available from this trial.

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

There was no difference between zolpidem 10 mg and any dose of eszopiclone on objective WASO (figure 5).

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



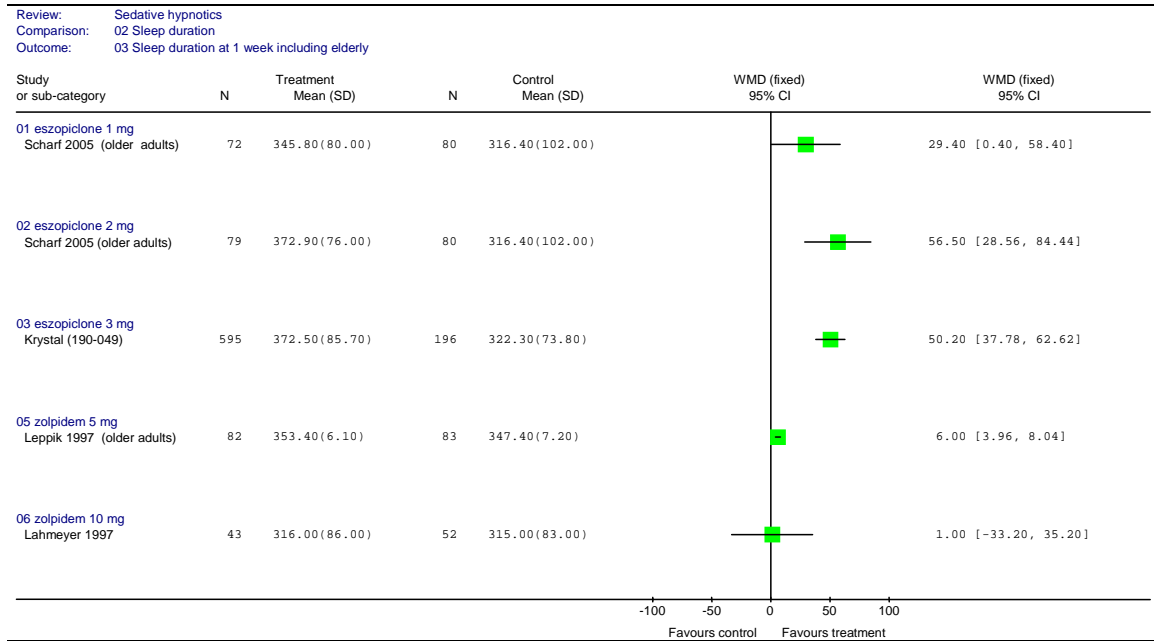
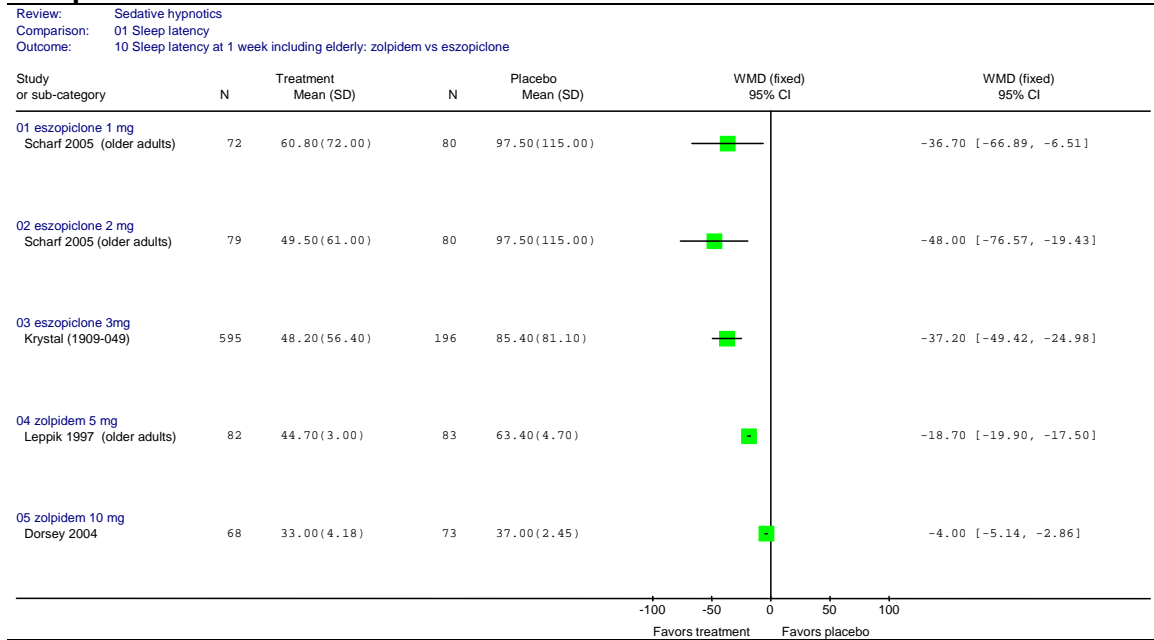
**Next-day effects.**

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

**Indirect comparisons**

Figure 6 shows outcomes at one week in placebo-controlled trials of eszopiclone and zolpidem. The studies are not directly comparable because the doses varied and populations differed in age and baseline severity of insomnia. In two studies in older adults, both zolpidem 5 mg and eszopiclone (1 mg and 2 mg) were more effective than placebo in reducing subjective sleep latency. In two studies in adults, eszopiclone 3 mg, but not zolpidem 10 mg, was more effective than placebo. These studies varied considerably in their placebo response rates (37 minutes in the zolpidem 10 mg study vs 85 minutes in the eszopiclone 3 mg study), so they do not provide indirect evidence that eszopiclone was more effective. Results for sleep duration were similar. On number of awakenings, zolpidem 10 mg and eszopiclone 3 mg were more effective than placebo, but eszopiclone 1 mg and 2 mg (in older adults) were not.

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



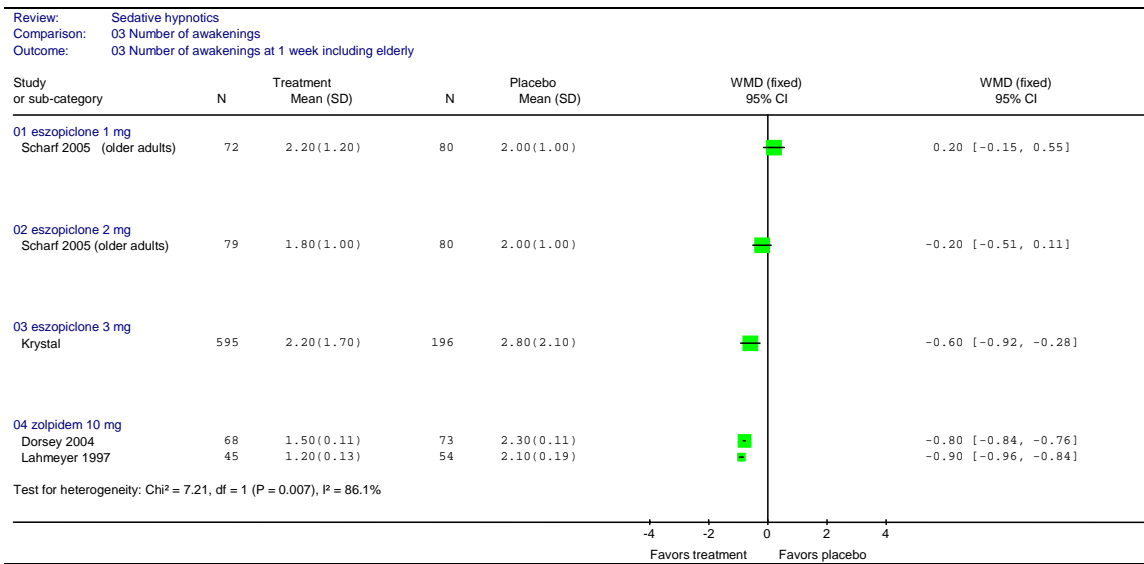
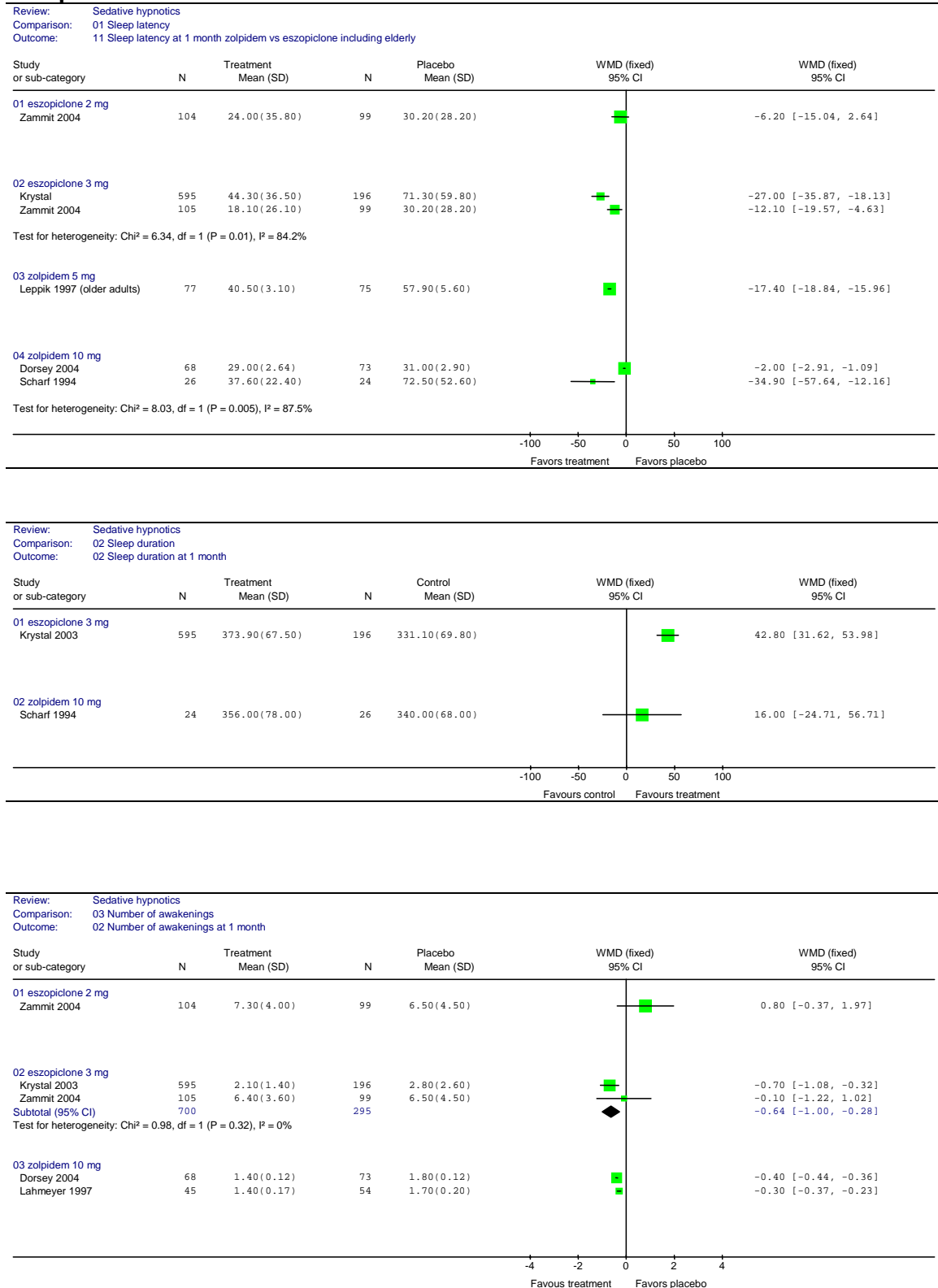


Figure 7 shows sleep outcomes at one month in placebo-controlled trials of zolpidem and eszopiclone. Sleep latency was reported in 5 trials. One trial of zolpidem 5 mg was conducted in older adults. Sleep latency was significantly shorter than placebo (mean difference  $-17.4$  minutes; 95% CI  $-18.8$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

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

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



Two placebo-controlled trials of eszopiclone also reported WASO, measured polysomnographically. Results at different time periods are shown in Table 7 below. No other placebo-controlled trials reported this outcome, so it is not possible to make indirect comparisons to other drugs on this outcome.

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

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

### Eszopiclone vs Zaleplon

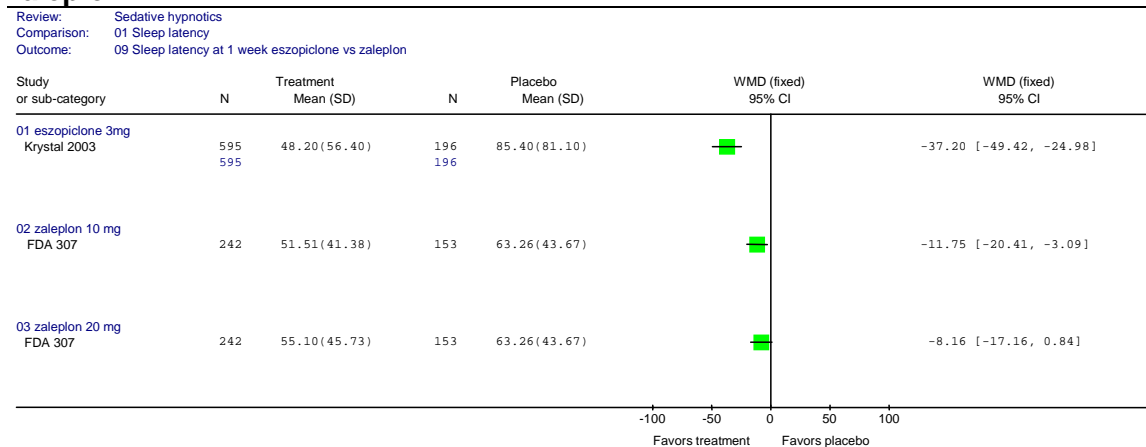
#### Direct comparisons

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

#### Indirect comparisons

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

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



## Zaleplon vs Zopiclone

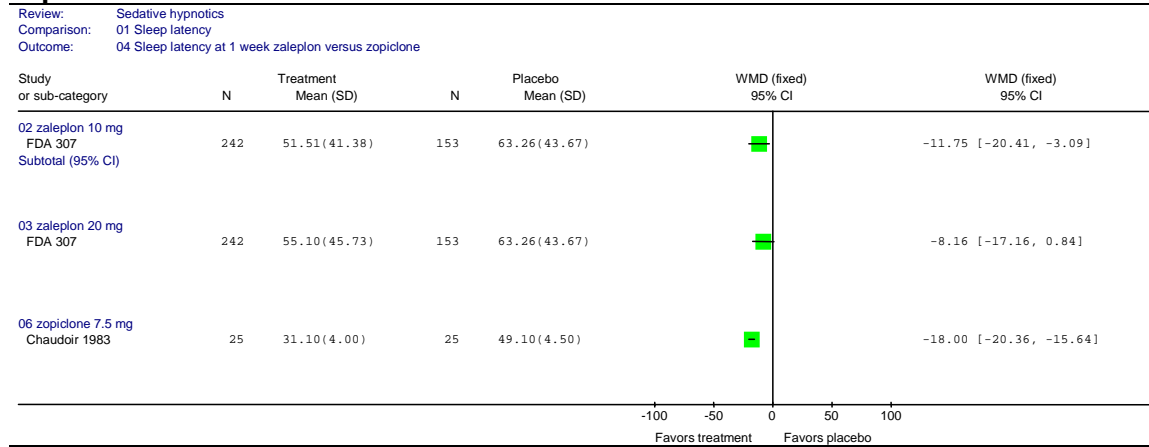
### Direct Comparisons

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

### Indirect comparisons

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

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



One trial compared zaleplon to triazolam<sup>24</sup> and two compared zopiclone to triazolam.<sup>33, 54</sup> On sleep outcomes (time to sleep onset and duration of sleep), both zaleplon and zopiclone were similarly efficacious to triazolam 0.25 mg. It is difficult to draw conclusions about the comparative efficacy of zaleplon versus zopiclone from active-control studies, however, because the duration of treatment and populations differed.

### Summary by Drug and Outcome

Table 8 summarizes the comparative evidence for short-term efficacy by drug and outcome. Although there are some differences between the drugs on some outcomes no one drug appeared to be consistently superior.



**Table 8. Summary of short-term efficacy by drug and outcome**

Outcome	Zolpidem		Zaleplon		Eszopiclone		Zopiclone	
	Direct evidence	Indirect evidence	Direct evidence	Indirect evidence	Direct evidence	Indirect evidence	Direct evidence	Indirect evidence
<b>Shorter sleep latency</b>	= eszopiclone (PSG)*	=eszopiclone	>zolpidem	>zolpidem =zopiclone	= zolpidem (PSG)*	=zolpidem	=zolpidem (PSG)*	=zaleplon >zolpidem
<b>Longer sleep duration</b>	>zaleplon					>zolpidem	=zolpidem	
<b>Fewer number of awakenings</b>	=zaleplon =zopiclone		= zolpidem		PSG*: =zolpidem		=zolpidem	
<b>Improved sleep quality</b>	>zaleplon							
<b>Daytime alertness</b>	=eszopiclone =zaleplon		=zolpidem		=zolpidem			
<b>Less rebound insomnia</b>	>zopiclone		>zolpidem					

\*measured polysomnographically in a sleep laboratory

## Newer sedative hypnotics vs benzodiazepines

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

There are no trials of eszopiclone versus benzodiazepines, and the evidence for zaleplon versus benzodiazepines is limited to two fair-quality trials versus triazolam.<sup>24, 57</sup>

**Zolpidem.** We included one study of zolpidem versus flurazepam,<sup>27</sup> two versus temazepam,<sup>35, 55</sup> and four versus triazolam.<sup>35, 39, 45, 48</sup>

In one study of zolpidem 10 mg or 20 mg versus flurazepam 30 mg, zolpidem was more effective for sleep outcomes.<sup>27</sup> Adverse events were similar for zolpidem 10 mg vs flurazepam, but zolpidem 20 mg was associated with more adverse events.

Two studies of zolpidem versus temazepam,<sup>35, 55</sup> found the drugs similar in efficacy and rebound insomnia.

In two studies comparing zolpidem 10 mg to triazolam 0.25 mg,<sup>45, 48</sup> sleep outcomes were similar for the two drugs, but triazolam caused more rebound insomnia. There was also more rebound insomnia with triazolam 0.25 mg compared to zolpidem 5 mg,<sup>45</sup> and with triazolam 0.5 mg compared to zolpidem 10 mg.<sup>39</sup>

The NICE review<sup>93</sup> presents an analysis of two studies of zolpidem versus nitrazepam that were excluded from our review because they are not English language. (Kazamatsuri, 1993 and Kudo, 1993) There were no significant differences between drugs in sleep latency or duration. In one study, more patients reported improved sleep quality with zolpidem (66.7% vs 37.5%,  $p=0.031$ ), (Kudo, 1993) and there were fewer awakenings with zolpidem in the other. (Kazamatsuri, 1993) There were no differences in adverse event rates (OR 0.70, 95% CI 0.37 to 1.30), and no difference in daytime alertness or global impression of treatment in either study.

**Zaleplon.** In two trials of zaleplon compared to triazolam, the drugs were similar on most sleep outcomes and short-term adverse events.<sup>24, 57</sup> In one study, triazolam 0.25 mg was associated with more nausea than zaleplon 5 mg.<sup>57</sup> However, this outcome was with a low dose of zaleplon (5 mg). In the same study, there was no difference between zaleplon 10 mg and triazolam 0.25 mg.<sup>57</sup>

**Zopiclone.** Zopiclone has been compared to four benzodiazepines (flurazepam, nitrazepam, temazepam, and triazolam). In five studies of zopiclone versus flurazepam,<sup>21, 26, 38, 40, 49</sup> most comparisons found the two drugs to be similar in efficacy and adverse effects.

Zopiclone and triazolam were similar in efficacy and adverse events.<sup>23, 32, 33</sup> For rebound insomnia, results were mixed in two studies, with one finding triazolam causing more rebound<sup>28</sup> and the other finding no difference.<sup>31</sup>

In studies of zopiclone versus nitrazepam,<sup>17, 34</sup> efficacy and safety were similar, but nitrazepam was associated with more rebound insomnia.

The NICE review<sup>93</sup> presents an analysis of four studies of zopiclone versus temazepam. No significant differences were found in the two studies that made direct comparisons on sleep outcomes (sleep latency, sleep duration, number of awakenings, and sleep quality). Adverse events were similar in the one study that made a direct comparison.

### Newer sedative hypnotics vs trazodone

We identified one short-term, fair-quality study of zolpidem 10 mg versus trazodone 50 mg.<sup>56</sup> Sleep latency was shorter with zolpidem after 1 week of treatment (48.2 vs 57.7 minutes,  $p=0.037$ ), but the difference was not significant at week 2 (48.4 vs 54.5 minutes,  $p$  not reported). Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2. The total numbers of adverse events and withdrawals due to adverse events were similar between the drugs. More patients reported somnolence with trazodone (16% vs 23%).

A trial of trazodone versus zaleplon, conducted in psychiatric inpatients, was rated poor quality and does not provide additional comparative information about newer sedative hypnotics versus trazodone.<sup>47</sup>

### Long-term Effectiveness and Safety

A fair-quality, 6-month placebo-controlled trial of eszopiclone 3 mg in 788 adults with insomnia is the longest-term trial of a newer sedative hypnotic.<sup>75</sup> Results of this trial are summarized in Table 9.

**Table 9. Results of 6-month placebo-controlled trial of eszopiclone 3 mg**

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

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

This is the longest-term trial of a newer sedative hypnotic. Although it provides evidence that eszopiclone 3 mg is efficacious versus placebo for up to 6 months, it does

not provide any information about the comparative efficacy and safety of eszopiclone versus other sedative hypnotics. There are no long-term trials of eszopiclone at lower doses, although 2 mg is the recommended initial dose.

### Long-Term Safety

There is limited evidence about the long-term safety of newer sedative hypnotics, and no direct evidence about their comparative long-term safety. Results of observational studies of adverse events are shown in Evidence Table 17.

Zaleplon. A one-year, open-label extension of a head-to-head trial<sup>8</sup> was conducted to assess the longer-term safety of zaleplon 5 mg in older patients.<sup>96</sup> In order to qualify for the extension phase, patients were required to have completed the trial and a placebo run-out period of 7 days without adverse effects, so this study is limited to a highly selected sample of patients less likely to experience discontinuation effects.

Sixty-four percent of patients completed 12 months of treatment. The most frequent adverse events were headache (27%) and infection (13%). The most frequent adverse events resulting in discontinuation were pain (5%), somnolence or dizziness (4%), and gastrointestinal disturbances (2%). There was a significant increase in rebound sleep latency, number of awakenings, and reduced total time slept on the first night after discontinuation.

Zolpidem. Two open-label studies in general practice patients in France assessed the safety of 6 months of treatment with zolpidem.<sup>105,110</sup>

In an open-label study of zolpidem 10 mg or 20 mg,<sup>105</sup> 96 patients over age 40 in general practice in France were followed for 6 months. Forty-nine patients continued treatment for an additional 6 months. Patients were evaluated every 30 days. About 70% of patients used the 10 mg dose. In the first 6 months, 7.3% of patients withdrew due to adverse events considered related to the drug, including a feeling of strangeness (1 patient), feeling of drunkenness (1 patient), anterograde amnesia (2 patients), nausea (1 patient), confusional episode (1 patient), malaise (1 patient), vertigo (4 patients), daytime drowsiness (2 patients), unpleasant awakening (1 patient), and diplopia (1 patient). Four of the 49 patients who continued treatment after 180 days withdrew (8%); two experienced nightmares, but these were not considered to be related to the study drug. There were no reports of withdrawal or rebound phenomena.

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

Eszopiclone. In a 6-month placebo-controlled trial of eszopiclone 3 mg,<sup>75</sup> rates of serious adverse events were 2.9% for eszopiclone and 1.0% for placebo. The most common serious adverse events were gastrointestinal disorder (0.5% per group) and chest pain (0.5% per group). Following discontinuation of the drug, there were similar overall rates of “new” events (defined as those not seen during the treatment period, or a worsening of an event) in the placebo (10.7%) and eszopiclone (11.2%) groups. There were no reports of seizures, hallucinations, or perceptual-disturbance events. There was one report of anxiety in the eszopiclone group.

Adverse events occurred in 81.1% of the eszopiclone group versus 70.8% of the placebo group. The most common adverse event was unpleasant taste (26.1% eszopiclone vs 5.6% placebo). Over 6 months, the rate of discontinuation due to adverse events was 12.8% in the eszopiclone group and 7.1% in the placebo group. The most common reasons for discontinuation were somnolence (2.2% eszopiclone vs 1.5%

placebo), depression (2.0% vs 0%), unpleasant taste (1.7% vs 0.5%), headache (0% vs 2%), asthenia (1% vs 1.5%), and insomnia (0% vs 1.5%).

### Abuse and Dependence

Cases of abuse and dependence have been associated with zolpidem and zopiclone.<sup>113-115, 124, 126, 127, 132, 133, 136, 140</sup> A recent review of case reports and epidemiological data of zolpidem abuse and dependence potential found most patients had a history of drug or alcohol abuse or other psychiatric conditions.<sup>141</sup>

A 2003 survey of 297 patients admitted to addiction treatment sites in the United Kingdom<sup>104</sup> found that while zopiclone was used by many more subjects than zolpidem (53.7% vs 5.8%), both drugs were similar in their use to induce sleep (88% vs 82%) or to get high (22.9% vs 23.5%).

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

### Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one newer sedative hypnotic is more effective or associated with fewer adverse events?

#### Summary of the Evidence

- Older adults (age  $\geq 65$  years)
  - In a 2-week head-to-head trial of zolpidem vs zaleplon in older adults, efficacy was similar to that in younger adults.
  - Somnolence was more common ( $p < 0.05$ ) with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%), but there was no difference in overall adverse events or in withdrawals due to adverse effects.
  - A case-control study of the relationship of the use of zolpidem to hip fracture in 6,110 elderly women found an increased risk in patients using zolpidem (adjusted odds ratio 1.95; 95% CI 1.09-3.51). The risk was higher than for benzodiazepines (adjusted odds ratio 1.46; 1.21-1.76)
- We found no evidence that one newer sedative hypnotic is safer or more effective in any subgroup based on gender or race.
- Pregnancy
  - In a prospective cohort study in 40 women with exposure to zopiclone in the first trimester of pregnancy, zopiclone use was associated with lower mean birth weight ( $3249 \pm 676$  grams vs  $3624 \pm 536$  grams;  $p = 0.01$ ) and gestational age ( $38.3 \pm 2.7$  weeks vs  $40.0 \pm 1.6$  weeks;  $p = 0.002$ ), but there were no differences in other pregnancy outcomes.
  - No evidence is available about use in pregnancy for other newer sedative hypnotics.
- Comorbid conditions
  - There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol, patients with generalized anxiety disorder, and inpatients with stroke.

- Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in patients with COPD.

## Detailed Assessment

### Older adults

One head-to-head trial (discussed under Key Questions 1 and 2),<sup>8</sup> six active-control trials (Evidence Tables 7-9),<sup>21, 25, 34, 35, 45, 54</sup> and three observational studies (Evidence Table 17)<sup>96, 106, 111</sup> were conducted in older adults.

In a 2-week trial in older adults,<sup>8</sup> somnolence was significantly more common ( $p < 0.05$ ) with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%). There was no difference in overall adverse events or in withdrawals due to adverse events (see Table 6). A one-year, open-label extension of this trial was conducted to assess the longer-term safety of zaleplon in older patients.<sup>96</sup> In order to qualify for the extension phase, patients were required to have completed the trial and a placebo run-out period of 7 days without adverse effects, so this study is limited to a highly selected sample of patients less likely to experience discontinuation effects.

A case-control study of the relationship of the use of zolpidem or other medications to hip fracture in 6,110 elderly women found an increased risk in patients using zolpidem (adjusted Odds Ratio 1.95; 95% CI 1.09-3.51).<sup>111</sup> The risk was higher than for benzodiazepines (adjusted Odds Ratio 1.46; 1.21-1.76). This study did not include other newer sedative hypnotics, so it does not provide information about the comparative risk of zolpidem versus other newer sedative hypnotics.

### Gender and Racial Groups

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

### Use in Pregnancy

A prospective cohort study in Canada evaluated pregnancy outcomes following first-trimester exposure to zopiclone in 40 women.<sup>101</sup> The sample consisted of women who had initiated contact with a program that provides counseling for pregnant women, so it is not representative of the total population of women who were exposed to zopiclone in pregnancy.

Newborns in the zopiclone group had a significantly lower mean birth weight ( $3249 \pm 676$  grams vs  $3624 \pm 536$  grams;  $p = 0.01$ ) and lower gestational age ( $38.3 \pm 2.7$  weeks vs  $40.0 \pm 1.6$  weeks;  $p = 0.002$ ). Once birth weight was adjusted for gestational age, the differences were no longer significant. There were no differences in outcome of pregnancy, delivery method, assisted deliveries, fetal distress, presence of meconium at birth, preterm deliveries, or neonatal intensive care admissions between study and control groups.

There are no observational studies of the use of other sedative hypnotics in pregnancy.

### Patients with Comorbid Conditions

There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol,<sup>18</sup> patients with generalized anxiety disorder,<sup>29</sup> and inpatients with stroke.<sup>36</sup>

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.<sup>50</sup>

Placebo-controlled trials of zolpidem have been conducted in patients with depression<sup>63</sup> and other psychiatric conditions,<sup>87</sup> and in patients with fibromyalgia.<sup>78</sup> Zaleplon has been studied in placebo-controlled trials in patients undergoing kidney dialysis.<sup>84</sup> Zopiclone has been compared to placebo in trials of patients with upper airway resistance syndrome,<sup>77</sup> rheumatoid arthritis,<sup>69</sup> fibromyalgia,<sup>68, 71</sup> and in shiftworkers.<sup>80</sup> While these studies provide evidence that these drugs are effective for some sleep outcomes in certain patients with co-morbid conditions, they do not provide evidence about the comparative efficacy of newer sedative hypnotics in these subgroups.

**Table 10. Summary of the evidence by key question**

Key Questions 1 and 2: Benefits and Harms	Quality of Evidence	Conclusion
<b>Short-term efficacy and safety</b>	Good for zolpidem vs zaleplon	There is evidence from four fair-quality head-to-head trials that zaleplon is more effective than zolpidem for sleep latency, but zolpidem is more effective than zaleplon for sleep duration and sleep quality. The drugs were similar for number of awakenings and daytime alertness. Zolpidem caused more rebound insomnia than zaleplon on the first night after discontinuation. Short-term adverse events and withdrawals due to adverse events were similar.
	Fair for zolpidem vs zopiclone	One fair-quality head-to-head trial found that zolpidem and zopiclone were similar in efficacy on patient-rated sleep outcomes and investigator's global assessment of improvement. Zopiclone caused more rebound sleep latency insomnia than zolpidem. Overall adverse events and effects of withdrawal were similar in another study designed to measure withdrawal effects. There is limited indirect evidence that zopiclone was more effective for sleep latency at one week.
	Fair for zolpidem vs eszopiclone	In one fair-quality head-to-head trial, zolpidem and eszopiclone had similar objective sleep latency and Wake Time After Sleep Onset. There was no difference between zolpidem and eszopiclone on subjective measures of next-day effects. Limited indirect comparisons provide evidence that the drugs were similar for sleep latency and number of awakenings, but eszopiclone was more effective for increasing sleep duration.
	Poor for zaleplon vs zopiclone and eszopiclone	There are no head-to-head trials. Limited indirect comparisons suggest the drugs are similar for sleep latency at one week. Indirect comparisons for other sleep outcomes were not possible.
	Fair to poor for newer sedative hypnotics vs benzodiazepines	There are no trials of eszopiclone versus benzodiazepines. Most comparisons found the newer sedative hypnotics to be similar to benzodiazepines in efficacy and short-term adverse events. Some studies found less rebound insomnia with newer sedative hypnotics.
	Poor for newer sedative hypnotics vs trazodone	We identified one fair-quality, short-term trial of zolpidem versus trazodone. Sleep latency was shorter with zolpidem after 1 week of treatment, but the difference was not significant at week 2. Sleep duration, number of awakenings, sleep quality, and patients' global impressions of treatment were similar for the drugs at weeks 1 and 2. More patients reported somnolence with trazodone. Withdrawals due to adverse events and overall adverse events were similar between the drugs. A trial of zaleplon versus trazodone was rated poor quality.



<b>Long-term efficacy and safety</b>	Poor	Evidence about long-term efficacy and safety is limited; there is no comparative evidence. One longer-term placebo-controlled trial provides evidence that eszopiclone 3 mg is efficacious for up to 6 months, but does not add any information about the <i>comparative</i> efficacy and safety of eszopiclone versus other sedative hypnotics. No withdrawal effects were observed, and rebound insomnia was not reported. There are case reports of dependence with both zolpidem and zopiclone.
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<b>Key Question 3: Subgroups</b>	<b>Quality of Evidence</b>	<b>Conclusion</b>
Older adults (age $\geq$ 65 years)	Fair	In a 2-week head-to-head trial of zolpidem vs zaleplon in older adults, efficacy was similar to that in younger adults. Somnolence was more common with zolpidem 5 mg (10%) than with placebo (2%) or zaleplon 5 mg (4%), but there was no difference in overall adverse events or in withdrawals due to adverse effects. A case-control study of the relationship of the use of zolpidem to hip fracture in 6,110 elderly women found an increased risk in patients using zolpidem (adjusted odds ratio 1.95; 95% CI 1.09-
Gender and race	Poor	We found no evidence that one newer sedative hypnotic is safer or more effective in any subgroup based on gender or race.
Pregnancy	Fair for zopiclone, poor for others	In a prospective cohort study in 40 women with exposure to zopiclone in the first trimester of pregnancy, zopiclone use was associated with lower mean birth weight and gestational age, but there were no differences in other pregnancy outcomes. No evidence is available about use in pregnancy for other newer sedative hypnotics.
Patients with comorbid conditions.	Poor	There is no comparative evidence in patients with comorbid conditions. There is evidence from active control trials that zopiclone is similar to benzodiazepines for sleep outcomes and adverse effects in patients withdrawing from alcohol, patients with generalized anxiety disorder, and inpatients with stroke. Zolpidem 5 mg, but not 10 mg, was more effective than triazolam 0.25 mg for some sleep outcomes in patients with COPD. Placebo-controlled trials do not provide additional comparative evidence.

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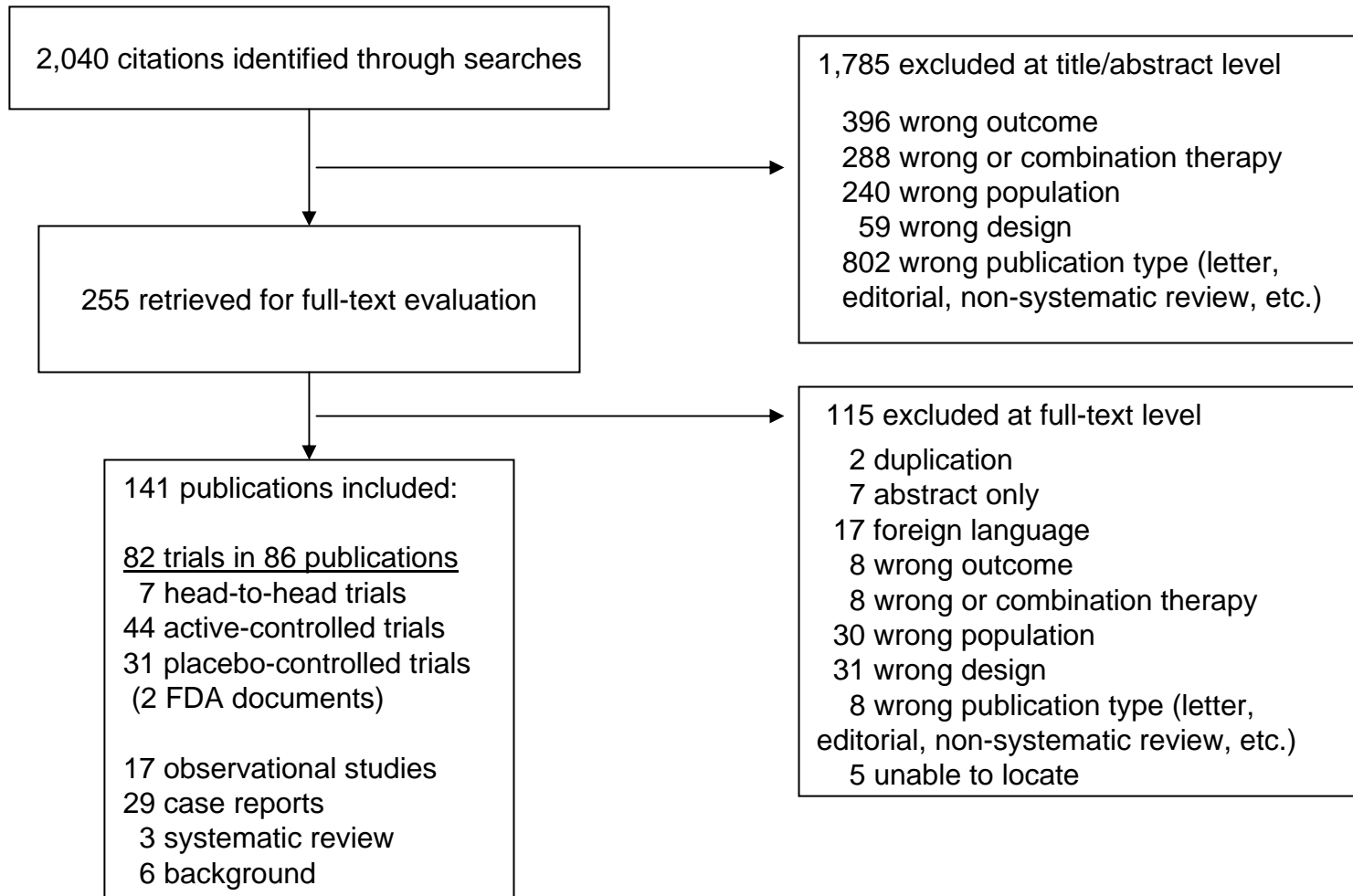


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**Figure 1. Newer sedative hypnotics: Results of literature search**



## Appendix A. Literature search strategies

Sedatives search strategies were: zaleplon, zolpidem, zopiclone, eszopiclone,  
limits: English language and Human

Database: Medline 1966 -- March week 2 2005  
Embase 1985 -- 2005 (March)  
Cochrane -- 2<sup>st</sup> Quarter 2005  
PsycINFO --1985 to May Week 2 2005>

### Search Strategy:

- 
- 1 (zaleplon or zolpidem or zopiclone or eszopiclone).mp. [mp=title, short title, abstract, full text, keywords, caption text]
  - 2 (sonata or ambien or Imovane or lunesta or estorra).mp. [mp=title, short title, abstract, full text, keywords, caption text]
  - 3 1 or 2
  - 4 (sonata or ambien or Imovane or lunesta or estorra or stilnoct or zimovane or zileze).mp. [mp=title, short title, abstract, full text, keywords, caption text]
  - 5 3 and 4
  - 6 from 3 keep 1-7

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

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

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

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

### ***For Controlled Trials:***

#### Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
  - Adequate approaches to sequence generation:
    - Computer-generated random numbers
    - Random numbers tables
  - Inferior approaches to sequence generation:
    - Use of alternation, case record numbers, birth dates or week days
  - Not reported
  
2. Was the treatment allocation concealed?
  - Adequate approaches to concealment of randomization:
    - Centralized or pharmacy-controlled randomization
    - Serially-numbered identical containers
    - On-site computer based system with a randomization sequence that is not readable until allocation
    - Other approaches sequence to clinicians and patients
  - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days  
Open random numbers lists  
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

#### Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

***For Studies Reporting Complications/Adverse Effects*****Assessment of Internal Validity**

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainment; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

**Assessment of External Validity**

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

***Systematic Reviews:***

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

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,



i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

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

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

3. Is the validity of included studies adequately assessed?

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

## Appendix C. Excluded Trials

238 trials were excluded with the exclusion code shown below:

### Codes:

- 1 = Foreign language
- 2 = Wrong outcome
- 3 = Wrong drug (including combination therapy)
- 4 = Wrong population
- 5 = Wrong publication type (letter, editorial, non-systematic review, etc.)
- 6 = Wrong design (including placebo trials  $\leq$  3 months' duration, dose-ranging study, pharmacokinetics, single-dose study, drug interaction)
- 7 = cannot find the study
- 8 = duplicated study
- AO = abstract only

Trial	Code
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. <i>European Journal of Clinical Pharmacology</i> . 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). <i>Sleep</i> . 2001;24(Abstr Suppl):A332.	(AO)
Allain H, Patat A, Lieury A, et al. Comparative study of the effects of zopiclone (7.5 mg), zolpidem, flunitrazepam and a placebo on nocturnal cognitive performance in healthy subjects, in relation to pharmacokinetics. <i>European Psychiatry</i> . 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. <i>European Journal of Clinical Pharmacology</i> . 1993;45(4):313-320.	(4)
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. <i>Journal of Clinical Psychiatry</i> . 2003;64(2):208-214.	(3)
Amsterdam JD, Brunswick DJ, Hundert M. A single-site, double-blind, placebo-controlled, dose-ranging study of YKP10A - A putative, new antidepressant. <i>Progress in Neuro-Psychopharmacology and Biological Psychiatry</i> . 2002;26(7-8):1333-1338.	(3)
Aranko K, Luurila H, Backman JT, Neuvonen PJ, Olkkola KT. The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. <i>British Journal of Clinical Pharmacology</i> . 1994;38(4):363-367.	(4)

Trial	Code
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. <i>Journal of the European College of Neuropsychopharmacology</i> . 1999;9(Suppl 5):S309.	(AO)
Balkin TJ, O'Donnell VM, Wesensten N, McCann U, Belenky G. Comparison of the daytime sleep and performance effects of zolpidem versus triazolam. <i>Psychopharmacology</i> . 1992;107(1):83-88.	(4)
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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. <i>Neuropsychobiology</i> . 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. <i>American Journal of Respiratory &amp; Critical Care Medicine</i> . 1996;153(6 Pt 1):1864-1869.	(4)
Beaupre A, Soucy R, Phillips R, Bourgooin J. Respiratory center output following zopiclone or diazepam administration in patients with pulmonary disease. <i>Respiration</i> . 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. <i>International Journal of Neuropsychopharmacology</i> . Sep 2004;7(3):283-290.	(3)
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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. <i>Journal of Clinical Pharmacology</i> . 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. <i>Psychopharmacology</i> . 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. <i>British Journal of Clinical Pharmacology</i> . 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. <i>Pharmacopsychiatry</i> . 1995;28(165).	(6)

Trial	Code
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. <i>Journal of Clinical Psychopharmacology</i> . 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? <i>Journal of Psychopharmacology</i> . 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. <i>Pharmacological Research</i> . 2005;51(1):79-84.	(3)
Besset A, Tafti M, Villemin E, Borderies P, Billiard M. Effects of zolpidem on the architecture and cyclical structure of sleep in poor sleepers. <i>Drugs under Experimental and Clinical Research</i> . 1995;21(4):161-169.	(6)
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Biondi F, Casadei GL. Results of a multicenter trial with the hypnotic zolpidem in 1152 insomniac patients. <i>Current Therapeutic Research - Clinical and Experimental</i> . 1994;55(3):262-274.	(6)
Bliwise DL, Freeman A, Ingram CD, Rye DB, Chakravorty S, Watts RL. Randomized, double-blind, placebo-controlled, short-term trial of roprimole in restless legs syndrome. <i>Sleep Medicine</i> . 2005;6(2):141-147.	(3)
Blois R, Gaillard JM, Attali P, Coquelin JP. Effect of zolpidem on sleep in healthy subjects: a placebo-controlled trial with polysomnographic recordings. <i>Clinical Therapeutics</i> . 1993;15(5):797-809.	(4)
Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effect of zolpidem 10 mg and zopiclone 7.5 mg versus flunitrazepam 1 mg and placebo on driving performance and ocular saccades. <i>Psychopharmacology</i> . 1999;143(4):373-379.	(4)
Boissl K, Dreyfus JF, Delmotte M. Studies on the dependence-inducing potential of zopiclone and triazolam. <i>International Pharmacopsychiatry</i> . 1982;17(2):242-247.	(4)
Bond A, Lader M. Correlations among measures of response to benzodiazepines in man. <i>Pharmacology, Biochemistry &amp; Behavior</i> . Feb 1983;18(2):295-298.	(6)
Boniface PJ, Martin IC, Nolan SL, Tan ST. Development of a method for the determination of zopiclone in whole blood. <i>Journal of Chromatography - Biomedical Applications</i> . 1992;584(2):199-206.	(2)
Busto UE, Sproule BA, Knight K, Herrmann N. Use of prescription and nonprescription hypnotics in a Canadian elderly population. <i>Canadian Journal of Clinical Pharmacology</i> . 2001;8(4):213-221.	(6)
Caldwell J, Caldwell JL. Comparison of the effects of zolpidem-induced prophylactic naps to placebo naps and forced rest periods in prolonged work schedules. <i>Sleep</i> . 1998;21(1):79-90.	(4)

<b>Trial</b>	<b>Code</b>
Cashman JN, Power SJ. An evaluation of tests of psychomotor function in assessing recovery following a brief anaesthetic. <i>Acta Anaesthesiologica Scandinavica</i> . 1989;33(8):693-697.	(2)
Cashman JN, Power SJ, Jones RM. Assessment of a new hypnotic imidazopyridine (zolpidem) as oral premedication. <i>British Journal of Clinical Pharmacology</i> . 1987;24(1):85-92.	(4)
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Chang M-Y, Lin J-L. Irreversible Ischemic Hand Following Intraarterial Injection of Zolpidem Powder. <i>Journal of Toxicology - Clinical Toxicology</i> . 2003;41(7):1025-1028.	(2)
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Cialdella P, Boissel JP, Belon P. Homeopathic specialities as a substitute for benzodiazepines: A double-blind vs. placebo study. <i>Therapie</i> . 2001;4:397-402.	(3)
Clauss RP, Guldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem. <i>South African Medical Journal</i> . 2000;90(1):68-72.	(2)
Cluydts R, De Roeck J, Cosyns P, Lacante P. Antagonizing the effects of experimentally induced sleep disturbance in healthy volunteers by lormetazepam and zolpidem. <i>Journal of Clinical Psychopharmacology</i> . 1995;15(2):132-137.	(4)
Cluydts R, Heyde K, De Volder I. Polysomnographic findings during non-continuous administration of zolpidem. <i>Sleep Medicine Reviews</i> . 2002;6(SUPPL. 1):S13-S19.	(6)
Cluydts R, Peeters K, De Bouyalsky I, Lavoisy J. A pilot, randomized, double-blind study of zolpidem 10 mg comparing intermittent versus continuous administration. <i>Sixth World Congress of Biological Psychiatry, Nice, France. June</i> . 1997.	(6)
Cluydts R, Peeters K, de Bouyalsky I, Lavoisy J. Comparison of continuous versus intermittent administration of zolpidem in chronic insomniacs: a double-blind, randomized pilot study. <i>Journal of International Medical Research</i> . 1998;26(1):13-24.	(6)
Cluydts RJ, De Roeck JM, Jolie AM. A three week multicentre general practitioner study of zoldipem in 651 patients with insomnia. <i>Acta Therapeutica</i> . 1993;19(1):73-91.	(6)
Cohn MA. Effects of zolpidem, codeine phosphate and placebo on respiration. A double-blind, crossover study in volunteers. <i>Drug Safety</i> . 1993;9(4):312-319.	(4)
Coleman DE, Ota K. Hallucinations with zolpidem and fluoxetine in an impaired driver. <i>Journal of Forensic Sciences</i> . Mar 2004;49(2):392-393.	(4)
Colle M, Rosenzweig P, Bianchetti G, et al. Nocturnal profile of growth hormone secretion during sleep induced by zolpidem: a double-blind study in young adults and children. <i>Hormone Research</i> . 1991;35(1):30-34.	(2)

<b>Trial</b>	<b>Code</b>
Conway DH, Turner SJ, Eddleston J, Guthrie E. Sedation on intensive care: A pathway into dependence. <i>Care of the Critically Ill</i> . 2001;17(5):170-171.	(6)
Corrigan MH, Gallen CC, Bonura ML, Merchant KM. Effectiveness of the selective D4 antagonist sonopiprazole in schizophrenia: A placebo-controlled trial. <i>Biological Psychiatry</i> . 2004;55(5):445-451.	(3)
Coskunol H, Gokden O, Ercan ES, Bayraktar E, Tuglular I, Saygili R. Long-term efficacy of sertraline in the prevention of alcoholic relapses in alcohol-dependent patients: A single-center, double-blind, randomized, placebo-controlled, parallel-group study. <i>Current Therapeutic Research - Clinical and Experimental</i> . 2002;63(11):759-771.	(3)
Danjou P, Paty I, Fruncillo R, et al. A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. <i>British Journal of Clinical Pharmacology</i> . 1999;48(3):367-374.	(4)
Darko W, Guharoy R, Rose F, Lehman D, Pappas V. Myoclonus secondary to the concurrent use of trazodone and fluoxetine. <i>Veterinary and Human Toxicology</i> . 2001;43(4):214-215.	(3)
Darwish M. The effects of zaleplon at the time of peak plasma concentration versus zolpidem and triazolam. <i>Journal of the European College of Neuropsychopharmacology</i> . 1999;9(Suppl 5):S360.	(4)
Darwish M, Parker V, Harper D, Leister C, Raible D, Fruncillo R. The lack of drug interactions between zaleplon and venlafaxine extended release. <i>155th Annual Meeting of the American Psychiatric Association</i> . 2002.	(7)
Declerck AC, Ruwe F, O'Hanlon JF, Vermeeren A, Wauquier A. Effects of zolpidem and flunitrazepam on nocturnal sleep of women subjectively complaining of insomnia.[erratum appears in <i>Psychopharmacology (Berl)</i> 1992;109(1-2):254]. <i>Psychopharmacology</i> . 1992;106(4):497-501.	(6)
Dehlin O, Bengtsson C, Rubin B. A comparison of zopiclone and propiomazine as hypnotics in outpatients: a multicentre, double-blind, randomized, parallel-group comparison of zopiclone and propiomazine in insomniacs. <i>Current Medical Research &amp; Opinion</i> . 1997;13(10):565-572.	(6)
Dehlin O, Rubin B, Rundgren A. Double-blind comparison of zopiclone and flunitrazepam in elderly insomniacs with special focus on residual effects. <i>Current Medical Research &amp; Opinion</i> . 1995;13(6):317-324.	(6)
Denise P, Bocca ML. Effects of zolpidem 10 mg, zopiclone 7.5 mg and flunitrazepam 1 mg on night-time motor activity. <i>European Neuropsychopharmacology</i> . 2003;13(2):111-115.	(4)
Dietrich B, Emilien G, Salinas E. Zaleplon improves sleep efficiency in a phase-advance model of transient insomnia. <i>XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland. 12th 16th July</i> . 1998.	(1)
Dingemans J, Bury M, Bock J, Joubert P. Comparative pharmacodynamics of Ro 41-3696, a new hypnotic, and zolpidem after night-time administration to healthy subjects. <i>Psychopharmacology</i> . 1995;122(2):169-174.	(4)

Trial	Code
Dingemans J, Bury M, Hussain Y, van Giersbergen P. Comparative tolerability, pharmacodynamics, and pharmacokinetics of a metabolite of a quinolizone hypnotic and zolpidem in healthy subjects. <i>Drug Metabolism &amp; Disposition</i> . 2000;28(12):1411-1416.	(4)
Disayavanish C, Srisurapanont M, Disayavanish P. Zopiclone in the treatment of insomnia: An open clinical trial. <i>Journal of the Medical Association of Thailand</i> . 1998;81(6):393-397.	(6)
D'Mello DA, Lyon DE, Colenda CC, Fernandes CL. Substance dependence and the use of pro re nata anxiolytic/hypnotic drugs in a hospital setting. <i>Addictive Behaviors</i> . 2000;25(3):441-443.	(2)
Dorian P, Sellers EM, Kaplan H, Hamilton C. Evaluation of zopiclone physical dependence liability in normal volunteers. <i>International Pharmacopsychiatry</i> . 1982;17(2):228-234.	(4)
Drover D, Lemmens H, Naidu S, Cevallos W, Darwish M, Stanski D. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. <i>Clinical Therapeutics</i> . 2000;22(12):1443-1461.	(4)
Dujardin K, Guieu JD, Leconte-Lambert C, Leconte P, Borderies P, de La Giclais B. Comparison of the effects of zolpidem and flunitrazepam on sleep structure and daytime cognitive functions. A study of untreated insomniacs. <i>Pharmacopsychiatry</i> . 1998;31(1):14-18.	(6)
Dundar Y, Dodd S, Strobl J, Boland A, Dickson R, Walley T. Comparative efficacy of newer hypnotic drugs for the short-term management of insomnia: A systematic review and meta-analysis. <i>Human Psychopharmacology</i> . 2004;19(5):305-322.	(1)
Dundee JW, Elwood RJ, Hildebrand PJ, Singleton M. Dose-finding and premedication studies with zopiclone. <i>Pharmacology</i> . 1983;27(2):210-215.	(4)
Duriez R, Barthelemy C, Rives H, et al. Clinical trial of zopiclone in insomnia. <ORIGINAL> TRAITEMENT DES TROUBLES DU SOMMEIL PAR LA ZOPICLONE. <i>Therapie (Paris)</i> . 1979;34(3):317-325.	(6)
Elger BS. Does insomnia in prison improve with time? Prospective study among remanded prisoners using the Pittsburgh Sleep Quality Index. <i>Medicine, Science &amp; the Law</i> . Oct 2003;43(4):334-344.	(6)
Elger BS. Management and evolution of insomnia complaints among non-substance-misusers in a Swiss remand prison. <i>Swiss Medical Weekly</i> . 2004;134(33-34):486-499.	(6)
Elie R, Deschenes JP. Efficacy and tolerance of zopiclone in insomniac geriatric patients. <ORIGINAL> EFFICACITE ET TOLERANCE DE LA ZOPICLONE CHEZ LE PATIENT GERIATRIQUE INSOMNIAQUE. <i>Rev Geriatr</i> . 1994;19(1):45-50.	(1)
Elwood RJ, Elliott P, Chestnutt WN, Hildebrand PJ, Dundee JW. A comparison of the onset and duration of action of zopiclone with diazepam [abstract]. <i>British Journal of Clinical Pharmacology</i> . 1983;16.	(5)

<b>Trial</b>	<b>Code</b>
Emilien G, Salinas E. Zaleplon decreases sleep latency in outpatients after 4 weeks of treatment CONFERENCE ABSTRACT. <i>11th European College of Neuropsychopharmacology Congress. Paris, France. 31st October 4th November. 1998.</i>	(5)
Erman MK, Erwin CW, Gengo FM, et al. Comparative efficacy of zolpidem and temazepam in transient insomnia. <i>Human Psychopharmacology.</i> 2001;16(2):169-176.	(4)
Erwin CW, Fry JM, Richardson GS, et al. A multicenter, placebo-controlled, polysomnographic study of zaleplon in elderly patients with chronic insomnia. <i>XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland. 12th 16th July. 1998.</i>	(7)
Evans SM, Funderburk FR, Griffiths RR. Zolpidem and triazolam in humans: behavioral and subjective effects and abuse liability. <i>Journal of Pharmacology &amp; Experimental Therapeutics.</i> 1990;255(3):1246-1255.	(4)
Fairweather DB, Kerr JS, Hindmarch I. The effects of acute and repeated doses of zolpidem on subjective sleep, psychomotor performance and cognitive function in elderly volunteers. <i>European Journal of Clinical Pharmacology.</i> 1992;43(6):597-601.	(4)
Fattapposta F, Sanarelli L, Valle E, et al. A double-blind study of the effects of zolpidem, a new imidazopyridine hypnotic, on contingent negative variation in patients with situational insomnia. <i>Curr Ther Res Clin Exp.</i> 1990;48(5):766-773.	(4)
Feige B, Voderholzer U, Riemann D, Hohagen F, Berger M. Independent sleep EEG slow-wave and spindle band dynamics associated with 4 weeks of continuous application of short-half-life hypnotics in healthy subjects. <i>Clinical Neurophysiology.</i> 1999;110(11):1965-1974.	(4)
Feinberg I, Maloney T, Campbell IG. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. <i>Journal of Psychiatric Research.</i> 2000;34(6):423-438.	(4)
Finelli LA, Landolt HP, Buck A, et al. Functional neuroanatomy of human sleep states after zolpidem and placebo: A H215O-PET study. <i>Journal of Sleep Research.</i> 2000;9(2):161-173.	(4)
Fischer W, Haase W, Ruther E, Clarenbach P, Hajak G. Problems in performing a double-blind multicenter study using a hypnotic in private practice. <i>Int J Clin Pharmacol Ther Toxicol.</i> 1992;30(11):474.	(AO)
Fossen A, Godlibsen OB, Loyning Y, Dreyfus JF. Effects of hypnotics on memory. <i>International Pharmacopsychiatry.</i> 1982;17 Suppl 2:116-126.	(4)
Frattola L, Maggioni M, Cesana B, Priore P. Double blind comparison of zolpidem 20 mg versus flunitrazepam 2 mg in insomniac in-patients. <i>Drugs Under Experimental &amp; Clinical Research.</i> 1990;16(7):371-376.	(6)
Garbarino S, Nobili L, Beelke M, Balestra V, Cordelli A, Ferrillo F. Sleep disorders and daytime sleepiness in state police shiftworkers. <i>Archives of Environmental Health.</i> 2002;57(2):167-173.	(2)
Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. <i>International Psychogeriatrics.</i> 2002;14(4):389-404.	(3)



<b>Trial</b>	<b>Code</b>
Giercksky KE, Wickstrom E. A dose-response study in situational insomnia with zopiclone, a new tranquilizer. <i>Clinical Therapeutics</i> . 1980;3(1):21-27.	(4)
Gieschke R, Cluydts R, Dingemans J, De Roeck J, De Cock W. Effects of bretazenil vs. zolpidem and placebo on experimentally induced sleep disturbance in healthy volunteers. <i>Methods &amp; Findings in Experimental &amp; Clinical Pharmacology</i> . 1994;16(9):667-675.	(4)
Gillin JC, Buchsbaum MS, Valladares-Neto DC, et al. Effects of zolpidem on local cerebral glucose metabolism during non-REM sleep in normal volunteers: a positron emission tomography study. <i>Neuropsychopharmacology</i> . 1996;15(3):302-313.	(4)
Ginsberg DL. Zolpidem Improvement of Cognition in Dementia. <i>Primary Psychiatry</i> . 2003;10(3):22-23.	(4)
Girault C, Muir JF, Mihaltan F, et al. Effects of repeated administration of zolpidem on sleep, diurnal and nocturnal respiratory function, vigilance, and physical performance in patients with COPD. <i>Chest</i> . 1996;110(5):1203-1211.	(6)
Gorenstein C, Tavares SM, Gentil V, Peres C, Moreno RA, Dreyfus JF. Psychophysiological effects and dose equivalence of zopiclone and triazolam administered to healthy volunteers. Methodological considerations. <i>Brazilian Journal of Medical &amp; Biological Research</i> . 1990;23(10):941-951.	(4)
Goto Y, Homma Y, Okuse S, et al. The clinical efficacy of zopiclone, a hypnotic, by the double-blind method. <i>Shinryotoshinyaku</i> . 1984;21(11):2191-2208.	(1)
Gowing L, Farrell M, Ali R, White J. Alpha2 adrenergic agonists for the management of opioid withdrawal [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> . 2005;2:2.	(3)
Greenblatt DJ, Harmatz JS, von Moltke LL, et al. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. <i>Clinical Pharmacology &amp; Therapeutics</i> . 1998;64(5):553-561.	(4)
Greenblatt DJ, Harmatz JS, von Moltke LL, et al. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. <i>Journal of Pharmacology &amp; Experimental Therapeutics</i> . 2000;293(2):435-443.	(4)
Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Differential impairment of triazolam and zolpidem clearance by ritonavir. <i>Journal of Acquired Immune Deficiency Syndromes: JAIDS</i> . 2000;24(2):129-136.	(4)
Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. <i>Clinical Pharmacology &amp; Therapeutics</i> . 1998;64(6):661-671.	(4)
Griffiths AN, Jones DM, Marshall RW, Allen EM, Richens A. A comparison of the psychomotor effects of zopiclone with three marketed benzodiazepines and placebo [abstract]. <i>British Journal of Clinical Pharmacology</i> . 1985;19.	(AO)
Griffiths AN, Jones DM, Richens A. Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam. <i>British Journal of Clinical Pharmacology</i> . 1986;21(6):647-653.	(4)

Trial	Code
Grobler LA, Schweltnus MP, Trichard C, Calder S, Noakes TD, Derman WE. Comparative effects of zopiclone and loperazolam on psychomotor and physical performance in active individuals. <i>Clinical Journal of Sport Medicine</i> . 2000;10(2):123-128.	(4)
Hajak G, Clarenbach P, Fischer W, Rodenbeck A, Bandelow B, E Rt. Rebound insomnia after abrupt hypnotic withdrawal. <i>10th European College of Neuropsychopharmacology Congress. Vienna, Austria. 13th 17th September</i> . 1997.	(8)
Hajak G, Cluydts R, Declerck A, et al. Continuous versus non-nightly use of zolpidem in chronic insomnia: results of a large-scale, double-blind, randomized, outpatient study.[erratum appears in <i>Int Clin Psychopharmacol</i> 2002 Jul;17(4):206]. <i>International Clinical Psychopharmacology</i> . 2002;17(1):9-17.	(6)
Harrigan EP, Miceli JJ, Anziano R, et al. A Randomized Evaluation of the Effects of Six Antipsychotic Agents on QTc, In the Absence and Presence of Metabolic Inhibition. <i>Journal of Clinical Psychopharmacology</i> . 2004;24(1):62-69.	(2)
Harrison C, Subhan Z, Hindmarch I. Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. <i>Drugs Under Experimental &amp; Clinical Research</i> . 1985;11(12):823-829.	(4)
Hart CL, Ward AS, Haney M, Foltin RW. Zolpidem-related effects on performance and mood during simulated night-shift work. <i>Experimental &amp; Clinical Psychopharmacology</i> . 2003;11(4):259-268.	(4)
Hedner J, Emilien G, Salinas E. Zaleplon reduces sleep latency and improves sleep quality in elderly patients with primary insomnia. <i>XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland. 12th 16th July</i> . 1998.	(7)
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Rhodes SP, Parry P, Hanning CD. A comparison of the effects of zolpidem and placebo on respiration and oxygen saturation during sleep in the healthy elderly. <i>British Journal of Clinical Pharmacology</i> . 1990;30(6):817-824.	(2)
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Ruther E, Clarenbach P, Hajak G, Fischer W, Haase W. Zopiclone in Patients with Disturbed Sleep. Impact on Sleep Quality and Day-time Well-being in Comparison to Flunitrazepam, Triazolam and Placebo. <i>Munchener Medizinische Wochenschrift</i> . 1992;134(46):753-757.	(1)
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Trial	Code
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<b>Trial</b>	<b>Code</b>
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### Appendix D. Summary of results of trials of newer sedative hypnotics versus benzodiazepines

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

Comparators	KQ outcome	Hypnotic		Benzodiazepine	(No. of Studies) Citations
Zopiclone vs Flurazepam					
	Effectiveness outcomes	Zopiclone 3.75mg	=	Flurazepam 30mg	(1) <sup>10</sup>
	Effectiveness outcomes	Zopiclone 7.5mg	=, ≥, =	Flurazepam 30mg	(3) <sup>10-12</sup>
	Effectiveness outcomes	Zopiclone 11.5mg	=, ≥	Flurazepam 30mg	(2) <sup>10, 11</sup>
	Effectiveness outcomes	Zopiclone 15mg	=	Flurazepam 30mg	(1) <sup>10</sup>
	Safety outcomes	Zopiclone 7.5mg	=, =	Flurazepam 30mg	(1) <sup>13, 14</sup>
	Less rebound	Zopiclone 7.5mg	≤	Flurazepam 30mg	(1) <sup>12</sup>
Zopiclone vs Nitrazepam					
	Effectiveness outcomes	Zopiclone 7.5mg	=, =	Nitrazepam 5mg	(2) <sup>15, 16</sup>
	Daytime alertness	Zopiclone 7.5mg	>, ≥	Nitrazepam 5mg	(2) <sup>15, 16</sup>
	Safety outcomes	Zopiclone 7.5mg	=	Nitrazepam 5mg	(1) <sup>15</sup>
Zopiclone vs Temazepam					
	Effectiveness outcomes	Zopiclone 7.5mg	=, =, =	Temazepam 20, 30mg	(3) <sup>17-19</sup>
	Safety outcomes	Zopiclone 7.5mg	=	Temazepam 20mg	(1) <sup>17</sup>
Zopiclone vs Triazolam					
	Effectiveness outcomes	Zopiclone 7.5mg	=, =, =	Triazolam 0.25mg	(3) <sup>20-22</sup>
	Safety outcomes	Zopiclone 7.5mg	=	Triazolam 0.25mg	(1) <sup>20</sup>
	Less rebound	Zopiclone 7.5mg	>, ≤	Triazolam 0.25mg	(2) <sup>21, 23</sup>

\**Efficacy outcomes*: Sleep Duration, total sleep time, length of sleep, total sleep time; Sleep Quality, sleep efficiency, No. of awakenings, Night awakenings, wake time after sleep onset, Daytime alertness, status of work, drowsiness, quality of morning awakening, morning state, feelings on awakenings, daytime well-being, Mental alertness on rising, morning sleepiness, morning alertness, Sleep latency, rapidity of sleep onset, sleep induction, sleep onset duration, Delay in falling sleep, latency to persistent sleep,  
*Safety outcomes*: Overall adverse events, side effects, safety,  
*Rebound insomnia*: Rebound, withdrawal effects

\*\**Explanation of symbols for individual studies*:

“>” some outcomes showed a preference for the newer sedative hypnotic and others were equivalent;

“≤” some outcomes showed a preference for the benzodiazepine and others were equivalent;

“>” all outcomes (or the majority of outcomes) showed a preference for the newer sedative hypnotic;

“<” all outcomes (or the majority of outcomes) showed a preference for the benzodiazepine;

“=” all outcomes (or the majority of outcomes) showed no difference;

“mixed” some outcomes showed a preference for the newer sedative hypnotic and others showed a preference for the benzodiazepine.

(See Evidence Tables x to x for details of the population, interventions, and outcomes of these studies).

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### Evidence Table 1. Head to head controlled trials: Efficacy

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<b>Author:</b> Allain	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2003	<b>Country:</b> France	<b>Funding:</b> Sanofi-Synthelabo

---

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 52  
Range: NR  
SD: 7  
**Gender:** 26 ( 49 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 53  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 53

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 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.

**Comments:**

**Intervention:**

**Run-in :** No  
**Wash out :** No  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	10 mg	52	1 day	0	/ 0
Zaleplon	10 mg	0			/

### Evidence Table 1. Head to head controlled trials: Efficacy

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**Author:** Allain                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2003                      **Country:** France                      **Funding:** Sanofi-Synthelabo

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**Outcome Measurement:**

- # Patient preference questionnaire
- # LSEQ
- # Visual analogue scale for day quality
- #
- #

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Patient's preference for drug
  - Getting to sleep
  - Quality of sleep (LSEQ)
  - Ease of waking up
  - Behavior following wakefulness
  - Day quality
  - Quality of sleep (VAS)
  - Consciousness
  - Dynamism
  - Drowsiness
  - Anxiety
  - Mood
  - Drowsiness duration (minutes)

**Results**

Patient preference

# Percentage of patients preferring a drug

Zolpidem	Zaleplon			P value
62 ( )	38 ( )	( )	( )	0.81
(%) ( )	( )	( )	( )	

Evidence Table 1. Head to head controlled trials: Efficacy

**Author: Allain**                      **Trial type: H2H**                      **Quality rating: Fair**  
**Year: 2003**                      **Country: France**                      **Funding: Sanofi-Synthelabo**

LSEQ

# Getting to sleep mean score (lower is better)	Zolpidem	Zaleplon			P value
	35.9 ( 20.0 )	45.3 ( 20.7 )	( )	( )	0.03
	Score ( SD )				
# Quality of sleep mean score (lower is better)	Zolpidem	Zaleplon			P value
	30.6 ( 18.6 )	44.3 ( 23.2 )	( )	( )	<0.0001
	Score ( SD )				
# Ease of waking up mean score (lower is better)	Zolpidem	Zaleplon			P value
	43.6 ( 22.8 )	43.8 ( 21.8 )	( )	( )	0.27
	Score ( SD )				
# Behavior following wakefulness mean score (lower is better)	Zolpidem	Zaleplon			P value
	47.4 ( 23.2 )	51.7 ( 17.2 )	( )	( )	0.31
	Score ( SD )				

### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Allain                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2003                      **Country:** France                      **Funding:** Sanofi-Synthelabo

VAS for day quality (0-100, higher is better)

# Quality of sleep mean score	Zolpidem	Zaleplon			P value
	68.8 ( 21.8 )	50.2 ( 28.1 )	( )	( )	<0.0001
Score ( SD )					
# Consciousness mean score	Zolpidem	Zaleplon			P value
	73.9 ( 21.3 )	73.1 ( 19.7 )	( )	( )	0.18
Score ( SD )					
# Dynamism mean score	Zolpidem	Zaleplon			P value
	62.6 ( 26.0 )	61.8 ( 24.9 )	( )	( )	0.47
Score ( SD )					
# Drowsiness mean score	Zolpidem	Zaleplon			P value
	28 ( 27.4 )	27.7 ( 26.5 )	( )	( )	0.53
Score ( SD )					
# Anxiety mean score	Zolpidem	Zaleplon			P value
	29.3 ( 30.1 )	26.7 ( 27.7 )	( )	( )	0.34
Score ( SD )					
# Mood mean score	Zolpidem	Zaleplon			P value
	21.6 ( 25.5 )	20.1 ( 21.6 )	( )	( )	0.92
Score ( SD )					
# Drowsiness duration (minutes)	Zolpidem	Zaleplon			P value
	43 ( 43.8 )	38 ( 21.2 )	( )	( )	0.83
Number ( SD )					

### Evidence Table 1. Head to head controlled trials: Efficacy

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<b>Author:</b> Ancoli-Israel	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 72  
Range:  
SD: 5  
**Gender:** 318 ( 58 % ) Female  
**Ethnicity:**  
Number Screened: 1224  
Eligible: 551  
Enrolled: 549  
Number Withdrawn: 2  
Lost to fu:  
Analyzed: 549

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Elderly

**Intervention:**

**Run-in :** 7  
**Wash out :** 7-21  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Placebo	mg	107	14 day	/
Zaleplon	5 mg	166	2 week	/
Zaleplon	10 mg	165	2 week	/
Zolpidem	5 mg	111	2 week	/

### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Ancoli-Israel  
**Year:** 1999

**Trial type:** H2H  
**Country:** US

**Quality rating:** Fair  
**Funding:** Wyeth-Ayerst

**Outcome Measurement:**

# Patient questionnaire

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- Sleep latency
- Total sleep time
- Number of awakenings
- Sleep quality

**Results**

Sleep latency

# Median subjective sleep latency (minutes) at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg		P value
( NS )	( <0.001 )	( <0.05 )	( )	
Number ( p vs placebo )				

# Median subjective sleep latency (minutes) at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg		P value
39 ( <0.001 )	( <0.001 )	( <0.01 )	( )	
Number ( p vs placebo )				

Total sleep time

# Median subjective total sleep time at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo		P value
( NS )	345 ( p<0.05 )	360 ( <0.00 )	318 ( )		
Number ( p vs placebo )					

# Median subjective total sleep time at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo		P value
( NS )	( NS )	360 ( <0.01 )	326 ( )		
Number ( p vs placebo )					

Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Ancoli-Israel  
**Year:** 1999

**Trial type:** H2H  
**Country:** US

**Quality rating:** Fair  
**Funding:** Wyeth-Ayerst

Number of awakenings

# Number of awakenings at week 1

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
1.8 ( NS )	1.8 ( NS )	1.7 ( <0.01 )	2.0 ( NA )	

Number ( p vs placebo )

# Number of awakenings at week 2

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
1.9 ( NS )	1.7 ( NS )	1.6 ( <0.05 )	1.9 ( NA )	

( )

Sleep quality

# Median sleep quality at week 1  
 (1=excellent, 7=extremely poor)

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
3.83 ( NS )	3.67 ( <0.05 )	3.50 ( <0.00 )	4.00 ( NA )	

Score ( p vs placebo )

# Median sleep quality at week 2  
 (1=excellent, 7=extremely poor)

Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	Placebo	P value
3.75 ( NS )	3.63 ( NS )	3.50 ( <0.00 )	4.00 ( NA )	

Score ( p vs placebo )

## Evidence Table 1. Head to head controlled trials: Efficacy

<b>Author:</b> Elie	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Multinational (Canada and Europe)	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42.8  
Range: NR  
SD: 12.4  
**Gender:** 394 ( 64 % ) Female  
**Ethnicity:** 99% white  
<1% black  
<1% Asian  
Number Screened: NR  
Eligible: NR  
Enrolled: 615  
Number Withdrawn: 41  
Lost to fu: NR  
Analyzed: 574

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

**Intervention:**

**Run-in :** Yes  
**Wash out :** Yes  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	113	4 week	/
Zaleplon	10 mg	112	4 week	/
Zaleplon	20 mg	116	4 week	/
Zolpidem	10 mg	0		/
Placebo		118	4 week	/



### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Elie                                      **Trial type:** H2H                                      **Quality rating:** Fair  
**Year:** 1999                                      **Country:** Multinational (Canada and Europe)                                      **Funding:** Wyeth-Ayerst

**Outcome Measurement:**

# Sleep maintenance and sleep quality questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep latency
  - Sleep duration
  - Number of awakenings
  - Sleep quality

**Results**

Sleep duration

# Median sleep duration at baseline (minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	313 ( NS )	331 ( NS )	328 ( NS )	330 ( NS )	
Number ( p vs placebo )					
# Median sleep duration at week 1 (minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	351 ( NS )	370 ( NS )	370 ( p<0.0 )	379 ( p<0.00 )	
Number ( p vs placebo )					
# Median sleep duration at week 2 (minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	359 ( NS )	368 ( NS )	369 ( p<0.0 )	387 ( p<0.00 )	
Number ( p vs placebo )					
# Median sleep duration at week 3 (minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	384 ( NS )	371 ( NS )	374 ( NS )	385 ( <0.001 )	
Number ( p vs placebo )					
# Median sleep duration at week 4 (minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	372 ( NS )	384 ( NS )	385 ( <0.05 )	400 ( <0.001 )	
Number ( p vs placebo )					





### Evidence Table 1. Head to head controlled trials: Efficacy

<b>Author: Elie</b>	<b>Trial type: H2H</b>	<b>Quality rating: Fair</b>
<b>Year: 1999</b>	<b>Country: Multinational (Canada and Europe)</b>	<b>Funding: Wyeth-Ayerst</b>

Sleep latency

# Time to sleep onset at week 1 (median, minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	42 ( 0.005 )	36 ( <0.001 )	33 ( <0.00 )	45 ( 0.47 )	
Number ( p vs placebo )					
# Median time to sleep onset at week 2 (median, minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	35 ( 0.002 )	32 ( 0.001 )	31 ( <0.00 )	37 ( 0.006 )	
Number ( p vs placebo )					
# Median time to sleep onset at week 3 (median, minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	31 ( 0.004 )	30 ( 0.004 )	28 ( <0.00 )	34 ( 0.043 )	
Number ( p vs placebo )					
# Median time to sleep onset at week 4 (median, minutes)	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
	31 ( 0.093 )	28 ( 0.010 )	27 ( 0.001 )	36 ( 0.054 )	
Number ( p vs placebo )					

## Evidence Table 1. Head to head controlled trials: Efficacy

<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42  
Range: NR  
SD: 12  
**Gender:** 351 ( 59 % ) Female  
**Ethnicity:** 11% Black; 3% Hispanic; <1% Native American; 1.5% Asian; <1% Other; 84% White  
Number Screened: NR  
Eligible: 830  
Enrolled: 595  
Number Withdrawn: 9  
Lost to fu: NR  
Analyzed: 586

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Patients with mild non-psychotic psychiatric disorders.  
Baseline characteristics reported only for 586/595 randomized (98%)  
Data on primary outcome (sleep latency) reported graphically only.

**Intervention:**

**Run-in :** 7  
**Wash out :** no  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	118	4 week	3 / 20
Zaleplon	10 mg	119	4 week	5 / 18
Zaleplon	20 mg	116	4 week	10 / 17
Zolpidem	10 mg	115	4 week	7 / 20
Placebo	mg	118	4 week	4 / 12

### Evidence Table 1. Head to head controlled trials: Efficacy

<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

**Outcome Measurement:**

# Patient questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep latency
  - Total sleep time
  - Number of awakenings
  - Sleep quality

**Results**

Sleep latency

# Time to sleep onset at week 1 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
45.36 ( 0.764 )	40.71 ( 0.490 )	35.71 ( 0.003 )	45.71 ( )	
Number ( p vs zolpidem 10 mg )				

# Time to sleep onset at week 2 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
43.57 ( 0.959 )	36.43 ( 0.183 )	31.67 ( <0.00 )	46.43 ( )	
Number ( p vs zolpidem 10 mg )				

# Time to sleep onset at week 3 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
40.71 ( 0.323 )	35.71 ( 0.110 )	30.00 ( <0.00 )	44.29 ( )	
Number ( p vs zolpidem 10 mg )				

# Time to sleep onset at week 4 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
45.63 ( 0.124 )	35.00 ( 0.988 )	30.00 ( 0.037 )	34.29 ( )	
Number ( p vs zolpidem 10 mg )				

Evidence Table 1. Head to head controlled trials: Efficacy

Author: Fry

Trial type: H2H

Quality rating: Fair

Year: 2000

Country: US

Funding: Wyeth-Ayerst

Total sleep time

# Total sleep time at week 1 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
360.0 ( NS )	360.6 ( NS )	368.6 ( <0.05 )	377.1 ( <0.001 )	

Number ( p vs placebo )

# Total sleep time at week 2 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
366.4 ( NS )	364.3 ( NS )	368.6 ( NS )	384.4 ( <0.05 )	

Number ( p vs placebo )

# Total sleep time at week 3 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
361.4 ( NS )	377.1 ( NS )	386.8 ( <0.05 )	392.1 ( <0.01 )	

Number ( p vs placebo )

# Total sleep time at week 4 (median, minutes)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
360.0 ( NS )	376.3 ( NS )	377.5 ( NS )	392.9 ( <0.05 )	

Number ( p vs placebo )

Number of awakenings

# Number of awakenings at week 1 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.93 ( NS )	1.69 ( NS )	1.75 ( NS )	1.59 ( <0.01 )	

Number ( p vs placebo )

# Number of awakenings at week 2 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.67 ( NS )	1.69 ( NS )	1.50 ( <0.00 )	1.50 ( <0.001 )	

Number ( p vs placebo )

# Number of awakenings at week 3 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.71 ( NS )	1.71 ( NS )	1.43 ( <0.05 )	1.71 ( NS )	

Number ( p vs placebo )

# Number of awakenings at week 4 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
1.71 ( NS )	1.57 ( NS )	1.60 ( NS )	1.67 ( NS )	

Number ( p vs placebo )

Evidence Table 1. Head to head controlled trials: Efficacy

Author: Fry

Trial type: H2H

Quality rating: Fair

Year: 2000

Country: US

Funding: Wyeth-Ayerst

Sleep quality (1=excellent, 7=extremely poor)

# Sleep quality at week 1 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 ( NS )	3.57 ( NS )	3.43 ( <0.01 )	3.38 ( <0.001 )	

Score ( p vs placebo )

# Sleep quality at week 2 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 ( NS )	3.57 ( NS )	3.43 ( NS )	3.29 ( <0.05 )	

Score ( p vs placebo )

# Sleep quality at week 3 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.43 ( NS )	3.43 ( NS )	3.29 ( NS )	3.29 ( <0.05 )	

Score ( p vs placebo )

# Sleep quality at week 4 (median)

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value
3.38 ( NS )	3.54 ( NS )	3.29 ( NS )	3.15 ( <0.05 )	

Score ( p vs placebo )



### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Sepracor Study #190-045 **Trial type:** H2H  
**Year:** NR **Country:** US

**Quality rating:** Fair  
**Funding:** Sepracor

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 40.6  
 Range: 21-65  
 SD: 9.7  
**Gender:** 16 ( 25 % ) Female  
**Ethnicity:** 44 (67.7%) white  
 13 (20.0%) black  
 3 (4.6%) asian  
 5 (67.7%) hispanic

Number Screened: NR  
 Eligible: NR  
 Enrolled: 64  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 64

**Eligibility criteria:**

Patients aged 21 to 65 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

**Exclusion criteria:**  
 NR

**Comments:**

**Intervention:** **Run-in :** 3-7  
**Wash out :** 3-7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	1 mg	0	2 day	NR / NR
Eszopiclone	2 mg	0	2 week	NR / NR
Eszopiclone	2.5 mg	0	2 day	NR / NR
Eszopiclone	3 mg	0	2 day	NR / NR
Zolpidem	10 mg	0	2 day	NR / NR
Placebo	NA mg	0	2 day	NR / NR

### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Sepracor Study #190-045 **Trial type:** H2H  
**Year:** NR **Country:** US

**Quality rating:** Fair  
**Funding:** Sepracor

**Outcome Measurement:**

- # questionnaire
- # polysomnography

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep efficiency
  - total sleep time
  - wake after sleep onset
  - wake time during sleep
  - number of awakenings

**Results**

questionnaire

# morning sleepiness

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
43.8 ( 0.1842 )	44.6 ( 0.0670 )	44.7 ( 0.041 )	45.4 ( 0.0307 )	
Mean ( p vs placebo )				

# morning sleepiness

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
42.3 ( 22 )	42 ( 21.3 )	45.3 ( 19.9 )	44.5 ( 22.8 )	
Median ( SD )				

# daytime alertness

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
52.5 ( 0.0968 )	55.2 ( 0.0094 )	50.7 ( 0.273 )	52.2 ( 0.0567 )	
Mean ( p vs placebo )				

# daytime alertness

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
57 ( 24.6 )	56.5 ( 24.3 )	50 ( 25.6 )	56 ( 27.5 )	
Median ( SD )				

# daytime ability to function

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
58.7 ( 0.0134 )	59.5 ( 0.0046 )	54.1 ( 0.460 )	56.6 ( 0.0424 )	
Mean ( p vs placebo )				

Evidence Table 1. Head to head controlled trials: Efficacy

**Author: Sepracor Study #190-045 Trial type: H2H Quality rating: Fair**  
**Year: NR Country: US Funding: Sepracor**

# daytime ability to function	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
	58 ( 21.9 )	59 ( 22.4 )	51 ( 23.8 )	60 ( 26.2 )	
	Media ( SD )				
# quality of sleep	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
	47 ( <0.05 )	58 ( <0.000 )	55 ( <0.05 )	62 ( <0.000 )	
	Median ( p vs placebo )				
# depth of sleep	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
	46 ( <0.05 )	56.5 ( <0.000 )	53 ( <0.00 )	59.9 ( <0.000 )	
	Median ( p vs placebo )				

Evidence Table 1. Head to head controlled trials: Efficacy

Author: **Sepracor Study #190-045** Trial type: **H2H**  
 Year: **NR** Country: **US**

Quality rating: **Fair**  
 Funding: **Sepracor**

polysomnography

# number of awakenings

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
7.8 ( 0.4795 )	7.6 ( 0.5983 )	7.1 ( 0.158 )	6.5 ( 0.0031 )	

Mean ( p vs placebo )

# sleep latency (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
25.2 ( <0.000 )	20.1 ( <0.000 )	18.6 ( <0.00 )	18.3 ( <0.000 )	

Mean ( p vs placebo )

# sleep efficiency (%)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
86.8 ( <0.05 )	88.9 ( <0.000 )	89.7 ( <0.00 )	89.2 ( <0.000 )	

Mean ( p vs placebo )

# total sleep time (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
381.3 ( NS )	412.5 ( <0.05 )	420.0 ( <0.05 )	420.0 ( <0.05 )	

Median ( p vs placebo )

# wake after sleep onset (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
41.4 ( NS )	36.0 ( NS )	33.1 ( <0.05 )	35.9 ( <0.05 )	

Mean ( p vs placebo )

# wake time during sleep (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
28 ( NS )	26 ( NS )	25.3 ( <0.05 )	23.3 ( <0.05 )	

Median ( p vs placebo )

# number of awakenings

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
7.5 ( 3.5 )	6.5 ( 4.5 )	7.0 ( 4.4 )	5.3 ( 4.4 )	

Median ( SD )

# sleep latency (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
16.8 ( 24.1 )	15.5 ( 17.6 )	13.8 ( 18.7 )	13.1 ( 19.6 )	

Median ( SD )

Evidence Table 1. Head to head controlled trials: Efficacy

Author: Sepracor Study #190-045 Trial type: H2H

Quality rating: Fair

Year: NR

Country: US

Funding: Sepracor

# sleep efficiency (%)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
88.6 ( 7.1 )	89.6 ( 7.0 )	90.4 ( 6.4 )	92.0 ( 8.1 )	

Median ( SD )

# wake after sleep onset (min)

Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value
35.5 ( 26.5 )	30.5 ( 25 )	29.5 ( 23.2 )	25.3 ( 31.7 )	

Median ( SD )

### Evidence Table 1. Head to head controlled trials: Efficacy

<b>Author:</b> Tsutsui	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2001	<b>Country:</b> Japan	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42.2  
Range: 20-64  
SD: 12.7  
**Gender:** 277 ( 58 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 479  
Number Withdrawn: 77  
Lost to fu: NR  
Analyzed: 428

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

**Comments:**

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).  
Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

**Intervention:** Run-in : no  
Wash out : 7  
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	209	2 week	14 / 32
Zopiclone	7.5 mg	219	2 week	20 / 45

### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Tsutsui                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** Japan                      **Funding:** Not reported

**Outcome Measurement:**

# Patient diary

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- Global improvement of sleep disorders
- Patient's impression of treatment efficacy

**Results**

Global improvement of sleep disorders

# Patients rated by the investigator as "markedly improved"

Zolpidem	Zopiclone			P value
18.7 ( )	16.4 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "moderately improved"

Zolpidem	Zopiclone			P value
49.3 ( )	45.2 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "slightly improved"

Zolpidem	Zopiclone			P value
26.8 ( )	31.1 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "unchanged"

Zolpidem	Zopiclone			P value
5.3 ( )	6.4 ( )	( )	( )	NS
(%) ( )				

### Evidence Table 1. Head to head controlled trials: Efficacy

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**Author:** Tsutsui                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** Japan                      **Funding:** Not reported

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Patient's impression of treatment efficacy

# Patients rating the treatment as "markedly effective"	Zolpidem	Zopiclone			P value
	18.2 ( )	16.0 ( )	( )	( )	NS
	(%) ( )	( )	( )	( )	
# Patients rating the treatment as "moderately effective"	Zolpidem	Zopiclone			P value
	46.4 ( )	45.2 ( )	( )	( )	NS
	(%) ( )	( )	( )	( )	
# Patients rating the treatment as "slightly effective"	Zolpidem	Zopiclone			P value
	29.7 ( )	33.3 ( )	( )	( )	NS
	(%) ( )	( )	( )	( )	
# Patients rating the treatment as "ineffective"	Zolpidem	Zopiclone			P value
	5.7 ( )	5.5 ( )	( )	( )	NS
	(%) ( )	( )	( )	( )	



## Evidence Table 2. Head to head controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Ancoli-Israel</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1999</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 72  
Range:  
SD: 5  
**Gender:** 31 ( 58 % ) Female  
**Ethnicity:**  
Number Screened: 1224  
Eligible: 551  
Enrolled: 549  
Number Withdrawn: 2  
Lost to fu:  
Analyzed: 549

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Elderly

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Placebo	mg	107	14 day	/
Zaleplon	5 mg	166	2 week	/
Zaleplon	10 mg	165	2 week	/
Zolpidem	5 mg	111	2 week	/

**Rebound:**

rebound

# rebound insomnia: sleep latency on discontinuation day 1 (minutes, median)

Zaleplon 5mg	Zaleplon 10mg	Zolpidem 5mg	Placebo	P value
30 ( NS )	45 ( NS )	60 ( <0.01 )	44 ( NA )	
Number ( p vs placebo )				

### Evidence Table 1. Head to head controlled trials: Efficacy

**Author:** Tsutsui                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** Japan                      **Funding:** Not reported

**Outcome Measurement:**

# Patient diary

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**



Global improvement of sleep disorders



Patient's impression of treatment efficacy

**Results**

Global improvement of sleep disorders

# Patients rated by the investigator as "markedly improved"

Zolpidem	Zopiclone			P value
18.7 ( )	16.4 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "moderately improved"

Zolpidem	Zopiclone			P value
49.3 ( )	45.2 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "slightly improved"

Zolpidem	Zopiclone			P value
26.8 ( )	31.1 ( )	( )	( )	NS
(%) ( )				

# Patients rated by the investigator as "unchanged"

Zolpidem	Zopiclone			P value
5.3 ( )	6.4 ( )	( )	( )	NS
(%) ( )				

## Evidence Table 2. Head to head controlled trials: Rebound Insomnia

**Author:** Ancoli-Israel      **Trial type:** H2H      **Quality rating:** Fair  
**Year:** 1999      **Country:** US      **Funding:** Wyeth-Ayerst

	Zaleplon 5mg	Zaleplon 10mg	Zolpidem 5mg	Placebo	P value
# rebound insomnia: sleep duration, total sleep time on discontinuation day 1 (minutes, median)	330 ( NS )	315 ( <0.05 )	300 ( <0.00 )	317.50 ( NA )	
	Number ( p vs placebo )				
	Zaleplon 5mg	Zaleplon 10mg	Zolpidem 5mg	Placebo	P value
# rebound insomnia: number of awakenings on discontinuation day 1 (median)	2 ( NS )	2 ( NS )	2 ( NS )	2 ( NA )	
	Number ( p vs placebo )				

### Evidence Table 2. Head to head controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Elie</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1999</b>	<b>Country:</b>	<b>Multinational (Canada and Europe)</b>	<b>Funding:</b>	<b>Wyeth-Ayerst</b>

		Number ( p vs placebo )				
#	Rebound: Sleep duration on night +1 (median, minutes)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
		344.3 ( NS )	349.6 ( NS )	339.2 ( NS )	324.7 ( <0.05 )	
		Number ( p vs placebo )				
#	Rebound: Number of awakenings on night +1 (median)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
		2.3 ( NS )	2.0 ( NS )	1.8 ( NS )	2.6 ( <0.01 )	
		Number ( p vs placebo )				

## Evidence Table 2. Head to head controlled trials: Rebound Insomnia

<b>Author:</b> Elie	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Multinational (Canada and Europe)	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42.8  
Range: NR  
SD: 12.4  
**Gender:** 39 ( 64 % ) Female  
**Ethnicity:** 99% white  
<1% black  
<1% Asian  
Number Screened: NR  
Eligible: NR  
Enrolled: 615  
Number Withdrawn: 41  
Lost to fu: NR  
Analyzed: 574

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	113	4 week	/
Zaleplon	10 mg	112	4 week	/
Zaleplon	20 mg	116	4 week	/
Zolpidem	10 mg	0		/
Placebo		118	4 week	/

**Rebound:**

Rebound insomnia

# Rebound: Sleep latency on night +1 (median, minutes)

Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
51.7 ( NS )	57.6 ( NS )	50.4 ( NS )	91.6 ( <0.00 )	

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42  
Range: NR  
SD: 12  
**Gender:** 35 ( 59 % ) Female  
**Ethnicity:** 11% Black  
3% Hispanic  
<1% Native American  
1.5% Asian  
<1% Other  
84% White

Number Screened: NR  
Eligible: 830  
Enrolled: 595  
Number Withdrawn: 9  
Lost to fu: NR  
Analyzed: 586

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Patients with mild non-psychotic psychiatric disorders.  
Baseline characteristics reported only for 586/595 randomized (98%)  
Data on primary outcome (sleep latency) reported graphically only.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zaleplon	5 mg	118	4 week	3 / 20
Zaleplon	10 mg	119	4 week	5 / 18
Zaleplon	20 mg	116	4 week	10 / 17
Zolpidem	10 mg	115	4 week	7 / 20
Placebo	mg	118	4 week	4 / 12

Evidence Table 2. Head to head controlled trials: Rebound Insomnia

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<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

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**Rebound:**

Rebound

# rebound : Sleep latency on discontinuation night 1 (minutes, median)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	45 ( NS )	40 ( NS )	30 ( NS )	60 ( <0.01 )	
	Number ( p vs placebo )				
# rebound : Number of awakenings on discontinuation night 1	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	2 ( NS )	2 ( NS )	2 ( NS )	2 ( <0.05 )	
	Number ( p vs placebo )				
# rebound : Sleep duration on discontinuation night 1 (median, minutes)	Zaleplon 5mg	Zaleplon 10mg	Zaleplon 20mg	Zolpidem 10mg	P value
	360 ( NS )	360 ( NS )	360 ( NS )	330 ( <0.00 )	
	Number ( p vs placebo )				

## Evidence Table 2. Head to head controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Tsutsui</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2001</b>	<b>Country:</b>	<b>Japan</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42.2  
Range: 20-64  
SD: 12.7  
**Gender:** 27 ( 58 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 479  
Number Withdrawn: 77  
Lost to fu: NR  
Analyzed: 428

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

**Comments:**

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).  
Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	209	2 week	14 / 32
Zopiclone	7.5 mg	219	2 week	20 / 45

**Rebound:**

Rebound insomnia: sleep latency

# rebound: patients with an aggravation of sleep onset latency by one grade or more at the end of followup

Zolpidem	Zopiclone			P value
4.5 ( )	15.4 ( )	( )	( )	0.005
% ( )	( )			



### Evidence Table 3. Head to head controlled trials: Adverse Events

**Author:** Allain                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2003                      **Country:** France                      **Funding:** Sanofi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** 52  
 Range: NR  
 SD: 7  
**Gender:** 26 ( 49 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 53  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 53

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 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.

**Comments:**

**Intervention:** Run-in : No  
 Wash out : No  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	10 mg	52	1 day	0	/ 0
Zaleplon	10 mg	0			/

**Adverse Events:**

Adverse events reported  
 # Any adverse event

Zolpidem	Zaleplon			P value:
5.7 ( 3/53 )	7.5 ( 4/53 )	( )	( )	NR
% ( number	)			

### Evidence Table 3. Head to head controlled trials: Adverse Events

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**Author: Allain****Trial type: H2H****Quality rating: Fair****Year: 2003****Country: France****Funding: Sanofi-Synthelabo**

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Total withdrawals: none

Withdrawals due to adverse events: none

### Evidence Table 3. Head to head controlled trials: Adverse Events

**Author:** Ancoli-Israel                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 1999                                      **Country:** US                                      **Funding:** Wyeth-Ayerst

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 72  
 Range:  
 SD: 5  
**Gender:** 318 ( 58 % ) Female  
**Ethnicity:**

Number Screened: 1224  
 Eligible: 551  
 Enrolled: 549  
 Number Withdrawn: 2  
 Lost to fu:  
 Analyzed: 549

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Elderly

**Intervention:**

**Run-in :** 7  
**Wash out :** 7-21  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Placebo	mg	107	14 day	/
Zaleplon	5 mg	166	2 week	/
Zaleplon	10 mg	165	2 week	/
Zolpidem	5 mg	111	2 week	/

**Adverse Events:**

Adverse events

# Frequency of treatment-emergent adverse events

Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	P value:
56 ( )	56 ( )	59 ( )	63 ( )	NS
% ( )	%			

### Evidence Table 3. Head to head controlled trials: Adverse Events

**Author:** Ancoli-Israel      **Trial type:** H2H      **Quality rating:** Fair  
**Year:** 1999      **Country:** US      **Funding:** Wyeth-Ayerst

# CNS adverse events	Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	P value:
	14 ( )	NR ( )	NR ( )	25 ( P<0.0 )	
	% ( p vs placebo )				
# Somnolence	Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zolpidem 5 mg	P value:
	2 ( )	4 ( )	NR ( )	10 ( p<0.0 )	
	% ( p vs placebo )				

Total withdrawals: NR

Withdrawals due to adverse events: NR

Evidence Table 3. Head to head controlled trials: Adverse Events

<b>Author:</b> Elie	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Multinational (Canada and Europe)	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel

**Setting** Multicenter

**Age:** 42.8  
Range: NR  
SD: 12.4

**Gender:** 394 ( 64 % ) Female

**Ethnicity:** 99% white  
<1% black  
<1% Asian

Number Screened: NR  
Eligible: NR  
Enrolled: 615

Number Withdrawn: 41  
Lost to fu: NR  
Analyzed: 574

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

**Intervention:**

**Run-in :** Yes

**Wash out :** Yes

**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	113	4 week	/
Zaleplon	10 mg	112	4 week	/
Zaleplon	20 mg	116	4 week	/
Zolpidem	10 mg	0		/
Placebo		118	4 week	/

### Evidence Table 3. Head to head controlled trials: Adverse Events

Author: Elie Trial type: H2H Quality rating: Fair  
 Year: 1999 Country: Multinational (Canada and Europe) Funding: Wyeth-Ayerst

**Adverse Events:**

Withdrawal effects

# Incidence of 3 or more new withdrawal symptoms after discontinuation of treatment

Zolpidem 10 mg	Zaleplon 10 mg			P value:
NR ( <0.05 )	NR ( NS )	( )	( )	

NR ( p vs placebo )

Adverse events

# Patients with treatment-emergent adverse events

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value:
59 ( 71 )	73 ( 87 )	61 ( 76 )	64 ( 78 )	

% ( N )

Total withdrawals NR

Withdrawals due to adverse events

# Withdrawals due to adverse events

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value:
2 ( 2 )	6 ( 7 )	2 ( 2 )	6 ( 7 )	

% ( N )

## Evidence Table 3. Head to head controlled trials: Adverse Events

<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42  
Range: NR  
SD: 12  
**Gender:** 351 ( 59 % ) Female  
**Ethnicity:** 11% Black; 3% Hispanic; <1%  
Native American; 1.5% Asian; <1%  
Other; 84% White

Number Screened: NR  
Eligible: 830  
Enrolled: 595  
Number Withdrawn: 9  
Lost to fu: NR  
Analyzed: 586

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Patients with mild non-psychotic psychiatric disorders.  
Baseline characteristics reported only for 586/595 randomized (98%)  
Data on primary outcome (sleep latency) reported graphically only.

**Intervention:**

**Run-in :** 7  
**Wash out :** no  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	118	4 week	3 / 20
Zaleplon	10 mg	119	4 week	5 / 18
Zaleplon	20 mg	116	4 week	10 / 17
Zolpidem	10 mg	115	4 week	7 / 20
Placebo	mg	118	4 week	4 / 12

## Evidence Table 3. Head to head controlled trials: Adverse Events

Author: Fry

Trial type: H2H

Quality rating: Fair

Year: 2000

Country: US

Funding: Wyeth-Ayerst

**Adverse Events:**Tolerance: Sleep latencyTolerance: Number of awakeningsTolerance: Total sleep timeTotal withdrawals

# Total withdrawals

Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	P value:
16.9 ( )	15.0 ( )	14.5 ( )	17.2 ( )	NR
% ( )				

Withdrawals due to adverse effects

# Withdrawals due to adverse effects

Zaleplon	Zaleplon	Zaleplon	Zolpidem	P value:
3 ( )	4 ( )	9 ( )	6 ( )	NR
% ( )				



Evidence Table 3. Head to head controlled trials: Adverse Events

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<b>Author:</b> Lemoine	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 1995	<b>Country:</b> France	<b>Funding:</b> Not reported

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:**  
Range:  
SD:  
**Gender:** ( % ) Female  
**Ethnicity:**  
Number Screened: NR  
Eligible: NR  
Enrolled: 394  
Number Withdrawn: 15  
Lost to fu: 2  
Analyzed: 390

**Eligibility criteria:**

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.

**Exclusion criteria:**

History of depression or other psychiatric disorder, a current depressive episode (total score on the QD2A questionnaire  $\geq 7$ ) 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.

**Comments:**

Study of withdrawal effects- separate studies of zopiclone and zolpidem; efficacy not assessed. Comparisons were treatment vs withdrawal within drug groups.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
	mg	100		/

**Adverse Events:**

### Evidence Table 3. Head to head controlled trials: Adverse Events

**Author:** Sepracor Study #190-045 **Trial type:** H2H  
**Year:** NR **Country:** US

**Quality rating:** Fair  
**Funding:** Sepracor

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 40.6  
 Range: 21-65  
 SD: 9.7  
**Gender:** 16 ( 25 % ) Female  
**Ethnicity:** 44 (67.7%) white  
 13 (20.0%) black  
 3 (4.6%) asian  
 5 (67.7%) hispanic

Number Screened: NR  
 Eligible: NR  
 Enrolled: 64  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 64

**Eligibility criteria:**

Patients aged 21 to 65 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

**Exclusion criteria:**  
 NR

**Comments:**

**Intervention:** **Run-in :** 3-7  
**Wash out :** 3-7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	1 mg	0	2 day	NR / NR
Eszopiclone	2 mg	0	2 week	NR / NR
Eszopiclone	2.5 mg	0	2 day	NR / NR
Eszopiclone	3 mg	0	2 day	NR / NR
Zolpidem	10 mg	0	2 day	NR / NR
Placebo	NA mg	0	2 day	NR / NR

**Adverse Events:**

[adverse events](#)

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: Sepracor Study #190-045 Trial type: H2H

Quality rating: Fair

Year: NR

Country: US

Funding: Sepracor

# dizziness	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	3.2 ( )	0 ( )	0 ( )	4.9 ( )	
	% ( )				
# dizziness	Zolpidem	Placebo			P value:
	23.4 ( )	7.9 ( )	( )	( )	
	% ( )				
# hallucinations	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	0 ( )	0 ( )	0 ( )	0 ( )	
	% ( )				
# hallucination	Zolpidem	Placebo			P value:
	10.9 ( )	0 ( )	( )	( )	
	% ( )				
# somnolence	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	4.8 ( )	3.2 ( )	3.1 ( )	4.7 ( )	
	% ( )				
# somnolence	Zolpidem	Placebo			P value:
	9.4 ( )	3.2 ( )	( )	( )	
	% ( )				
# headache	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	4.8 ( )	6.3 ( )	3.1 ( )	9.4 ( )	
	% ( )				
# headache	Zolpidem	Placebo			P value:
	9.4 ( )	9.5 ( )	( )	( )	
	% ( )				

Evidence Table 3. Head to head controlled trials: Adverse Events

Author: Sepracor Study #190-045 Trial type: H2H

Quality rating: Fair

Year: NR

Country: US

Funding: Sepracor

# nausea	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	3.2 ( )	1.6 ( )	3.1 ( )	3.1 ( )	
	% ( )				
# nausea	Zolpidem	Placebo			P value:
	6.3 ( )	3.2 ( )	( )	( )	
	% ( )				
# unpleasant taste	Eszopiclone 1mg	Eszopiclone 2mg	Eszopiclone 2.5mg	Eszopiclone 3mg	P value:
	4.8 ( )	4.8 ( )	9.2 ( )	7.8 ( )	
	% ( )				
# unpleasant taste	Zolpidem	Placebo			P value:
	0 ( )	1.6 ( )	( )	( )	
	% ( )				

## Evidence Table 3. Head to head controlled trials: Adverse Events

<b>Author:</b> Tsutsui	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2001	<b>Country:</b> Japan	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 42.2  
Range: 20-64  
SD: 12.7  
**Gender:** 277 ( 58 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 479  
Number Withdrawn: 77  
Lost to fu: NR  
Analyzed: 428

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.

**Comments:**

Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%).

Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline ( $p < 0.01$ , data not reported).

**Intervention:** Run-in : no  
Wash out : 7  
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	209	2 week	14 / 32
Zopiclone	7.5 mg	219	2 week	20 / 45

**Adverse Events:**

Total withdrawals

### Evidence Table 3. Head to head controlled trials: Adverse Events

**Author:** Tsutsui                      **Trial type:** H2H                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** Japan                      **Funding:** Not reported

# Total withdrawals	Zolpidem	Zopiclone			P value:
	13.9 ( )	18.1 ( )	( )	( )	NS
	% ( )	( )			
<u>Withdrawals due to adverse events</u>					
# Withdrawals due to adverse events	Zolpidem	Zopiclone			P value:
	6.1 ( )	8.1 ( )	( )	( )	NR
	% ( )	( )			
<u>Adverse events</u>					
# Patients experiencing adverse events "related", "possibly related" or "probably related" to study medication	Zolpidem	Zopiclone			P value:
	31 ( )	45 ( )	( )	( )	0.004
	% ( )	( )			

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Anderson                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                              **Country:** UK                              **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** NR  
 Range: 20-69  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 119  
 Number Withdrawn: 5  
 Lost to fu: 15  
 Analyzed: 99

**Eligibility criteria:**

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

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 7  
 Wash out : 7  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg		14 day	1 / 2
Nitrazepam	5 mg		14 day	1 / 1
Placebo	NA mg		14 day	1 / 2

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Anderson      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1987      **Country:** UK      **Funding:** Not reported

**Outcome Measurement:**

- # Diary
- # 100-mm visual analogue scales
- # sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- The time they took medicine
  - Sleep duration
  - No. of times woke-up
  - Wake up earlier then wished
  - Sleep latency
  - How much they dreamed
  - Slept well - sleep quality
  - Feeling wide awake
  - 
  -

**Results**

100-mm visual analogue scales

# sleep quality at week 3 (in figure), higher score=better

Zopiclone	Nitrazepam	Placebo		P value
68 ( <0.05 )	66 ( <0.05 )	49 ( NA )	( )	
Score ( p vs placebo )				

# time to fall asleep at week 3 (in figure), higher score=better

Zopiclone	Nitrazepam	Placebo		P value
61 ( <0.05 )	63 ( <0.05 )	44 ( NA )	( )	
Score ( p vs placebo )				

# all sleep parameters

Zopiclone	Nitrazepam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				



Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Anderson      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1987      **Country:** UK      **Funding:** Not reported

sleep questionnaire

# early morning awakenings at week 3  
 (in figure), higher score=worse

Zopiclone	Nitrazepam	Placebo		P value
0.38 ( <0.05 )	0.35 ( <0.05 )	0.78 ( NA )	( )	

proportion ( p vs placebo )

# physicians global assessment

Zopiclone	Nitrazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

# wide-awake in the morning

Zopiclone	Nitrazepam			P value
better ( )	- ( )	( )	( )	0.02

Score ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b>	<b>Autret</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	

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**Design:**

**Study design** CT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** 46.3  
 Range:  
 SD: 11.7  
**Gender:** 85 ( 70 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 121  
 Number Withdrawn: NR  
 Lost to fu: 8  
 Analyzed: 113

**Eligibility criteria:**

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.

**Exclusion criteria:**

NR

**Comments:**

Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

**Intervention:**

**Run-in :** 4  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Autret                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1987                      **Country:** France                      **Funding:**

**Outcome Measurement:**

- # Spiegel and Norris' visual analogue scale
- # rated by physicians

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep latency
  - Sleep quality
  - Sleep duration
  - Night waking
  - Dreams
  - Morning state
  - Global evaluation
  - severity of insomnia
  - therapeutic efficacy
  - intensity of side-effects

**Results**

Spiegel and Norris' visual analogue scale

# Delay in falling asleep (higher score=better)- change from baseline

Zopiclone	Triazolam			P value
1.86 ( 1.35 )	1.43 ( 1.12 )	( )	( )	<0.01
Score ( SD )				

# quality of sleep (higher score=better)- change from baseline

Zopiclone	Triazolam			P value
1.98 ( 1.25 )	1.47 ( 1.06 )	( )	( )	<0.01
Score ( SD )				

# length of sleep (higher score=better)- change from baseline

Zopiclone	Triazolam			P value
1.47 ( 1.26 )	1.26 ( 0.97 )	( )	( )	NS
Score ( SD )				

# night waking (higher score=better)- change from baseline

Zopiclone	Triazolam			P value
1.64 ( 1.38 )	1.34 ( 1.11 )	( )	( )	<0.05
Score ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Autret</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	

# dream (higher score=better)- change from baseline	Zopiclone	Triazolam			P value
	0.40 ( 1.44 )	0.32 ( 1.10 )	( )	( )	NS
	Score ( SD )				
# morning state (higher score=better)- change from baseline	Zopiclone	Triazolam			P value
	1.66 ( 1.46 )	1.13 ( 1.04 )	( )	( )	<0.001
	Score ( SD )				
# global evaluation (higher score=better)- change from baseline	Zopiclone	Triazolam			P value
	1.96 ( 1.40 )	1.43 ( 1.04 )	( )	( )	<0.001
	Score ( SD )				
<u>rated by physicians</u>					
# therapeutic efficacy- preferences of the patients	Zopiclone	Temazepam			P value
	62 ( 54.9 )	26 ( 23 )	( )	( )	<0.01
	Number ( % )				

### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Begg	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1992	<b>Country:</b> NR	<b>Funding:</b> Roche Products (NZ) Ltd.

**Design:**

**Study design** RCT  
SB  
Parallel  
**Setting** Single Center

**Age:** NR  
Range: >18  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 88  
Number Withdrawn: 4  
Lost to fu: 33  
Analyzed: 51

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 infestation within four hours of retiring or more tna one glass (10 g) alcohol in the previous 24 hours were not permitted.

**Comments:**

Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

**Intervention:**

**Run-in :** 2  
**Wash out :** 2  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	28	11 day	1 /
Midazolam	15 mg	23	11 day	3 /

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Begg                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1992                      **Country:** NR                      **Funding:** Roche Products (NZ) Ltd.

**Outcome Measurement:**

**Efficacy Outcome List:**

# Leeds sleep evaluation questionnaire (LSEQ)

**Results**

LSEQ - pre vs. during intervention

# all 10 items (low=beneficial effect)

Zopiclone				P value
Low ( )	( )	( )	( )	p<0.01
Score ( )				

# 6 of the 10 items - getting to sleep and quality of sleep

Midazolam				P value
Low ( )	( )	( )	( )	p<0.01
Score ( )				

# all 10 items

Zopiclone	Midazolam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

LSEQ - pre vs. two nights after medication was discontinued (rebound)

# 5 of 10 items

Zopiclone				P value
High ( )	( )	( )	( )	<0.01
Score ( )				

# all 10 items

Midazolam				P value
NR ( )	( )	( )	( )	NS
Score ( )				

# all 10 items

Zopiclone	Midazolam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Chaudoir                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** UK                              **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 50.9  
 Range: 30-65  
 SD:  
**Gender:** 27 ( 71 % ) Female  
**Ethnicity:** 100% caucasian

Number Screened: NR  
 Eligible: NR  
 Enrolled: 38  
 Number Withdrawn: 4  
 Lost to fu: NR  
 Analyzed: 38

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** no  
**Wash out :** 7  
**Allow other medication :** No medication known to cause drowsiness

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	19	1 week	0 / 1
Triazolam	0.25 mg	19	1 week	1 / 3

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Chaudoir      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1990      **Country:** UK      **Funding:** Not reported

**Outcome Measurement:**

- # LSEQ
- # Patient diary

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- LSEQ: Ease of getting to sleep
  - LSEQ: Quality of sleep
  - LSEQ: Ease of awakening
  - LSEQ: Behavior following wakefulness
  - Global assessment of efficacy

**Results**

LSEQ: Ease of getting to sleep

# Mean score at week 1

Zopiclone	Triazolam			P value
57.91 ( )	65.18 ( )	( )	( )	NS (NR)
Score ( )				

LSEQ: Quality of sleep

# Mean score at week 1

Zopiclone	Triazolam			P value
67.13 ( )	72.13 ( )	( )	( )	NS (NR)
Score ( )				

LSEQ Ease of awakening

# Mean score at week 1

Zopiclone	Triazolam			P value
68.79 ( )	53.03 ( )	( )	( )	NS (NR)
Score ( )				

LSEQ Behavior following wakefulness

# Mean score at week 1

Zopiclone	Triazolam			P value
58.35 ( )	54.49 ( )	( )	( )	NS (NR)
Score ( )				



Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Chaudoir                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** UK                              **Funding:** Not reported

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Global assessment of efficacy

# Physicians' global assessment of efficacy

Zopiclone	Triazolam			P value
NR, high ( )	NR, high ( )	( )	( )	NS
Score ( )				

# Patients' global assessment of efficacy

Zopiclone	Triazolam			P value
NR, high ( )	NR, high ( )	( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (1)                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2000                              **Country:** US                              **Funding:** Wyeth-Ayerst Research

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 41.6  
 Range: 21-60  
 SD: 9.5  
**Gender:** 24 ( 51 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 47  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 47

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : NR  
 Wash out : 5-12  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10 mg	47	2 day	0 / NR
Zaleplon	40 mg	47	2 day	0 / NR
Triazolam	0.25 mg	47	2 day	0 / NR
Placebo	NA mg	47	2 day	0 / NR

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (1)      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

**Outcome Measurement:**

- # polysomnography
- # patient reports

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- latency to persistent sleep
  - total sleep time
  - sleep quality
  - ease of falling asleep

**Results**

polysomnography

# latency to persistent sleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
22.5 ( NS )	18.6 ( <0.05 )	27.5 ( NA )	( )	
minutes ( p vs triazolam )				

# total sleep time

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
386.3 ( <0.05 )	392.6 ( <0.05 )	407.8 ( NA )	( )	
minutes ( p vs triazolam )				

## Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (1)      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

patient reports

# latency to sleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
38.8 ( NS )	29.3 ( NS )	36.4 ( NA )	( )	

minutes ( p vs triazolam )

# total sleep time

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
358.1 ( NS )	375.5 ( NS )	386.8 ( NA )	( )	

minutes ( p vs triazolam )

# sleep quality

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
2.5 ( NS )	2.7 ( NS )	2.7 ( NA )	( )	

Score ( p vs triazolam )

# ease of falling asleep

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value
65.4 ( NS )	74.1 ( NS )	67.3 ( NA )	( )	

Score ( p vs triazolam )

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (2)                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2000                                  **Country:** US                                  **Funding:** Wyeth-Ayerst Research

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 38.1  
 Range: 21-60  
 SD: 11.1  
**Gender:** 14 ( 39 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 36  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 36

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** NR  
**Wash out :** 5-12  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	20 mg	36	2 day	/
Zaleplon	60 mg	36	2 day	/
Triazolam	0.25 mg	36	2 day	/
Placebo	NA mg	36	2 day	/

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (2)      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

**Outcome Measurement:**

- # polysomnography
- # patient reports

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- latency to persistent sleep
  - total sleep time
  - sleep quality
  - ease of falling asleep

**Results**

polysomnography

# latency to persistent sleep

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
30.5 ( NS )	21.7 ( <0.05 )	27.6 ( NA )	( )	
minutes ( p vs triazolam )				

# total sleep time

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
391.3 ( <0.05 )	404.7 ( <0.05 )	422.8 ( NA )	( )	
minutes ( p vs triazolam )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Drake (2)      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

patient reports

# latency to sleep

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
45.5 ( NS )	36.6 ( NS )	41.9 ( NA )	( )	
minutes ( p vs triazolam )				

# total sleep time

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
356 ( <0.05 )	376.3 ( NS )	393.5 ( NA )	( )	
minutes ( p vs triazolam )				

# sleep quality (higher score=better)

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
2.3 ( <0.05 )	2.4 ( NS )	2.7 ( NA )	( )	
Score ( p vs triazolam )				

# ease of falling asleep (lower score=better)

Zaleplon 20mg	Zaleplon 60mg	Triazolam 0.25mg		P value
58.8 ( NS )	64.5 ( NS )	61 ( NA )	( )	
Score ( p vs triazolam )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 37.6  
Range:  
SD: 1.84  
**Gender:** 24 ( 67 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 36  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 36

**Eligibility criteria:**

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,

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 7  
Wash out : 3  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	28 day	0 / 0
Flurazepam	30 mg	12	28 day	0 / 0
Placebo	NA mg	12	28 day	0 / 0



### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Outcome Measurement:**

# post-sleep questionnaire

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- rapidity of sleep onset
- duration of sleep
- nocturnal awakenings

**Results**

post-sleep questionnaire

# rapidity of sleep onset at week 4 (higher score=better)

Zopiclone	Flurazepam	Placebo		P value
11.6 ( NS )	11.2 ( NS )	10.5 ( NA )	( )	

Score ( p vs placebo )

# duration of sleep at week 4 (higher score=better)

Zopiclone	Flurazepam	Placebo		P value
7.3 ( NS )	7.1 ( NS )	6.5 ( NA )	( )	

Score ( p vs placebo )

# nocturnal awakenings at week 4 (higher score=worse)

Zopiclone	Flurazepam	Placebo		P value
3.5 ( <0.01 )	3.5 ( <0.01 )	5.5 ( NA )	( )	

Score ( p vs placebo )

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Fleming                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1995                              **Country:** Canada                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** NR  
 Range: 33-37  
 SD:  
**Gender:** 69 ( 48 % ) Female  
**Ethnicity:** NR  
 Number Screened: 222  
 Eligible: 144  
 Enrolled: 144  
 Number Withdrawn: 7  
 Lost to fu: 1  
 Analyzed: 141

**Eligibility criteria:**

(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 these criteria was to be present for at least 6 months prior to study entry.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 1  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	35	3 day	0 / 0
Zolpidem	20 mg	35	3 day	6 / 7
Flurazepam	30 mg	36	3 day	0 / 1
Placebo	NA mg	35	3 day	0 / 0

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Fleming	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1995	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Outcome Measurement:**

- # questionnaire
- # polysomnography

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - wake time
  - sleep quality
  - sleep efficiency

**Results**

polysomnography

# sleep latency

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
-14.7 ( <0.05 )	-28.4 ( <0.05 )	-11.8 ( NA )	( )	

minutes ( p vs flurazepam )

# sleep efficiency

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
NR ( NS )	NR ( NS )	NR ( NS )	( )	

minutes ( p vs placebo )

# wake time during sleep

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
NR ( NS )	NR ( NS )	NR ( NS )	( )	

minutes ( p vs placebo )

questionnaire

# sleep quality at day 3, (higher score=better)

Zolpidem 10mg	Zolpidem 20mg	Flurazepam		P value
2.4 ( <0.05 )	2.5 ( <0.05 )	1.9 ( NA )	( )	<0.05

Score ( p vs flurazepam )

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Fleming_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 45.5  
Range:  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 52  
Number Withdrawn: 4  
Lost to fu: 0  
Analyzed: 48

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, analgesis, 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.

**Comments:**

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

**Intervention:** Run-in : 3  
Wash out : 4  
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Fleming_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Outcome Measurement:**

- # post-sleep questionnaire
- # Hamilton Anxiety Scale

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- speed and quality of sleep onset
  - duration of sleep
  - perceived quality of sleep
  - no. of awakenings
  - dreaming
  - ease of awakening
  - the time taken to full alertness
  - daytime alertness

**Results**

Hamilton Anxiety Scale

# total score

Zopiclone	Triazolam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Hajak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998, 1995, 1994              **Country:** Germany                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 51  
 Range: 18-71  
 SD: 11  
**Gender:** 940 ( 62 % ) Female  
**Ethnicity:** 99.3% Caucasian  
 0.9% Others

Number Screened: NR  
 Eligible: NR  
 Enrolled: 1507  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 1507

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Patients were observed for a further period of 14 days without medication for rebound.

**Intervention:**

**Run-in :** 7  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	612	28 day	26 / 190
Triazolam	0.2 mg	307	28 day	11 / 187
Placebo	NA mg	298	28 day	25 / 193

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Hajak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998, 1995, 1994              **Country:** Germany                      **Funding:** Not reported

**Outcome Measurement:**

- # Visual Analogue Scale for evening (VIS-A)
- # Visual Analogue Scale for morning (VIS-M)

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- daytime anxiety
  - total sleep time
  - number of nocturnal awakenings
  - a feeling of being refreshed on awakening i
  - daytime tiredness
  - daytime anxiety

**Results**

Total response

# Improved sleep quality and daytime well-being

Zopiclone	Triazolam	Placebo		P value
37.4 ( <=0.00 )	32.2 ( NS )	26.8 ( NA )	( )	
% ( p vs placebo )				

# Improved sleep quality and daytime well-being- treatment period

Zopiclone	Triazolam			P value
42.3 ( )	36.3 ( )	( )	( )	0.1133
% ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Hayoun</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported (corresponding</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 47.9  
Range: 18-65  
SD:  
**Gender:** 90 ( 66 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 136  
Number Withdrawn: 9  
Lost to fu: 0  
Analyzed: 127

**Eligibility criteria:**

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).

**Exclusion criteria:**

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.

**Comments:**

Sleep aid, drug abuse???  
More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04).  
More patients described themselves as tranquil compared with patients on zopiclone.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	67	7 day	0 / 0
Triazolam	0.25 mg	69	7 day	0 / 0



### Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Hayoun                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1989                              **Country:** France                      **Funding:** Not reported (corresponding

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**Outcome Measurement:**

- # Norris visual analogue auto-evaluation scale
- # global physician's evaluation scale
- # self-evaluation questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep duration
  - no. of awakenings
  - sleep soundness
  - awakening without concentration difficultie

**Results**

Norris visual analogue auto-evaluation scale

# overall

Zopiclone	Triazolam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

global physicians' evaluation scale

# Efficacy- good or excellent

Zopiclone	Triazolam			P value
73 ( )	69 ( )	( )	( )	NS
% ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Hayoun      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** France      **Funding:** Not reported (corresponding

self-evaluation questionnaire

# falling asleep in less than 30 minutes	Zopiclone	Triazolam			P value
	63 ( )	84 ( )	( )	( )	NS
	% ( )				
# sleep more than 7 hours	Zopiclone	Triazolam			P value
	50 ( )	69 ( )	( )	( )	NS
	% ( )				
# awakening at night once or not at all	Zopiclone	Triazolam			P value
	64 ( )	89 ( )	( )	( )	NS
	% ( )				
# sleep heavily while still reporting a good awakening state	Zopiclone	Triazolam			P value
	55 ( )	70 ( )	( )	( )	NS
	% ( )				
# feel more rest	Zopiclone	Triazolam			P value
	80 ( )	92 ( )	( )	( )	NS
	% ( )				
# awakening with no concentration difficulties (with a significant investigator-by-treatment group interaction, p<0.01)	Zopiclone	Triazolam			P value
	56 ( )	82 ( )	( )	( )	0.04
	% ( )				
# medication aided sleep	Zopiclone	Triazolam			P value
	multiple d ( )	multiple d ( )	( )	( )	NS
	% ( )				

### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Liu	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1997	<b>Country:</b> Taiwan	<b>Funding:</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 40.1  
Range: 20-58  
SD: 10.9  
**Gender:** 11 ( 73 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 15  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 15

**Eligibility criteria:**

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.

**Exclusion criteria:**

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abuse or drug abuse.

**Comments:**

Poor quality- baseline characteristics not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

**Intervention:**

**Run-in :** 0  
**Wash out :** 7  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	15	14 day	0 / 0
Triazolam	0.25 mg	15	14 day	0 / 0
Placebo	NA mg	15	14 day	0 / 0

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Liu	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1997	<b>Country:</b> Taiwan	<b>Funding:</b>

**Outcome Measurement:**

- # Spiegel's sleep questionnaire (SSQ)
- # Clinical Global Impression Scale (CGI)
- # Hamilton Anxiety Rating Scale
- # Leed's sleep evaluation questionnaire (LSEQ)

**Efficacy Outcome List:**

- |                          |                         |
|--------------------------|-------------------------|
| <b>Primary outcome</b>   | <b>Outcome:</b>         |
| <input type="checkbox"/> | therapeutic efficacy    |
| <input type="checkbox"/> | delay in falling asleep |
| <input type="checkbox"/> | quality of sleep        |
| <input type="checkbox"/> | length of sleep         |
| <input type="checkbox"/> | night waking            |
| <input type="checkbox"/> | dream                   |
| <input type="checkbox"/> | morning state           |
| <input type="checkbox"/> | global evaluation       |

**Results**

Clinical Global Impression Scale (CGI)

# therapeutic efficacy

Zopiclone	Triazolam			P value
NR ( <0.005 )	NR ( <0.005 )	( )	( )	NS
Score ( p vs baseline )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

Author: **Liu**      Trial type: **Active**      Quality rating: **Poor**  
 Year: **1997**      Country: **Taiwan**      Funding:

Spiegel's sleep questionnaire (SSQ)

# therapeutic efficacy

Zopiclone	Triazolam			P value
NR ( <0.005 )	NR ( <0.005 )	( )	( )	NS

Score ( p vs baseline )

# delay in falling asleep at day 14

Zopiclone	Triazolam			P value
3.94 ( 0.70 )	4.13 ( 0.64 )	( )	( )	NS

Score ( SD )

# quality of sleep at day 14

Zopiclone	Triazolam			P value
4.33 ( 0.62 )	3.47 ( 0.64 )	( )	( )	<0.05

Score ( SD )

# length of asleep at day 14

Zopiclone	Triazolam			P value
3.73 ( 0.70 )	3.53 ( 0.74 )	( )	( )	NS

Score ( SD )

# night waking at day 14

Zopiclone	Triazolam			P value
4.20 ( 0.68 )	3.33 ( 0.62 )	( )	( )	<0.05

Score ( SD )

# dream at day 14

Zopiclone	Triazolam			P value
3.93 ( 0.70 )	3.73 ( 1.03 )	( )	( )	NS

Score ( SD )

# morning state at day 14

Zopiclone	Triazolam			P value
3.93 ( 0.80 )	3.60 ( 0.91 )	( )	( )	NS

Score ( SD )

# global evaluation at day 14

Zopiclone	Triazolam			P value
4.13 ( 0.92 )	3.93 ( 0.96 )	( )	( )	NS

Score ( SD )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Liu    **Trial type:** Active    **Quality rating:** Poor  
**Year:** 1997    **Country:** Taiwan    **Funding:**

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Leed's sleep evaluation questionnaire (LSEQ)

# 2 out of 10 items shows more effectiveness in zopiclone: quality of sleep

Zopiclone	Triazolam			P value
NR ( )	NR ( )	( )	( )	<0.05
Score ( )	( )			

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Mamelak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 50  
 Range: 32-60  
 SD:  
**Gender:** 21 ( 70 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 30  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 30

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Ethanol-drug interaction study.

**Intervention:** Run-in : 2  
 Wash out : 3  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	10	12 day	0 / 0
Flurazepam	30 mg	10	12 day	1 / 1
Placebo	NA mg	10	12 day	0 / 0

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Mamelak      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1987      **Country:** Canada      **Funding:** Not reported

**Outcome Measurement:**

# sleep questionnaire

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- total sleep time
- sleep latency
- no. of awakenings
- duration of early wakefulness

**Results**

sleep questionnaire

# total sleep time at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
417.5 ( <0.05 )	410.5 ( <0.05 )	328.0 ( <0.05 )	( )	
minutes ( p vs baseline )				

# sleep latency at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
28.8 ( <0.05 )	31.5 ( <0.05 )	69.8 ( NS )	( )	
minutes ( p vs baseline )				

# no of awakenings at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
1.15 ( <0.05 )	1.55 ( <0.05 )	1.65 ( <0.05 )	( )	
Number ( p vs baseline )				

# duration of early wakefulness at day 14, the end of treatment

Zopiclone	Flurazepam	Placebo		P value
37.0 ( NS )	14.7 ( NS )	43.1 ( NS )	( )	
minutes ( p vs baseline )				

# all sleep itmes at day 14, the end of treatment

Zopiclone	Flurazepam			P value
as above ( )	as above ( )	( )	( )	NS
minutes ( )				



### Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b> Monti	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1994	<b>Country:</b> Uruguay	<b>Funding:</b> Not reported

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 47.3  
Range: 21-65  
SD:  
**Gender:** 21 ( 88 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 24  
Number Withdrawn: 1  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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 waketime >20 minutes; number of nocturnal awakenings >3.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 3  
Wash out : 3  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	10 mg	8	27 day	0	0
Triazolam	0.5 mg	8	27 day	1	1
Placebo	NA mg	8	27 day	0	0

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Monti                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1994                      **Country:** Uruguay                      **Funding:** Not reported

**Outcome Measurement:**

- # polysomnogram
- # sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - total sleep time
  - wake time after sleep onset
  - total waketime
  - number of awakenings

**Results**

polysomnogram

# wake time (change from baseline) - night 15-16	Zolpidem	Triazolam			P value
	-130 ( 135.9 )	-32 ( 36.10 )	( )	( )	NR
	minutes ( SD )				
# wake time (change from baseline) - night 29-30	Zolpidem	Triazolam			P value
	-117 ( 114.6 )	-39 ( 44.5 )	( )	( )	NR
	minutes ( SD )				
# total sleep time (change from baseline) - night 15-16	Zolpidem	Triazolam			P value
	127 ( 136.7 )	33 ( 35.8 )	( )	( )	NR
	minutes ( SD )				
# total sleep time (change from baseline) - night 29-30	Zolpidem	Triazolam			P value
	113 ( 116.2 )	41 ( 44.1 )	( )	( )	NR
	minutes ( SD )				
# number of sleep cycles (change from baseline) - night 4-5	Zolpidem	Triazolam			P value
	1.8 ( 2.1 )	0.3 ( 1.3 )	( )	( )	NR
	Number ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Monti                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1994                      **Country:** Uruguay                      **Funding:** Not reported

# number of sleep cycles (change from baseline) - night 15-16	Zolpidem	Triazolam			P value
	1.7 ( 2.0 )	0 ( 1 )	( )	( )	NR
	Number ( SD )				
# number of sleep cycles (change from baseline) - night 29-30	Zolpidem	Triazolam			P value
	1.2 ( 1.3 )	0.3 ( 1.5 )	( )	( )	NR
	Number ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b>	<b>Nair</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

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**Design:**

**Study design** RCT  
DB  
Parallel

**Setting** Single Center

**Age:** 46.9  
Range:  
SD: 1.4

**Gender:** 28 ( 47 % ) Female

**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60

Number Withdrawn:  
Lost to fu:  
Analyzed:

**Eligibility criteria:**

(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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** 1  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	3.75 mg	10	7 day	0 / 0
Zopiclone	7.5 mg	10	7 day	0 / 0
Zopiclone	11.2 mg	10	7 day	1 / 1
Zopiclone	15 mg	10	7 day	1 / 1
Flurazepam	30 mg	10	7 day	0 / 0
Placebo	NA mg	10	7 day	1 / 2

### Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Nair                              **Trial type:** Active                              **Quality rating:** Fair  
**Year:** 1990                              **Country:** Canada                              **Funding:** Rhone-Poulenc Pharma

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**Outcome Measurement:**

- # sleep questionnaire
- # clinical global impression (CGI)

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep induction time
  - quality of sleep
  - quality of morning awakening
  - hangover effects

**Results**

sleep questionnaire

# sleep induction time

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

# quality of sleep

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

# quality of morning awakening

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

# hangover effects (except zopiclone 3.75mg)

Zopiclone	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

# hangover effects (zopiclone 3.75mg only), (higher score=better)

Zopiclone	Flurazepam			P value
7 ( )	5.5 ( )	( )	( )	<0.05
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Nair                                      **Trial type:** Active                                      **Quality rating:** Fair  
**Year:** 1990    **Country:** Canada                                      **Funding:** Rhone-Poulenc Pharma

CGI

# Severity of illness (except Zopiclone 3.75mg)

Zopiclone	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

# Severity of illness (Zopiclone 3.75mg only)

Zopiclone	Flurazepam			P value
NR ( )	better ( )	( )	( )	NR

Score ( )

# global improvement

Zopiclone(any dose)	Flurazepam			P value
NR ( )	NR ( )	( )	( )	NS

Score ( )

## Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Ngen</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Malaysia</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 38.4  
Range:  
SD:  
**Gender:** 31 ( 52 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 44

**Eligibility criteria:**

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

**Exclusion criteria:**

(a) serious concomitant disease, (b) likely to require concomitant medication known to cause drwosiness, (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

**Comments:**

**Intervention:** Run-in : 7  
Wash out : NR  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	20	14 day	2 / 7
Temazepam	20 mg	20	14 day	0 / 7
Placebo	NA mg	20	14 day	1 / 10

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Ngen                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                      **Country:** Malaysia                      **Funding:** Rhone-Poulenc Pharma

**Outcome Measurement:**

- # sleep diary
- # global assessment efficacy

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - no. of times of awakening
  - total duration sleep

**Results**

sleep diary

# total duration of sleep at treatment week 1	Zopiclone	Temazepam			P value
	5.97 ( <0.01 )	5.90 ( <0.05 )	( )	( )	
	hours ( p vs baseline )				
# total duration of sleep at treatment week 2	Zopiclone	Temazepam			P value
	6.03 ( <0.01 )	5.62 ( NS )	( )	( )	
	hours ( p vs baseline )				
# sleep latency at treatment week 1	Zopiclone	Temazepam			P value
	84 ( <0.05 )	25.9 ( <0.05 )	( )	( )	
	Minutes ( p vs baseline )				
# sleep latency at treatment week 2	Zopiclone	Temazepam			P value
	64.5 ( <0.05 )	26.1 ( NS )	( )	( )	
	Minutes ( p vs baseline )				
# no. of awakenings at treatment week 1	Zopiclone	Temazepam			P value
	0.77 ( NS )	1.2 ( <0.05 )	( )	( )	
	Number ( p vs baseline )				
# no. of awakenings at treatment week 2	Zopiclone	Temazepam			P value
	0.62 ( <0.05 )	1.28 ( NS )	( )	( )	
	Number ( p vs baseline )				



### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Ngen	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Malaysia	<b>Funding:</b> Rhone-Poulenc Pharma

global assessmnet efficacy

# efficacy- good response

Zopiclone	Temazepam			P value
10 ( <0.02 )	12 ( <0.01 )	( )	( )	NS
Number ( p vs placebo	)			

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Ponciano</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Portugal</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 30  
Range: 18-60  
SD: 9  
**Gender:** 12 ( 46 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 26  
Number Withdrawn: 2  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

**Intervention:**  
**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	8	21 day	0 / 0
Flurazepam	30 mg	8	21 day	0 / 0
Placebo	NA mg	10	21 day	1 / 2

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Ponciano                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** Portugal                      **Funding:** Not reported

**Outcome Measurement:**

- # Leeds sleep evaluation questionnaire (LSEQ)
- # visual analogue rating scale
- # clinical interview

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- the ease of getting to sleep
  - quality of sleep
  - ease of awakening
  - integrity of daytime behavior
  - mood changes
  - sleep onset
  - sleep duration time

**Results**

clinical interview

# sleep onset latency at day 21

Zopiclone	Flurazepam	Placebo		P value
30 ( 0.02 )	28 ( 0.04 )	60 ( NA )	( )	
minutes ( p vs placebo )				

# sleep duration

Zopiclone	Flurazepam	Placebo		P value
393 ( NS )	425 ( 0.05 )	410 ( NA )	( )	
minutes ( p vs placebo )				

visual analogue rating scale

# mood changes

Zopiclone	Flurazepam	Placebo		P value
NR ( )	NR ( )	NR ( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Quadens                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1983                              **Country:** Belgium                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** NR  
 Range: 50-59  
 SD:  
**Gender:** 12 ( 100 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 12  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 12

**Eligibility criteria:**

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

**Exclusion criteria:**

(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.

**Comments:**

Poor quality- insufficient information to assess quality.

**Intervention:**

**Run-in :** 6  
**Wash out :** 35  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	/

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Quadens      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 1983      **Country:** Belgium      **Funding:** Not reported

**Outcome Measurement:**

# sleep questionnaire

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- no. of awakenings
- total sleep time
- sleep onset latency
- sleep efficiency index

**Results**

sleep questionnaire

# no. of awakenings

Zopiclone	Flurazepam	Placebo		P value
3.2 ( <0.05 )	1.9 ( <0.05 )	6 ( NA )	( )	
Number ( p vs placebo )				

# total sleep time

Zopiclone	Flurazepam	Placebo		P value
24903 ( <0.01 )	25129 ( <0.05 )	23225 ( NA )	( )	
seconds ( p vs placebo )				

# sleep onset latency

Zopiclone	Flurazepam	Placebo		P value
1117 ( <0.05 )	1174 ( <0.1 )	1452 ( NA )	( )	
seconds ( p vs placebo )				

# sleep efficiency index

Zopiclone	Flurazepam	Placebo		P value
91.4 ( <0.01 )	92.2 ( <0.05 )	83.6 ( NA )	( )	
Score ( p vs placebo )				

# All sleep items comparing two treatment

Zopiclone	Flurazepam			P value
as above ( )	as above ( )	( )	( )	NS
Number ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Rosenberg</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Denmark</b>	<b>Funding:</b>	<b>Synthelabo Scandinavia A/S</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 54  
Range: 25-79  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 178  
Number Withdrawn: 5  
Lost to fu: 34  
Analyzed: 139

**Eligibility criteria:**

Patients between 18-80 years old, have had insomnia for at least 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.

**Exclusion criteria:**

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

**Comments:**

Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; 31% male.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	71	14 day	/
Triazolam	0.25 mg	68	14 day	/

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Rosenberg      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 1994      **Country:** Denmark      **Funding:** Synthelabo Scandinavia A/S

**Outcome Measurement:**

- # reported by patients
- # visual analogue scales

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- duration of sleep
  - no. of nocturnal awakenings
  - sleep quality
  - day quality

**Results**

reported by patients

# total sleep times

Zolpidem	Triazolam			P value
6.9 ( 4.8-9.1 )	7.1 ( 5.0-8.4 )	( )	( )	NS
hours	( range )			

# No. of awakenings

Zolpidem	Triazolam			P value
1 ( 0-4 )	1 ( 0-5 )	( )	( )	NS
Number	( range )			

### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Rosenberg	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1994	<b>Country:</b> Denmark	<b>Funding:</b> Synthelabo Scandinavia A/S

visual analogue scales

# sleep quality, bad-good

Zolpidem	Triazolam			P value
69 ( 15-96 )	69 ( 18-98 )	( )	( )	NS
Score ( Range )				

# morning feeling, bad-good

Zolpidem	Triazolam			P value
64 ( 8-94 )	56 ( 9-98 )	( )	( )	NS
Score ( Range )				

# daytime alertness. unalert-alert

Zolpidem	Triazolam			P value
65 ( 6-92 )	63 ( 26-92 )	( )	( )	NS
Score ( Range )				

# subjective day feeling

Zolpidem	Triazolam			P value
64 ( 6-93 )	60 ( 9-92 )	( )	( )	NS
Score ( Range )				



Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 33.6  
Range: NR  
SD: 10.4  
**Gender:** 12 ( 55 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 22  
Number Withdrawn: 0  
Lost to fu: 2  
Analyzed: 20

**Eligibility criteria:**

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 of awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

**Exclusion criteria:**

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 (myoclones, kinaesthesia 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.

**Comments:**

**Intervention:** Run-in : 3  
Wash out : No  
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	10	2 week	0 / 0
Triazolam	0.25 mg	12	2 week	0 / 2

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Silvestri      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1996      **Country:** Italy      **Funding:** Not reported

**Outcome Measurement:**

- # polysomnography
- # visual analogue scale
- # questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- total sleep time
  - sleep onset latency
  - sleep efficiency
  - no. of awakenings
  - wake time after sleep onset
  - REM sleep
  - quiet-disturbed sleep
  - alert-drowsy awakening

**Results**

polysomnography

# sleep onset latency- change from baseline- night 14

Zolpidem	Triazolam			P value
-23 ( 21.38 )	-14.8 ( 30.92 )	( )	( )	NS
minutes ( SD )				

# total sleep time- change from baseline- night 14

Zolpidem	Triazolam			P value
61.1 ( 43.97 )	54.4 ( 49.70 )	( )	( )	NS
minutes ( SD )				

# sleep efficiency- change from baseline- night 14

Zolpidem	Triazolam			P value
14.3 ( 10.39 )	10.7 ( 7.35 )	( )	( )	NS
% ( SD )				

# wake time after sleep onset- change from baseline- night 14

Zolpidem	Triazolam			P value
-44.9 ( 44.82 )	-37 ( 25.62 )	( )	( )	NS
minutes ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Silvestri      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1996      **Country:** Italy      **Funding:** Not reported

# no. of awakenings- change from baseline- night 14

Zolpidem	Triazolam			P value
-2.2 ( 3.51 )	-3.5 ( 2.45 )	( )	( )	NS
Number ( SD )				

questionnaire

# time to fall asleep- change from baseline- night 14

Zolpidem	Triazolam			P value
-41.8 ( 32.51 )	-19.9 ( 36.83 )	( )	( )	NS
minutes ( SD )				

# total sleep time- change from baseline- night 14

Zolpidem	Triazolam			P value
66.9 ( 44.53 )	81.4 ( 46.9 )	( )	( )	NS
minutes ( SD )				

# total wake time- change from baseline- night 14

Zolpidem	Triazolam			P value
-12.1 ( 9.88 )	-11.4 ( 8.53 )	( )	( )	NS
minutes ( SD )				

# no. of nocturnal awakenings- change from baseline- night 14

Zolpidem	Triazolam			P value
-1.4 ( 0.75 )	-1.2 ( 1.63 )	( )	( )	NS
Number ( SD )				

visual analogue scale

# sleep quality- change from baseline- night 14

Zolpidem	Triazolam			P value
-22.8 ( 17.90 )	-31.8 ( 20.66 )	( )	( )	NS
Score ( SD )				

# awakening quality- change from baseline- night 14

Zolpidem	Triazolam			P value
-16.3 ( 18.14 )	-26.9 ( 23.32 )	( )	( )	NS
Score ( SD )				

## Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b> Singh	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Rhone-Poulenc Pharma Inc.

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 39.6  
Range: 19-64  
SD: 1.5  
**Gender:** 32 ( 53 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 61  
Enrolled: 60  
Number Withdrawn: 3  
Lost to fu: 0  
Analyzed: 57

**Eligibility criteria:**  
NR

**Exclusion criteria:**

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.

**Comments:**

Two patients were taking a benzodiazepine hypnotic medication at time of recruitment and they both fulfilled the inclusion criteria after a 4-day minimum washout period. The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?)

**Intervention:**

**Run-in :** 4  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg		24 day	0 / 0
Zopiclone	11.2 mg		24 day	1 / 2
Flurazepam	30 mg		24 day	0 / 1

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Singh      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Rhone-Poulenc Pharma Inc.

**Outcome Measurement:**

- # post-sleep questionnaire
- # clinical global impression (CGI)

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- duration of sleep onset
  - sleep soundness
  - quality of sleep

**Results**

post-sleep questionnaire

# duration of sleep onset at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
6.7 ( <0.01 )	6.9 ( <0.01 )	7.5 ( <0.01 )	( )	
Score ( p vs placebo )				

# sleep soundness at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
6.7 ( <0.01 )	6.6 ( <0.01 )	7.5 ( <0.01 )	( )	
Score ( p vs placebo )				

# quality of sleep at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
11.2 ( <0.01 )	11.0 ( <0.01 )	12.2 ( <0.01 )	( )	
Score ( p vs placebo )				

# duration of sleep onset, sleep soundness, quality of sleep at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
as above ( NS )	as above ( NS )	as above ( NA )	( )	
Score ( p vs flurazepam )				

CGI

# therapeutic index (less score=worse) at week 4

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value
3.2 ( )	3 ( )	2.5 ( )	( )	<0.05
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Stip	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 42.6  
Range:  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn: 2  
Lost to fu: 8  
Analyzed: 50

**Eligibility criteria:**

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.

**Exclusion criteria:**  
NR

**Comments:**

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week.  
Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

**Intervention:** Run-in : 7  
Wash out : 7  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	19	21 day	0 / 0
Temazepam	30 mg	16	21 day	0 / 1
Placebo	NA mg	15	21 day	0 / 1

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Stip                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1999                      **Country:** Canada                      **Funding:** Not reported

**Outcome Measurement:**

- # Hamilton scale for anxiety
- # Self-rating questionnaire for sleep
- # auditory and visual span test

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- anxiety
  - quality of sleep
  - sleep onset
  - sleep depth
  - wakefulness and attention

**Results**

Hamilton scale for anxiety

# anxiety

Zopiclone	Temazepam	Placebo		P value
NR ( )	NR ( )	NR ( )	( )	NS
Score ( )				

Self-rating questionnaire for sleep

# sleep onset at treatment week 1

Zopiclone	Temazepam			P value
NR (<0.01 )	NR (<0.01 )	( )	( )	
Score ( p vs placebo )				

# sleep depth at treatment week 1

Zopiclone	Temazepam			P value
NR (<0.01 )	NR (<0.01 )	( )	( )	
Score ( p vs placebo )				

auditory and visual span test

# alertness over all 5 weeks

Zopiclone	Nitrazepam	Placebo		P value
multiple d ( )	multiple d ( )	multiple ( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Tamminen	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1987	<b>Country:</b> Finland	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 47  
Range: 26-71  
SD:  
**Gender:** 72 ( 77 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 130  
Enrolled: 94  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 94

**Eligibility criteria:**

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, noctural awakenings >2 per night, time to fall asleep after at least one noctural awakening >30min, awakening >2hour before scheduled time.

**Exclusion criteria:**

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causeing 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.

**Comments:**

Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

**Intervention:**

**Run-in :** 7  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	52	42 day	3 / 3
Nitrazepam	5 mg	46	42 day	1 / 1



### Evidence Table 4. Active controlled trials (Adults): Efficacy

<b>Author:</b> Tamminen	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1987	<b>Country:</b> Finland	<b>Funding:</b> Not reported

**Outcome Measurement:**

- # diary
- # sleep questionnaire
- # global evaluation
- # Norris Mood Rating

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep onset latency
  - sleep quality
  - night awakenings
  - duration of sleep

**Results**

diary

# sleep onset latency, mean score

Zopiclone	Nitrazepam			P value
32.6 ( )	33.1 ( )	( )	( )	NS
Score ( )				

# quality of sleep, mean score

Zopiclone	Nitrazepam			P value
34 ( )	30.2 ( )	( )	( )	
Score ( )				

global evaluation

# efficacy (1=poor; 5=excellent)

Zopiclone	Nitrazepam			P value
3.2 ( )	3.1 ( )	( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Tamminen      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 1987      **Country:** Finland      **Funding:** Not reported

sleep questionnaire

# latency of sleep onset >30 min

Zopiclone	Nitrazepam			P value
38 ( )	44.4 ( )	( )	( )	0.07
% ( )				

# duration of sleep <6.5 hours

Zopiclone	Nitrazepam			P value
37.5 ( )	37.7 ( )	( )	( )	NS
% ( )				

# >2 night awakenings

Zopiclone	Nitrazepam			P value
18.4 ( )	24.4 ( )	( )	( )	NS
% ( )				

# time to fall asleep after a night awakenings >30 min

Zopiclone	Nitrazepam			P value
14.6 ( )	22.2 ( )	( )	( )	NS
% ( )				

# awakening at least 2 hours before expected time

Zopiclone	Nitrazepam			P value
20.4 ( )	20 ( )	( )	( )	NS
% ( )				

Norris Mood Rating

# overall

Zopiclone	Nitrazepam			P value
- ( )	better ( )	( )	( )	<0.05
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** NR

**Age:** 53  
 Range: 28-69  
 SD:  
**Gender:** 39 ( 71 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: 60  
 Enrolled: 55  
 Number Withdrawn: 2  
 Lost to fu: 0  
 Analyzed: 53

**Eligibility criteria:**

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

**Exclusion criteria:**

1. Patients taking a non-benzodiazapine hypnotic prior to the studym 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 benzodiazapine tranquilizers 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

**Comments:**

**Intervention:** Run-in : 2  
 Wash out : 7  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	53	5 day	1 / 1
Temazepam	20 mg	53	5 day	1 / 1

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

**Outcome Measurement:**

# Questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep quality
  - Latency of sleep onset
  - Status after awaking

**Results**

Questionnaire in the morning about sleep

# Sleep quality - average score

Zopiclone	Temazepam			P value
3.9 ( 0.2 )	3.9 ( 0.21 )	( )	( )	0.096
Score ( SD )				

# Sleep quality - average score

Zopiclone	Placebo			P value
3.9 ( 0.2 )	3.4 ( 0.21 )	( )	( )	<0.001
Score ( SD )				

# Latency of sleep onset - average score

Zopiclone	Temazepam			P value
3.8 ( 0.2 )	3.7 ( 0.2 )	( )	( )	0.106
Score ( SD )				

# Latency of sleep onset - average score

Zopiclone	Placebo			P value
3.8 ( 0.2 )	3.1 ( 0.22 )	( )	( )	<0.01
Score ( SD )				

# Status after awaking - average score

Zopiclone	Temazepam			P value
3.5 ( 0.19 )	3.4 ( 0.18 )	( )	( )	0.45
Score ( SD )				

# Status after awaking - average score

Zopiclone	Placebo			P value
3.5 ( 0.19 )	3.2 ( 0.19 )	( )	( )	<0.01
Score ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

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Preference

# Sleep better

Zopiclone	Temazepam	Placebo	Z and T	P value
16 ( )	10 ( )	6 ( )	2 ( )	NR

Number ( )

# Better status during the day

Zopiclone	Temazepam	Placebo	Z and T	P value
29 ( )	23 ( )	0 ( )	0 ( )	NR

Number ( )

# Preferred drug to continue

Zopiclone	Temazepam	Placebo	Z and T	P value
8 ( )	3 ( )	5 ( )	2 ( )	NR

( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Voshaar                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** Netherlands                      **Funding:** Sanfi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 46.1  
 Range:  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 221  
 Number Withdrawn: 9  
 Lost to fu: 5  
 Analyzed: 159

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

**Intervention:** Run-in : NR  
 Wash out : 4  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	74	28 day	N / NR
Temazepam	20 mg	85	28 day	N / NR

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Voshaar      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 2004      **Country:** Netherlands      **Funding:** Sanfi-Synthelabo

**Outcome Measurement:**

- # sleep/wake diary
- # SWEL self-report questionnaires
- # State-Trait-Anxiety-Inventory version DY-1

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Total sleep time (TST)
  - Sleep onset latency (SOL)
  - Wake time after sleep onset (WASO)
  - Time in bed (TIB)

**Results**

Sleep/wake diaries

# total sleep time

Zolpidem	Temazepam			P value
413 ( 78 )	386 ( 82 )	( )	( )	NS
minutes ( SD )				

# sleep onset latency

Zolpidem	Temazepam			P value
46 ( 33 )	46 ( 34 )	( )	( )	NS
minutes ( SD )				

# wake time after sleep

Zolpidem	Temazepam			P value
40 ( 36 )	39 ( 38 )	( )	( )	NS
minutes ( SD )				

# time in bed

Zolpidem	Temazepam			P value
530 ( 77 )	508 ( 58 )	( )	( )	NS
minutes ( SD )				

# SWEL total score

Zolpidem	Temazepam			P value
35.7 ( 7.7 )	35.8 ( 9.2 )	( )	( )	NS
Score ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Voshaar                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** Netherlands                      **Funding:** Sanfi-Synthelabo

# STAI-DY-1 sum score

Zolpidem	Temazepam			P value
41.6 ( 12 )	39 ( 10.7 )	( )	( )	NS
Score ( SD )				



## Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b> Walsh	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1998a	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

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### Design:

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 21-65  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: 589  
Enrolled: 306  
Number Withdrawn: 28  
Lost to fu: 0  
Analyzed: 278

### Eligibility criteria:

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.

### Exclusion criteria:

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.

### Comments:

Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

### Intervention:

**Run-in :** 7  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	102	14 day	5 / 11
Trazodone	50 mg	100	14 day	5 / 10
Placebo	NA mg	104	14 day	2 / 7

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998a                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # morning questionnaire
- # patients global impressions
- # Sheehan Disability Scale
- # 100mm visual analog scales

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep duration
  - ease of falling asleep
  - number of awakenings
  - wake time after sleep onset
  - quality of sleep
  - morning sleepiness
  - ability to concentrate in the morning
  - disruption caused by insomnia
  - social life or family life

**Results**

morning questionnaire and 100mm visual analog scales

# sleep latency at week 1	Zolpidem	Trazodone			P value
	48.2 ( 2.7 )	57.7 ( 4.0 )	( )	( )	<0.037
	minutes ( SD )				
# sleep latency at week 2	Zolpidem	Trazodone			P value
	48.1 ( 3.1 )	54.5 ( 4.1 )	( )	( )	NS
	minutes ( SD )				
# sleep duration at week 1	Zolpidem	Trazodone			P value
	378.8 ( 5.3 )	366.4 ( 6.4 )	( )	( )	NR
	minutes ( SD )				
# sleep duration at week 2	Zolpidem	Trazodone			P value
	NR ( NR )	NR ( NR )	( )	( )	NS
	minutes ( SD )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1998a      **Country:** US      **Funding:** Lorex Pharmaceuticals

# ease of falling asleep at week 2	Zolpidem	Trazodone			P value
	44.3 ( 1.8 )	44.0 ( 2.3 )	( )	( )	NS
Score ( SD )					
# number of awakenings at week 2	Zolpidem	Trazodone			P value
	1.5 ( 0.2 )	1.4 ( 0.1 )	( )	( )	NS
minutes ( SD )					
# subjective waking time after sleep onset at week 2	Zolpidem	Trazodone			P value
	39.5 ( 3.6 )	42.1 ( 4.3 )	( )	( )	NS
minutes ( SD )					
# sleep quality at week 2	Zolpidem	Trazodone			P value
	2.45 ( 0.05 )	2.43 ( 0.07 )	( )	( )	NS
minutes ( SD )					
<u>patients global impressions</u>					
# sleep status (excellent and good) at week 2	Zolpidem	Trazodone			P value
	49 ( 53.8 )	47 ( 52.2 )	( )	( )	NS
Number ( % )					
# sleep improvement (a lot and somewhat) at week 2	Zolpidem	Trazodone			P value
	60 ( 66 )	62 ( 68.8 )	( )	( )	NS
Number ( % )					
# time to fall asleep (shortened a lot and shortened somewhat) at week 2	Zolpidem	Trazodone			P value
	56 ( 61.5 )	50 ( 55.5 )	( )	( )	NS
Number ( % )					
# sleep time (increased a lot and increased somewhat) at week 2	Zolpidem	Trazodone			P value
	56 ( 61.5 )	61 ( 67.8 )	( )	( )	NS
Number ( % )					

Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Walsh                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998a                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

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Sheehan Disability Scale

# overall

Zolpidem	Trazodone			P value
NR ( )	NR ( )	( )	( )	NS
Score ( )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_                      **Trial type:** Active                      **Quality rating:** Good  
**Year:** 1998b                      **Country:** US                      **Funding:** Wyeth Ayerst

**Design:**

**Study design**

DB  
 Parallel

**Setting**

**Eligibility criteria:**

Patients with a DSM-III-R 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).

**Comments:**

day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

**Intervention:**

**Run-in :** 3  
**Wash out :** 2  
**Allow other medication :** NR

**Age:**

40.3  
 Range: 18-60  
 SD:

**Gender:** 77 ( 58 % ) Female

**Ethnicity:** NR

Number Screened: 673  
 Eligible: 456  
 Enrolled: 132

Number Withdrawn: 7  
 Lost to fu: 0  
 Analyzed: 125

**Exclusion criteria:**

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 zaleplone, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	34	14 day	1 / 3
Zaleplon	10 mg	33	33 day	0 / 1
Triazolam	0.25 mg	31	14 day	0 / 0
Placebo	NA mg	34	14 day	0 / 3

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_                      **Trial type:** Active                      **Quality rating:** Good  
**Year:** 1998b                      **Country:** US                      **Funding:** Wyeth Ayerst

**Outcome Measurement:**

- # Polysomnography
- # Sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Total sleep time
  - Sleep duration
  - No. of awakenings
  - % of total sleep time spent in each sleep st

**Results**

Polysomnography

# Total sleep time day 4-5 and day 16-17, minutes	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	413.6 ( 18 )	402 ( 396.8 )	400 ( 411.3 )	( )	NS
during ( after )					
# Total sleep time- day 4-5	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	413.6 ( <0.001 )	402 ( 0.014 )	431 ( NA )	400 ( <0.001 )	
Minute ( p vs triazolam )					
# Total sleep time- day 16-17	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	418 ( 0.63 )	396.8 ( 0.22 )	420 ( NA )	411.3 ( 0.35 )	
Minute ( p vs triazolam )					
# Latency to persistent sleep- day 4-5	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	17 ( 0.019 )	19.25 ( 0.039 )	18.5 ( NR )	25.38 ( NA )	
Minute ( p vs placebo )					
# Latency to persistent sleep- day 16-17	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	18 ( 0.019 )	16.75 ( 0.039 )	23.75 ( NR )	20.5 ( NA )	
Minute ( p vs placebo )					

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_      **Trial type:** Active      **Quality rating:** Good  
**Year:** 1998b      **Country:** US      **Funding:** Wyeth Ayerst

# No. of awakenings- day 4-5 and day 16-17	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( )	NR ( )	NR ( )	NR ( )	NS
Number ( )					
# % of total sleep time spent in each sleep stage- day 4-5 and day 16-17	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( )	NR ( )	NR ( )	NR ( )	NS
Number ( )					
# Latency to persistent sleep- day 16-17	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	416.5 ( NS )	400 ( NS )	406.75 ( NS )	408.5 ( NA )	NS
Minute ( p vs placebo )					

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_      **Trial type:** Active      **Quality rating:** Good  
**Year:** 1998b      **Country:** US      **Funding:** Wyeth Ayerst

Sleep questionnaire

# Subjective sleep latency- day 4-5, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	shorter ( 0.003 )	shorter ( 0.056 )	shorter ( 0.015 )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective sleep latency- day 6-14, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	shorter ( 0.67 )	shorter ( 0.03 )	shorter ( 0.168 )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective total sleep time- day 1-2, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( NS )	NR ( NS )	NR ( <0.00 )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective total sleep time- day 3-19, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( NS )	NR ( NS )	NR ( NS )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective no. of awakenings- day 6-14, number	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( NS )	NR ( NS )	NR ( 0.046 )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective sleep latency after discontinuation night, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( NS )	NR ( NS )	longer ( 0.036 )	NR ( NA )	
vs placebo ( p vs placebo )					
# Subjective total sleep time after discontinuation night, score	Zaleplon 5mg	Zaleplon 10mg	Triazolam 0.25mg	Placebo	P value
	NR ( NS )	NR ( NS )	shorter ( 0.022 )	NR ( NA )	
vs placebo ( p vs placebo )					



Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_\_                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 2000                              **Country:** US                              **Funding:** Wyeth-Ayerst Research

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** 42  
 Range: 22-49  
 SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: 73  
 Eligible: 39  
 Enrolled: 30  
 Number Withdrawn: 2  
 Lost to fu: 0  
 Analyzed: 22

**Eligibility criteria:**

Men and women with sleep maintenance insomnia, 18 to 60 years of age.

**Exclusion criteria:**

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, previous exposure to zaleplon, benzodiazepine sensitivity, use of another investigational drug, psychotropic medication, tryptophan, or melatoanthistamine in the past week, or use of medications that would interfere with the absorption or metabolism of the study drugs.

**Comments:**

The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were analyzed, 11 men; mean age, 42 y; range, 22-49.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10 mg	22	2 day	/
Flurazepam	30 mg	22	2 day	/
Placebo	NA mg	22	2 day	/

### Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_\_      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

**Outcome Measurement:**

- # sleep latency testing
- # sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep latency
  - Number of minutes sleep

**Results**

Sleep latency testing

# 5 hours after drug administration, score

Zaleplon					P value
16.6	( 20.0 )	( )	( )	( )	0.071
Mean	( Median	)			

# 5 hours after drug administration, score

Flurazepam					P value
6.8	( 5.5 )	( )	( )	( )	<0.001
Mean	( Median	)			

# 5 hours after drug administration, score

Flurazepam					P value
6.8	( 5.5 )	( )	( )	( )	<0.001
Mean	( Median	)			

# 6.5 hours after drug administration, score

Zaleplon					P value
14.7	( 15.5 )	( )	( )	( )	0.111
Mean	( Median	)			

# 6.5 hours after drug administration, score

Flurazepam					P value
5.6	( 4.3 )	( )	( )	( )	<0.001
Mean	( Median	)			

# 6.5 hours after drug administration, score

Flurazepam					P value
5.6	( 4.3 )	( )	( )	( )	<0.001
Mean	( Median	)			

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Walsh\_\_      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 2000      **Country:** US      **Funding:** Wyeth-Ayerst Research

sleep questionnaire

# time to sleep (minute)

Zaleplon	Flurazepam			P value
27.5 ( )	22.5 ( )	( )	( )	NR

Median ( )

# number of minutes sleep

Zaleplon				P value
195 ( )	( )	( )	( )	NR

Median ( )

# number of minutes sleep

Flurazepam				P value
206.3 ( )	( )	( )	( )	<0.01

Median ( )

# number of minutes sleep

Flurazepam				P value
206.3 ( )	( )	( )	( )	<0.05

Median ( )

Evidence Table 4. Active controlled trials (Adults): Efficacy

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<b>Author:</b> Ware	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1997	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

---

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 21-55  
SD:  
**Gender:** 64 ( 58 % ) Female  
**Ethnicity:** 69% white

Number Screened: 358  
Eligible: NR  
Enrolled: 110  
Number Withdrawn: 11  
Lost to fu: NR  
Analyzed: 99

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

**Intervention:**

**Run-in :** 2  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	37	28 day	3 / NR
Triazolam	0.5 mg	30	28 day	4 / NR
Placebo	NA mg	35	28 day	0 / NR

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Ware                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # polysomnography
- # evening questionnaire
- # drug effects questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep Latency
  - Sleep Efficiency
  - no. of awakenings
  - waking time during sleep
  - wake time after sleep
  - % of time spent in REM and deep sleep
  - quality of sleep
  - morning sleepiness
  - ability to concentrate

**Results**

polysomnography

# latency to persistent sleep- night 27 & 28	Zolpidem -7 ( NS )	Triazolam 0 ( NS )	Placebo -15 ( <0.05 )	( )	P value
	minutes ( p vs baseline )				
# sleep efficiency- night 27 & 28	Zolpidem 1 ( NS )	Triazolam 3 ( <0.05 )	Placebo 5 ( <0.05 )	( )	P value
	% ( p vs baseline )				
# no. of awakenings- night 27 & 28	Zolpidem 1 ( NS )	Triazolam -2 ( <0.05 )	Placebo -1 ( NS )	( )	P value
	Number ( p vs baseline )				
# waking time during sleep	Zolpidem 0 ( NS )	Triazolam -20 ( <0.05 )	Placebo 2 ( NS )	( )	P value
	minutes ( p vs baseline )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

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**Author:** Wheatley                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1985                              **Country:** NR                              **Funding:** Not reported

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**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** NR

**Age:** 53.2  
 Range: 25-82  
 SD: 2.1  
**Gender:** 22 ( 61 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 36  
 Number Withdrawn: 2  
 Lost to fu: 0  
 Analyzed: 36

**Eligibility criteria:**

Patients aged 18 years and over suffering from difficulty in sleeping, provided that symptoms had been present for at least one week.

**Exclusion criteria:**

NR

**Comments:**

zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

**Intervention:**

**Run-in :** 3  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	36	7 day	2 / 2
Temazepam	20 mg	36	7 day	0 / 0

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Wheatley      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1985      **Country:** NR      **Funding:** Not reported

**Outcome Measurement:**

# Patient Questionnaires

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- Sleep latency
- No. time waking
- Quality of sleep
- Duration of sleep
- Dreaming
- State on waking

**Results**

Patient Questionnaires

# Sleep latency

Zopiclone	Placebo			P value
30.8 ( <0.01 )	29.1 ( <0.01 )	( )	( )	
Minutes ( p vs baseline )				

# No. time waking

Zopiclone	Temazepam			P value
0.75 ( <0.01 )	0.66 ( <0.01 )	( )	( )	
Number ( p vs baseline )				

# Quality of sleep (0-4)

Zopiclone	Temazepam			P value
0.93 ( <0.01 )	0.87 ( <0.01 )	( )	( )	
Score ( p vs baseline )				

# Duration of sleep

Zopiclone	Temazepam			P value
6.6 ( <0.01 )	6.6 ( <0.01 )	( )	( )	
Hours ( p vs baseline )				

# Dreaming (0-4)

Zopiclone	Temazepam			P value
0.46 ( NS )	0.46 ( NS )	( )	( )	
Score ( p vs baseline )				

Evidence Table 4. Active controlled trials (Adults): Efficacy

**Author:** Wheatley      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1985      **Country:** NR      **Funding:** Not reported

# State on waking (0-3)	Zopiclone	Temazepam			P value
	0.39 ( NS )	0.38 ( NS )	( )	( )	
Score ( p vs baseline )					
# At work (0-3)	Zopiclone	Temazepam			P value
	0.51 ( <0.05 )	0.54 ( NS )	( )	( )	
Score ( p vs baseline )					
# With others (0-3)	Zopiclone	Temazepam			P value
	0.63 ( NS )	0.67 ( NS )	( )	( )	
Score ( p vs baseline )					
# Driving (0-3)	Zopiclone	Temazepam			P value
	0.35 ( NS )	0.57 ( NS )	( )	( )	
Score ( p vs baseline )					
# All measures	Zopiclone	Temazepam			P value
	as above ( )	as above ( )	( )	( )	NS
( )					



Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 37.6  
Range:  
SD: 1.84  
**Gender:** 24 ( 67 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 36  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 36

**Eligibility criteria:**

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,

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	28 day	0 / 0
Flurazepam	30 mg	12	28 day	0 / 0
Placebo	NA mg	12	28 day	0 / 0

**Rebound:**

post-sleep questionnaire

# rebound: rapidity of sleep onset at day 29 (higher score=better)	Zopiclone	Flurazepam	Placebo		P value
	5.8 ( NS )	7.3 ( NS )	10 ( <0.01 )	( )	
	Score ( p vs baseline )				
# rebound: duration of sleep at day 29 (higher score=better)	Zopiclone	Flurazepam	Placebo		P value
	3.6 ( NS )	6.2 ( NS )	7.3 ( <0.05 )	( )	
	Score ( p vs baseline )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Elie</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990b</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

# rebound: nocturnal awakenings at day 29 (higher score=worse)

Zopiclone	Flurazepam	Placebo		P value
5.0 ( NS )	6.3 ( NS )	8.0 ( NS )	( )	
Score ( p vs baseline )				

### Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Fleming_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 45.5  
Range:  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 52  
Number Withdrawn: 4  
Lost to fu: 0  
Analyzed: 48

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, analgesis, 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.

**Comments:**

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

**Rebound:**

post-sleep questionnaire

# rebound: sleep duration at the last withdrawal day	Zopiclone	Triazolam			P value
	4.3 ( )	5.9 ( )	( )	( )	<0.05
	Score ( )				
# rebound: sleep induction at the last withdrawal day	Zopiclone	Triazolam			P value
	4.7 ( )	6.1 ( )	( )	( )	NS
	Score ( )				

## Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Fleming\_      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Not reported

# rebound: sleep soundness at the last withdrawal day	Zopiclone	Triazolam			P value
	7.4 ( )	8.6 ( )	( )	( )	NS
	Score ( )				
<u>withdrawal effects</u>					
# rebound insomnia	Zopiclone	Triazolam			P value
	73 ( )	71 ( )	( )	( )	NS
	% ( )				
# rebound: sleep induction, duration and soundness at the first withdrawal nights	Zopiclone	Triazolam			P value
	NR ( NS )	NR, wor ( <0.05 )	( )	( )	
	Score ( p vs baseline )				
# rebound: sleep soundness	Zopiclone	Triazolam			P value
	NR ( )	NR, bett ( )	( )	( )	<0.05
	Score ( )				
# rebound: withdrawal symptoms	Zopiclone	Triazolam			P value
	3 ( )	2 ( )	( )	( )	NS
	Number ( )				

### Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Hajak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998, 1995, 1994</b>	<b>Country:</b>	<b>Germany</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 51  
Range: 18-71  
SD: 11  
**Gender:** 940 ( 62 % ) Female  
**Ethnicity:** 99.3% Caucasian  
0.9% Others

Number Screened: NR  
Eligible: NR  
Enrolled: 1507  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 1507

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Patients were observed for a further period of 14 days without medication for rebound.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	612	28 day	26 / 190
Triazolam	0.2 mg	307	28 day	11 / 187
Placebo	NA mg	298	28 day	25 / 193

**Rebound:**

Total response

# rebound: Improved sleep quality and daytime well-being	Zopiclone	Triazolam			P value
	27.0 ( )	18.8 ( )	( )	( )	0.00126
	% ( )	( )			

Rebound rates in treatment responders

# overall rebound	Zopiclone	Triazolam			P value
	46.07 ( 1.42 )	46.63 ( 1.93 )	( )	( )	NS
	% ( SD	( )			

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Hajak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998, 1995, 1994              **Country:** Germany                      **Funding:** Not reported

# Rebound: overall rebound	Zopiclone	Placebo			P value
	46.07 ( 1.42 )	48.56 ( 3.28 )	( )	( )	<=0.01
	% ( SD )				
# Rebound: Responder	Zopiclone	Triazolam			P value
	9.05 ( 1.16 )	7.70 ( 0.88 )	( )	( )	<=0.01
	% ( SD )				
# Rebound: Responder	Zopiclone	Placebo			P value
	9.05 ( 1.16 )	4.92 ( 1.20 )	( )	( )	<=0.01
	% ( SD )				
# Rebound: Nonresponder	Zopiclone	Triazolam			P value
	36.02 ( 1.35 )	38.93 ( 1.45 )	( )	( )	<=0.01
	% ( SD )				
<u>Rebound rates for items of sleep quality</u>					
# Rebound: sleep quality - 1 item	Zopiclone	Triazolam			P value
	14.33 ( 1.11 )	16.32 ( 1.33 )	( )	( )	<0.001
	(% ) ( SD )				
# Rebound: sleep quality - 2 items	Zopiclone	Triazolam			P value
	6.76 ( 0.83 )	8.27 ( 1.04 )	( )	( )	<=0.05
	(% ) ( SD )				
# Rebound: sleep quality - 3 items	Zopiclone	Triazolam			P value
	2.36 ( 0.47 )	2.39 ( 0.85 )	( )	( )	NS
	(% ) ( SD )				
<u>Rebound rates for items of daytime well-being</u>					
# Rebound: daytime well-being - 1 item	Zopiclone	Triazolam			P value
	18.52 ( 1.44 )	19.04 ( 2.00 )	( )	( )	NS
	% ( SD )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Hajak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998, 1995, 1994</b>	<b>Country:</b>	<b>Germany</b>	<b>Funding:</b>	<b>Not reported</b>

# Rebound: daytime well-being - 2 items	Zopiclone	Triazolam			P value
	14.09 ( 1.11 )	13.10 ( 1.91 )	( )	( )	NS
	% ( SD )				
# Rebound: daytime well-being - 3 items	Zopiclone	Triazolam			P value
	7.89 ( 0.82 )	7.73 ( 1.33 )	( )	( )	NS
	% ( SD )				

### Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Liu	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1997	<b>Country:</b> Taiwan	<b>Funding:</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 40.1  
Range: 20-58  
SD: 10.9  
**Gender:** 11 ( 73 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 15  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 15

**Eligibility criteria:**

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.

**Exclusion criteria:**

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abuse or drug abuse.

**Comments:**

Poor quality- baseline characteristics not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	15	14 day	0 / 0
Triazolam	0.25 mg	15	14 day	0 / 0
Placebo	NA mg	15	14 day	0 / 0

**Rebound:**

Spiegel's sleep questionnaire (SSQ)

# rebound: 6 out of 7 items shows less rebound effects in Zopiclone	Zopiclone	Triazolam			P value
	multiple d ( )	multiple ( )	( )	( )	<0.05
	Score ( )				

Leed's sleep evaluation questionnaire (LSEQ)

# rebound: 9/10 items show more withdrawal sleep disturbance of triazolam	Zopiclone	Triazolam			P value
	NR ( )	NR ( )	( )	( )	<0.05
	Score ( )				



Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Mamelak	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1987	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 50  
Range: 32-60  
SD:  
**Gender:** 21 ( 70 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 30  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 30

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Ethanol-drug interaction study.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	10	12 day	0 / 0
Flurazepam	30 mg	10	12 day	1 / 1
Placebo	NA mg	10	12 day	0 / 0

**Rebound:**

sleep questionnaire

# rebound: total sleep time at day 15

Zopiclone	Flurazepam	Placebo		P value
313.5 ( NS )	356.5 ( NS )	313.5 ( NS )	( )	
minutes ( p vs baseline )				

# rebound: sleep latency at day 15

Zopiclone	Flurazepam	Placebo		P value
105.0 ( <0.05 )	39.7 ( <0.05 )	75.5 ( NS )	( )	
minutes ( p vs baseline )				

## Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Mamelak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                              **Country:** Canada                      **Funding:** Not reported

# rebound: no. of awakenings at day 15	Zopiclone	Flurazepam	Placebo		P value
	2.10 ( NS )	2.05 ( <0.05 )	1.70 ( <0.05 )	( )	
minutes ( p vs baseline )					
# rebound: duration of early wakefulness at day 15	Zopiclone	Flurazepam	Placebo		P value
	41.5 ( NS )	27.8 ( NS )	46.9 ( NS )	( )	
minutes ( p vs baseline )					
# rebound: sleep latency at day 15	Zopiclone	Flurazepam			P value
	105.0 ( )	39.7 ( )	( )	( )	<0.05
minutes ( )					
# rebound: no. of awakenings at day 17	Zopiclone	Flurazepam			P value
	3.15 ( )	2.05 ( )	( )	( )	<0.05
Number ( )					
# other rebounds	Zopiclone	Flurazepam			P value
	multiple d ( )	multiple ( )	( )	( )	NS
number ( )					

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 47.3  
Range: 21-65  
SD:  
**Gender:** 21 ( 88 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 24  
Number Withdrawn: 1  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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 waketime >20 minutes; number of nocturnal awakenings >3.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	10 mg	8	27 day	0 / 0	
Triazolam	0.5 mg	8	27 day	1 / 1	
Placebo	NA mg	8	27 day	0 / 0	

**Rebound:**

polysomnogram

# rebound: mean wake time (change from baseline)	Zolpidem	Triazolam			P value
	-80 ( 118 )	43 ( 47.4 )	( )	( )	NR
	minutes ( SD )				
# rebound: mean total sleep time (change from baseline)	Zolpidem	Triazolam			P value
	80 ( 118.5 )	-40 ( 52.2 )	( )	( )	NR
	minutes ( SD )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Monti                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1994                      **Country:** Uruguay                      **Funding:** Not reported

# rebound: mean number of sleep cycles (change from baseline)	Zolpidem	Triazolam			P value
	1.3 ( 1.5 )	-0.7 ( 0.7 )	( )	( )	NR
	Number ( SD )				
<u>sleep questionnaire</u>					
# rebound: increased number of awakenings- day 32	Zolpidem	Triazolam	Placebo		P value
	3 ( 37.5 )	5 ( 62.5 )	0 ( 0 )	( )	NR
	Number ( % )				
# rebound: decreased sleep duration- day 32	Zolpidem	Triazolam	Placebo		P value
	3 ( 37.5 )	6 ( 75 )	2 ( 25 )	( )	NR
	Number ( % )				
# rebound: increased time to fall sleep- day 32	Zolpidem	Triazolam	Placebo		P value
	3 ( 37.5 )	8 ( 100 )	0 ( 0 )	( )	NR
	Number ( % )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Quadens	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1983	<b>Country:</b> Belgium	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** NR  
Range: 50-59  
SD:  
**Gender:** 12 ( 100 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 12  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 12

**Eligibility criteria:**

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

**Exclusion criteria:**

(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.

**Comments:**

Poor quality- insufficient information to assess quality.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	/

**Rebound:**

sleep questionnaire

# rebound: no. of awakenings

Zopiclone	Flurazepam			P value
5.5 ( <0.05 )	6.1 ( <0.01 )	( )	( )	

Number ( p vs treatment data )

# rebound: total sleep time

Zopiclone	Flurazepam			P value
23490 ( <0.05 )	23184 ( <0.05 )	( )	( )	

seconds ( p vs treatment data )

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Quadens</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>Belgium</b>	<b>Funding:</b>	<b>Not reported</b>

# rebound: sleep onset latency	Zopiclone	Flurazepam			P value
	1255 ( NS )	1042 ( NR )	( )	( )	
seconds ( p vs treatment data )					
# rebound: sleep efficiency index	Zopiclone	Flurazepam			P value
	86.9 ( NS )	84.9 ( <0.01 )	( )	( )	
Score ( p vs treatment data )					

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 33.6  
Range: NR  
SD: 10.4  
**Gender:** 12 ( 55 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 22  
Number Withdrawn: 0  
Lost to fu: 2  
Analyzed: 20

**Eligibility criteria:**

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 of awakenings >3. These subjective inclusion criteria had to be confirmed by the objective assessment through polysomnography.

**Exclusion criteria:**

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 (myoclones, kinaesthesia 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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	10	2 week	0 / 0
Triazolam	0.25 mg	12	2 week	0 / 2

**Rebound:**

polysomnography

# rebound: sleep onset latency- change from baseline- night 15	Zolpidem	Triazolam			P value
	-11.6 ( 31.98 ) minutes ( SD )	7.1 ( 30.73 ) ( )	( )	( )	NS
# rebound: total sleep time- change from baseline- night 15	Zolpidem	Triazolam			P value
	43.8 ( 62.54 ) minutes ( SD )	-34.5 ( 50.24 ) ( )	( )	( )	<0.01

## Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

Author:	Silvestri	Trial type:	Active	Quality rating:	Fair
Year:	1996	Country:	Italy	Funding:	Not reported
# rebound: sleep efficiency- change from baseline- night 15	Zolpidem 9.9 ( 13.63 ) % ( SD	Triazolam -6.3 ( 8.55 ) )	( )	( )	P value <0.01
# rebound: wake time after sleep onset- change from baseline- night 15	Zolpidem 9.9-37.5 ( 49.01 ) minutes ( SD	Triazolam 17.3 ( 31.89 ) )	( )	( )	P value <0.01
# rebound: no. of awakenings- change from baseline- night 15	Zolpidem -1.9 ( 7.16 ) Number ( SD	Triazolam -1.2 ( 4.67 ) )	( )	( )	P value NS
<u>questionnaire</u>					
# rebound: time to fall asleep- change from baseline- night 15	Zolpidem -20.8 ( 28.23 ) minutes ( SD	Triazolam 8.6 ( 31.65 ) )	( )	( )	P value <0.05
# rebound: total sleep time- change from baseline- night 15	Zolpidem 51.9 ( 45.4 ) minutes ( SD	Triazolam -35.6 ( 127.9 ) )	( )	( )	P value <0.01
# rebound: total wake time- change from baseline- night 15	Zolpidem -2.2 ( 12.96 ) minutes ( SD	Triazolam 13.2 ( 38.71 ) )	( )	( )	P value NS
# rebound: no. nocturnal awakenings- change from baseline- night 15	Zolpidem -0.3 ( 2.32 ) Number ( SD	Triazolam 0.4 ( 0.86 ) )	( )	( )	P value NS
<u>visual analogue scale</u>					
# rebound: sleep quality- change from baseline- night 15	Zolpidem -12.9 ( 20.59 ) Score ( SD	Triazolam 0.8 ( 22.88 ) )	( )	( )	P value NS



Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

# rebound: awakening quality- change from baseline- night 15	Zolpidem	Triazolam			P value
	-12.9 ( 21.34 )	-1.5 ( 21.36 )	( )	( )	NS
	Score ( SD	)			

### Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b> Stip	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 42.6  
Range:  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn: 2  
Lost to fu: 8  
Analyzed: 50

**Eligibility criteria:**

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.

**Exclusion criteria:**

NR

**Comments:**

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week. Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	19	21 day	0 / 0
Temazepam	30 mg	16	21 day	0 / 1
Placebo	NA mg	15	21 day	0 / 1

**Rebound:**

Self-rating questionnaire for sleep

# sleep onset after discontinuation - rebound	Zopiclone	Temazepam			P value
	NR ( NS )	NR, wor ( <0.05 )	( )	( )	
	Score ( p vs placebo )				
# sleep depth after discontinuation-rebound	Zopiclone	Temazepam			P value
	NR, wors ( <0.01 )	NR, wor ( <0.01 )	( )	( )	
	Score ( p vs placebo )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Voshaar                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** Netherlands                      **Funding:** Sanfi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 46.1  
 Range:  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 221  
 Number Withdrawn: 9  
 Lost to fu: 5  
 Analyzed: 159

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	74	28 day	N / NR
Temazepam	20 mg	85	28 day	N / NR

**Rebound:**

rebound

# rebound- mean total sleep time	Zolpidem	Temazepam			P value
	370 ( 84 )	352 ( 89 )	( )	( )	NS
	minutes ( SD	)			
# rebound- prevalence rebound insomnia (TST)	Zolpidem	Temazepam			P value
	27 ( )	25.9 ( )	( )	( )	NS
	% ( )	)			
# rebound- sleep onset latency	Zolpidem	Temazepam			P value
	60 ( 51 )	73 ( 53 )	( )	( )	NS
	minutes ( SD	)			

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

<b>Author:</b>	<b>Voshaar</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>Netherlands</b>	<b>Funding:</b>	<b>Sanfi-Synthelabo</b>

# rebound- prevalence rebound insomnia (SOL)	Zolpidem	Temazepam			P value
	53.4 ( )	58.3 ( )	( )	( )	NS
	% ( )	( )			

### Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Ware                                      **Trial type:** Active                                      **Quality rating:** Fair  
**Year:** 1997                                      **Country:** US                                      **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 21-55  
SD:  
**Gender:** 64 ( 58 % ) Female  
**Ethnicity:** 69% white

Number Screened: 358  
Eligible: NR  
Enrolled: 110  
Number Withdrawn: 11  
Lost to fu: NR  
Analyzed: 99

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	37	28 day	3 / NR
Triazolam	0.5 mg	30	28 day	4 / NR
Placebo	NA mg	35	28 day	0 / NR

**Rebound:**

polysomnography

# rebound: latency to persistent sleep-discontinuation night 1	Zolpidem	Triazolam	Placebo	P value
	6 ( NS )	47 ( <0.05 )	-11 ( NS )	
	minutes ( p vs baseline )			
# rebound: latency to persistent sleep-discontinuation night 1	Zolpidem	Triazolam	Placebo	P value
	6 ( NS )	47 ( <0.05 )	-11 ( NS )	
	minutes ( p vs baseline )			

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Ware                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

	Zolpidem	Triazolam	Placebo		P value
# rebound: sleep efficiency-discontinuation night 1	-3 ( NS )	-15 ( <0.05 )	5 ( <0.05 )	( )	
	% ( p vs baseline )				
<u>rebound questionnaire- discontinuation night 1</u>					
# rebound: sleep latency	14 ( NS )	72 ( <0.05 )	-16 ( )	( )	
	minutes ( p vs baseline )				
# rebound: total sleep time	-4 ( NS )	-63 ( <0.05 )	49 ( 0.05 )	( )	
	minutes ( p vs baseline )				
# rebound: no. of awakenings	1 ( NS )	1 ( NS )	-1 ( <0.05 )	( )	
	Number ( p vs baseline )				
# rebound: wake min during sleep	-4 ( NS )	48 ( <0.05 )	-29 ( <0.05 )	( )	
	minutes ( p vs baseline )				
# rebound: quality latency	0.3 ( NS )	0.8 ( <0.05 )	-0.4 ( <0.05 )	( )	
	Score ( p vs baseline )				
# rebound: morning sleepiness	-5 ( NS )	-6.7 ( NS )	4.5 ( NS )	( )	
	Score ( p vs baseline )				
# rebound: ability to concentrate	0.2 ( <0.05 )	0.1 ( NS )	-0.1 ( NS )	( )	
	Score ( p vs baseline )				

Evidence Table 5. Active controlled trials (Adults): Rebound Insomnia

**Author:** Ware                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

# rebound: over all repounds

Zolpidem	Triazolam	Placebo		P value
15 ( )	43 ( )	11 ( )	( )	
% ( )	( )	( )		

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Anderson                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                              **Country:** UK                              **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** NR  
 Range: 20-69  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 119  
 Number Withdrawn: 5  
 Lost to fu: 15  
 Analyzed: 99

**Eligibility criteria:**

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

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 7  
 Wash out : 7  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg		14 day	1 / 2
Nitrazepam	5 mg		14 day	1 / 1
Placebo	NA mg		14 day	1 / 2



### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Anderson</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	<b>Not reported</b>

**Adverse Events:**

bitter tastes

# no. of patients

Zopiclone	Nitrazepam			P value:
9 ( 24.3 )	NR ( NR )	( )	( )	

Number ( % )

withdrawals

# total withdrawals

Zopiclone	Nitrazepam	Placebo		P value:
2 ( )	1 ( )	2 ( )	( )	

Number ( )

# withdrawals due to AEs

Zopiclone	Nitrazepam	Placebo		P value:
1 ( )	1 ( )	1 ( )	( )	

Number ( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

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<b>Author:</b> Autret	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1987	<b>Country:</b> France	<b>Funding:</b>

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**Design:**

**Study design** CT  
DB  
Crossover  
**Setting** Single Center

**Age:** 46.3  
Range:  
SD: 11.7  
**Gender:** 85 ( 70 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 121  
Number Withdrawn: NR  
Lost to fu: 8  
Analyzed: 113

**Eligibility criteria:**

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.

**Exclusion criteria:**

NR

**Comments:**

Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

**Intervention:**

**Run-in :** 4  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	121	7 day	0 / 8
Triazolam	0.5 mg	121	7 day	0 / 8

Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** Autret                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1987                      **Country:** France                      **Funding:**

---

**Adverse Events:**

Guelfi side-effects check list

# 12 out of 18 items shows favour  
 Zopiclone

Zopiclone	Triazolam			P value:
NR, bett ( )	NR ( )	( )	( )	<0.05
Score (	)			

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Begg	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1992	<b>Country:</b> NR	<b>Funding:</b> Roche Products (NZ) Ltd.

**Design:**

**Study design** RCT  
SB  
Parallel  
**Setting** Single Center

**Age:** NR  
Range: >18  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 88  
Number Withdrawn: 4  
Lost to fu: 33  
Analyzed: 51

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 infestation within four hours of retiring or more tna one glass (10 g) alcohol in the previous 24 hours were not permitted.

**Comments:**

Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

**Intervention:**

**Run-in :** 2  
**Wash out :** 2  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	28	11 day	1 /
Midazolam	15 mg	23	11 day	3 /

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Begg                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1992                      **Country:** NR                      **Funding:** Roche Products (NZ) Ltd.

**Adverse Events:**

Averse Events

# No. of patients experiencing AEs (overall)	Zopiclone	Midazolam			P value:
	15 ( 31 )	16 ( 40 )	( )	( )	>0.05
Number ( % )					
# No. of AEs	Zopiclone	Midazolam			P value:
	21 ( )	28 ( )	( )	( )	>0.05
Number ( )					
# No. of patients experiencing AEs - Daytime tiredness	Zopiclone	Midazolam			P value:
	6 ( 12.5 )	6 ( 15 )	( )	( )	NR
Number ( % )					
# No. of patients experiencing AEs - Taste disturbance	Zopiclone	Midazolam			P value:
	6 ( 12.5 )	0 ( 0 )	( )	( )	NR
Number ( % )					
# No. of patients experiencing AEs - Dry mouth	Zopiclone	Midazolam			P value:
	2 ( 4.2 )	3 ( 7.5 )	( )	( )	NR
Number ( % )					
# No. of patients experiencing AEs - Indigestion/nousea/vomiting	Zopiclone	Midazolam			P value:
	1 ( 2.1 )	5 ( 12.5 )	( )	( )	NR
Number ( % )					
# No. of patients experiencing AEs - Clumsiness	Zopiclone	Midazolam			P value:
	0 ( 0 )	4 ( 10 )	( )	( )	NR
Number ( % )					

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Begg                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1992                      **Country:** NR                      **Funding:** Roche Products (NZ) Ltd.

# No. of patients experiencing AEs - Disturbed sleep pattern	Zopiclone	Midazolam			P value:
	2 ( 4.2 )	5 ( 12.5 )	( )	( )	NR
Number ( % )					
# No. of patients experiencing AEs - Others	Zopiclone	Midazolam			P value:
	4 ( 8.3 )	5 ( 12.5 )	( )	( )	NR
Number ( )					

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Chaudoir                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** UK                              **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 50.9  
 Range: 30-65  
 SD:  
**Gender:** 27 ( 71 % ) Female  
**Ethnicity:** 100% caucasian

Number Screened: NR  
 Eligible: NR  
 Enrolled: 38  
 Number Withdrawn: 4  
 Lost to fu: NR  
 Analyzed: 38

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** no  
**Wash out :** 7  
**Allow other medication :** No medication known to cause drowsiness

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	19	1 week	0 / 1
Triazolam	0.25 mg	19	1 week	1 / 3

## Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** Chaudoir                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** UK                              **Funding:** Not reported

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**Adverse Events:**reported by patients

# no. of patients experiencing severe side effect

Zopiclone	Triazolam			P value:
1 ( )	1 ( )	( )	( )	

Number ( )

withdrawals

# total withdrawals

Zopiclone	Triazolam			P value:
1 ( )	3 ( )	( )	( )	

Number ( )

# withdrawals due to Aes

Zopiclone	Triazolam			P value:
0 ( )	1 ( )	( )	( )	

Number ( )



Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Drake (1)</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst Research</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Multicenter

**Age:** 41.6  
Range: 21-60  
SD: 9.5  
**Gender:** 24 ( 51 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 47  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 47

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** NR  
**Wash out :** 5-12  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10 mg	47	2 day	0 / NR
Zaleplon	40 mg	47	2 day	0 / NR
Triazolam	0.25 mg	47	2 day	0 / NR
Placebo	NA mg	47	2 day	0 / NR

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Drake (1)</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst Research</b>

**Adverse Events:**

reported by patients

# no. of patients experiencing AEs

Zaleplon 10mg	Zaleplon 40mg	Triazolam		P value:
9 ( )	18 ( )	8 ( )	( )	

Number ( )

withdrawals

# total withdrawals

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value:
NR ( )	NR ( )	NR ( )	( )	

( )

# withdrawals due to AEs

Zaleplon 10mg	Zaleplon 40mg	Triazolam 0.25mg		P value:
0 ( )	0 ( )	0 ( )	( )	

( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Drake (2)</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst Research</b>

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 38.1  
 Range: 21-60  
 SD: 11.1  
**Gender:** 14 ( 39 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 36  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 36

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** NR  
**Wash out :** 5-12  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	20 mg	36	2 day	/
Zaleplon	60 mg	36	2 day	/
Triazolam	0.25 mg	36	2 day	/
Placebo	NA mg	36	2 day	/

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Drake (2)                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2000                                  **Country:** US                                  **Funding:** Wyeth-Ayerst Research

**Adverse Events:**

reported by patients

# no. of patients experiencing AEs

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
6 ( )	17 ( )	8 ( )	( )	

Number ( )

withdrawals

# total withdrawals

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
NR ( )	NR ( )	NR ( )	( )	

Number ( )

# withdrawals due to AEs

Zaleplon 20mg	Zaleplon 60mg	Triazolam		P value:
0 ( )	1 ( )	0 ( )	( )	

Number ( )

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

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<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 37.6  
Range:  
SD: 1.84  
**Gender:** 24 ( 67 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 36  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 36

**Eligibility criteria:**

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,

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 7  
Wash out : 3  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zopiclone	7.5 mg	12	28 day	0 / 0
Flurazepam	30 mg	12	28 day	0 / 0
Placebo	NA mg	12	28 day	0 / 0

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Adverse Events:**

overall AEs

# somnolence	Zopiclone	Flurazepam	Placebo		P value:
	11 ( )	12 ( )	9 ( )	( )	NS
Number ( )					
# loss of concentration	Zopiclone	Flurazepam	Placebo		P value:
	8 ( )	8 ( )	5 ( )	( )	NS
Number ( )					
# excitation	Zopiclone	Flurazepam	Placebo		P value:
	10 ( )	2 ( )	7 ( )	( )	NS
Number ( )					
# tension	Zopiclone	Flurazepam	Placebo		P value:
	10 ( )	7 ( )	9 ( )	( )	NS
Number ( )					
# taste disturbance	Zopiclone	Flurazepam	Placebo		P value:
	10 ( )	10 ( )	4 ( )	( )	<0.05
Number ( )					
# try mouth	Zopiclone	Flurazepam	Placebo		P value:
	11 ( )	7 ( )	8 ( )	( )	NS
Number ( )					
# thick tongue	Zopiclone	Flurazepam	Placebo		P value:
	9 ( )	7 ( )	5 ( )	( )	NS
Number ( )					

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Elie</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990b</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

withdrawals

# total withdrawals

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	
Number ( )				

# withdrawals due to Aes

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	
Number ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Fleming</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1995</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 33-37  
SD:  
**Gender:** 69 ( 48 % ) Female  
**Ethnicity:** NR

Number Screened: 222  
Eligible: 144  
Enrolled: 144  
Number Withdrawn: 7  
Lost to fu: 1  
Analyzed: 141

**Eligibility criteria:**

(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 these criteria was to be present for at least 6 months prior to study entry.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**  
**Run-in :** 1  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	35	3 day	0 / 0
Zolpidem	20 mg	35	3 day	6 / 7
Flurazepam	30 mg	36	3 day	0 / 1
Placebo	NA mg	35	3 day	0 / 0



Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Fleming                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1995                              **Country:** Canada                      **Funding:** Not reported

**Adverse Events:**

reported by patients

# any event

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
14 ( 40 )	23 ( 65.37 )	15 ( 41.7 )	15 ( 42.9 )	<0.05
Number ( % )				

# dry mouth

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( 0 )	1 ( 2.9 )	2 ( 5.6 )	0 ( 0 )	
Number ( % )				

# back pain

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( 0 )	2 ( 5.7 )	0 ( 0 )	0 ( 0 )	
Number ( % )				

# fatigue

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
3 ( 8.6 )	2 ( 5.7 )	0 ( 0 )	1 ( 2.9 )	
Number ( % )				

# ataxia

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
1 ( 2.9 )	3 ( 8.6 )	0 ( 0 )	1 ( 2.9 )	
Number ( % )				

# confusion

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( 0 )	2 ( 5.7 )	0 ( 0 )	0 ( 0 )	
Number ( % )				

# difficulty concentrating

Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
0 ( 0 )	0 ( 0 )	1 ( 2.8 )	2 ( 5.7 )	
Number ( % )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

Author:	Fleming	Trial type:	Active	Quality rating:	Fair
Year:	1995	Country:	Canada	Funding:	Not reported
# dizziness	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	0 ( 0 )	3 ( 8.6 )	1 ( 2.8 )	0 ( 0 )	
	Number ( % )				
# drugged feeling	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	0 ( 0 )	2 ( 5.7 )	1 ( 2.8 )	0 ( 0 )	
	Number ( % )				
# dysarthria	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	1 ( 2.9 )	3 ( 8.6 )	0 ( 0 )	0 ( 0 )	
	Number ( % )				
# headache	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	4 ( 11.4 )	2 ( 5.7 )	4 ( 11.1 )	3 ( 8.6 )	
	Number ( % )				
# light-headedness	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	0 ( 0 )	0 ( 0 )	2 ( 5.6 )	0 ( 0 )	
	Number ( % )				
# vomiting	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	0 ( 0 )	3 ( 8.6 )	0 ( 0 )	0 ( 0 )	
	Number ( % )				
# myalgia	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	0 ( 0 )	2 ( 5.7 )	1 ( 2.8 )	1 ( 2.9 )	
	Number ( % )				
# amnesia	Zolpidem 10mg	Zolpidem 20mg	Flurazepam 30mg	Placebo	P value:
	1 ( 2.9 )	3 ( 8.6 )	1 ( 2.8 )	0 ( 0 )	
	Number ( % )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

Author:	<b>Fleming</b>	Trial type:	<b>Active</b>	Quality rating:	<b>Fair</b>
Year:	<b>1995</b>	Country:	<b>Canada</b>	Funding:	<b>Not reported</b>
# nervousness	Zolpidem 10mg 1 ( 2.9 )	Zolpidem 20mg 2 ( 5.7 )	Flurazepam 30mg 1 ( 2.8 )	Placebo 0 ( 0 )	P value:
	Number ( % )				
# pharyngitis	Zolpidem 10mg 2 ( 5.7 )	Zolpidem 20mg 0 ( 0 )	Flurazepam 30mg 1 ( 2.8 )	Placebo 0 ( 0 )	P value:
	Number ( % )				
# abnormal vision	Zolpidem 10mg 0 ( 0 )	Zolpidem 20mg 2 ( 5.7 )	Flurazepam 30mg 0 ( 0 )	Placebo 0 ( 0 )	P value:
	Number ( % )				
<u>withdrawals</u>					
# total withdrawals	Zolpidem 10mg 0 ( )	Zolpidem 20mg 7 ( )	Flurazepam 30mg 1 ( )	Placebo 0 ( )	P value: NR
	( )				
# withdrawal due to AEs	Zolpidem 10mg 0 ( )	Zolpidem 20mg 6 ( )	Flurazepam 30mg 0 ( )	Placebo 0 ( )	P value: NR
	( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Fleming\_                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                              **Country:** Canada                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 45.5  
 Range:  
 SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 52  
 Number Withdrawn: 4  
 Lost to fu: 0  
 Analyzed: 48

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, analgesis, 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.

**Comments:**

Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

**Intervention:**

**Run-in :** 3  
**Wash out :** 4  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	24	21 day	2 / 2
Triazolam	0.25 mg	24	21 day	10 / 10

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Fleming_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Adverse Events:**

overall report

# no. of patients experiencing adverse effect	Zopiclone	Triazolam			P value:
	18 ( 75 )	20 ( 83.3 )	( )	( )	NS
	Number ( % )				
# taste percersion	Zopiclone	Triazolam			P value:
	NR ( )	NR, mor ( )	( )	( )	<0.05
	Number ( )				
# moderate or severe adverse effects reported	Zopiclone	Triazolam			P value:
	18 ( )	42 ( )	( )	( )	<0.05
	% ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Hajak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998, 1995, 1994              **Country:** Germany                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 51  
 Range: 18-71  
 SD: 11  
**Gender:** 940 ( 62 % ) Female  
**Ethnicity:** 99.3% Caucasian  
 0.9% Others

Number Screened: NR  
 Eligible: NR  
 Enrolled: 1507  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 1507

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Patients were observed for a further period of 14 days without medication for rebound.

**Intervention:**

**Run-in :** 7  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	612	28 day	26 / 190
Triazolam	0.2 mg	307	28 day	11 / 187
Placebo	NA mg	298	28 day	25 / 193

Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** Hajak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998, 1995, 1994              **Country:** Germany                      **Funding:** Not reported

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**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Triazolam	Placebo		P value:
190 ( )	187 ( )	193 ( )	( )	
Number ( )				

# withdrawals due to Aes

Zopiclone	Triazolam	Placebo		P value:
26 ( )	11 ( )	25 ( )	( )	
Number ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Hayoun</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported (corresponding</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 47.9  
Range: 18-65  
SD:  
**Gender:** 90 ( 66 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 136  
Number Withdrawn: 9  
Lost to fu: 0  
Analyzed: 127

**Eligibility criteria:**

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).

**Exclusion criteria:**

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.

**Comments:**

Sleep aid, drug abuse???  
More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04).  
More patients described themselves as tranquil compared with patients on zopiclone.

**Intervention:** Run-in : NR  
Wash out : NR  
Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	67	7 day	0 / 0
Triazolam	0.25 mg	69	7 day	0 / 0



Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Hayoun                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1989                      **Country:** France                      **Funding:** Not reported (corresponding

**Adverse Events:**

reported by patients

# overall side effects

Zopiclone	Zaleplon			P value:
NR ( )	NR ( )	( )	( )	NS
% ( )	( )			

global evaluation

# safety- good or excellent

Zopiclone	Triazolam			P value:
86 ( )	82 ( )	( )	( )	NS
% ( )	( )			

## Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Liu</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1997</b>	<b>Country:</b>	<b>Taiwan</b>	<b>Funding:</b>	

**Design:**

**Study design** RCT  
DB  
Crossover

**Setting** Single Center

**Age:** 40.1  
Range: 20-58  
SD: 10.9

**Gender:** 11 ( 73 % ) Female

**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 15

Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 15

**Eligibility criteria:**

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.

**Exclusion criteria:**

Patients with psychoses or mood disorders, history of severe physical illness, alcohol abuse or drug abuse.

**Comments:**

Poor quality- baseline characteristics not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

**Intervention:**

**Run-in :** 0  
**Wash out :** 7  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	15	14 day	0 / 0
Triazolam	0.25 mg	15	14 day	0 / 0
Placebo	NA mg	15	14 day	0 / 0

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Liu	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1997	<b>Country:</b> Taiwan	<b>Funding:</b>

**Adverse Events:**

rebound insomnia

# rebound insomnia- mild degree of poor sleep

Zopiclone	Triazolam			P value:
6 ( 40 )	1 ( 6.7 )	( )	( )	

Number ( % )

# rebound insomnia- moderate degree of poor sleep

Zopiclone	Triazolam			P value:
6 ( 40 )	4 ( 26.7 )	( )	( )	

Number ( % )

# rebound insomnia- severe degree of poor sleep

Zopiclone	Triazolam			P value:
3 ( 20 )	10 ( 67.6 )	( )	( )	

Number ( % )

overall AEs

# number of events reported

Zopiclone	Triazolam			P value:
10 ( )	16 ( )	( )	( )	

Number ( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Mamelak                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                              **Country:** Canada                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 50  
 Range: 32-60  
 SD:  
**Gender:** 21 ( 70 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 30  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 30

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Ethanol-drug interaction study.

**Intervention:** Run-in : 2  
 Wash out : 3  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	10	12 day	0 / 0
Flurazepam	30 mg	10	12 day	1 / 1
Placebo	NA mg	10	12 day	0 / 0

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Mamelak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	
Number ( )				

# withdrawals due to AEs

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	
Number ( )				

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 47.3  
Range: 21-65  
SD:  
**Gender:** 21 ( 88 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 24  
Number Withdrawn: 1  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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 waketime >20 minutes; number of nocturnal awakenings >3.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** 3  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	8	27 day	0 / 0
Triazolam	0.5 mg	8	27 day	1 / 1
Placebo	NA mg	8	27 day	0 / 0

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Monti                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1994                      **Country:** Uruguay                      **Funding:** Not reported

**Adverse Events:**

overall AEs

# Emergent adverse events

Zolpidem	Triazolam	Placebo		P value:
13 ( )	16 ( )	10 ( )	( )	NR
Number ( )				

AEs with significant differences

# rebound: pessimist

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.096
Number ( )				

# rebound: tense

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.061
Number ( )				

# rebound: pessimist

Zolpidem	Triazolam			P value:
lower ( )	higher ( )	( )	( )	0.040
Number ( )				

withdrawals

# total withdrawals

Zolpidem	Triazolam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	
Number ( )				

# withdrawals due to AEs

Zolpidem	Triazolam	Placebo		P value:
0 ( )	1 ( )	0 ( )	( )	
Number ( )				

## Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Nair</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 46.9  
Range:  
SD: 1.4  
**Gender:** 28 ( 47 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn:  
Lost to fu:  
Analyzed:

**Eligibility criteria:**

(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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 1  
Wash out : NR  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	3.75 mg	10	7 day	0 / 0
Zopiclone	7.5 mg	10	7 day	0 / 0
Zopiclone	11.2 mg	10	7 day	1 / 1
Zopiclone	15 mg	10	7 day	1 / 1
Flurazepam	30 mg	10	7 day	0 / 0
Placebo	NA mg	10	7 day	1 / 2



### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Nair</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

**Adverse Events:**

overall AEs

# Total number of patients

Zopiclone 3.75	Zopiclone 7.5mg	Zopiclone 11.25mg	Zopiclone 15mg	P value:
4 ( )	4 ( )	11 ( )	5 ( )	

Number ( )

# Total number of patients

Flurazepam	Placebo			P value:
10 ( )	5 ( )	( )	( )	

Number ( )

withdrawals

# total withdrawals

Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.5mg	Zopiclone 15mg	P value:
0 ( )	0 ( )	1 ( )	1 ( )	

Number ( )

# total withdrawals

Flurazepam	Placebo			P value:
0 ( )	2 ( )	( )	( )	

Number ( )

# withdrawals due to AEs

Zopiclone 3.75mg	Zopiclone 7.5mg	Zopiclone 11.5mg	Zopiclone 15mg	P value:
0 ( )	0 ( )	1 ( )	1 ( )	

Number ( )

# withdrawals due to AEs

Flurazepam	Placebo			P value:
0 ( )	1 ( )	( )	( )	

Number ( )

## Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Ngen	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Malaysia	<b>Funding:</b> Rhone-Poulenc Pharma

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 38.4  
Range:  
SD:  
**Gender:** 31 ( 52 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 44

**Eligibility criteria:**

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

**Exclusion criteria:**

(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

**Comments:**

**Intervention:** Run-in : 7  
Wash out : NR  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	20	14 day	2 / 7
Temazepam	20 mg	20	14 day	0 / 7
Placebo	NA mg	20	14 day	1 / 10

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Ngen	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Malaysia	<b>Funding:</b> Rhone-Poulenc Pharma

**Adverse Events:**

reported by patients

# excessive sedation

Zopiclone	Temazepam	Placebo		P value:
2 ( )	0 ( )	1 ( )	( )	

Number ( )

withdrawals

# total withdrawals

Zopiclone	Temazepam	Placebo		P value:
7 ( )	7 ( )	10 ( )	( )	

Number ( )

# withdrawals due to AEs

Zopiclone	Temazepam	Placebo		P value:
2 ( )	0 ( )	1 ( )	( )	

Number ( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Ponciano</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Portugal</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 30  
Range: 18-60  
SD: 9  
**Gender:** 12 ( 46 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 26  
Number Withdrawn: 2  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	8	21 day	0 / 0
Flurazepam	30 mg	8	21 day	0 / 0
Placebo	NA mg	10	21 day	1 / 2

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Ponciano</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Portugal</b>	<b>Funding:</b>	<b>Not reported</b>

**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	0 ( )	2 ( )	( )	
Number ( )				

# withdrawals due to AEs

Zopiclone	Flurazepam	Placebo		P value:
0 ( )	0 ( )	1 ( )	( )	
Number ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Quadens                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1983                              **Country:** Belgium                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** NR  
 Range: 50-59  
 SD:  
**Gender:** 12 ( 100 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 12  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 12

**Eligibility criteria:**

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

**Exclusion criteria:**

(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.

**Comments:**

Poor quality- insufficient information to assess quality.

**Intervention:**

**Run-in :** 6  
**Wash out :** 35  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	13 day	/
Flurazepam	30 mg	12	13 day	/

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Quadens	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1983	<b>Country:</b> Belgium	<b>Funding:</b> Not reported

**Adverse Events:**

Norris questionnaire

# clear headed-muzzy

Zopiclone	Flurazepam			P value:
28.1 ( 9.3 )	34.6 ( 13.4 )	( )	( )	<0.05
Score ( SD )				

# energic-lethargic

Zopiclone	Flurazepam			P value:
29.2 ( 12.7 )	34.9 ( 10.1 )	( )	( )	<0.05
Score ( SD )				

# tranquil-troubled

Zopiclone	Flurazepam			P value:
19.8 ( 11.2 )	24.7 ( 9.4 )	( )	( )	<0.05
Score ( SD )				

# relaxed-tense

Zopiclone	Flurazepam			P value:
21.4 ( 11.7 )	25.9 ( 10.8 )	( )	( )	<0.05
Score ( SD )				

# elated-depressed

Zopiclone	Flurazepam			P value:
48.1 ( 15.3 )	50.5 ( 14.0 )	( )	( )	<0.05
Score ( SD )				

# sociable-introverted

Zopiclone	Flurazepam			P value:
53.6 ( 15.3 )	52.3 ( 13.4 )	( )	( )	<0.05
Score ( SD )				

# other 12 items show no difference

Zopiclone	Flurazepam			P value:
multiple ( )	multiple ( )	( )	( )	NS
Score ( )				

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Quadens</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>Belgium</b>	<b>Funding:</b>	<b>Not reported</b>

withdrawals

# total

Zopiclone	Flurazepam			P value:
0 ( )	0 ( )	( )	( )	NR

Number ( )

# due to AEs

Zopiclone	Flurazepam			P value:
0 ( )	0 ( )	( )	( )	NR

Number ( )



Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Rosenberg</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Denmark</b>	<b>Funding:</b>	<b>Synthelabo Scandinavia A/S</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 54  
Range: 25-79  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 178  
Number Withdrawn: 5  
Lost to fu: 34  
Analyzed: 139

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; 31% male.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** No

<b>Drug name</b>	<b>dosage</b>	<b>N=</b>	<b>Duration</b>	<b>Withdrawals due to AEs/ Total withdrawal</b>
Zolpidem	10 mg	71	14 day	/
Triazolam	0.25 mg	68	14 day	/

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Rosenberg</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Denmark</b>	<b>Funding:</b>	<b>Synthelabo Scandinavia A/S</b>

**Adverse Events:**

Overall AEs

# CNS-related adverse events

	Zolpidem	Triazolam		P value:
( )	8 ( 11.3 )	10 ( 14.7 )	( )	NS

Number ( % )

# GI-related adverse events

	Zolpidem	Triazolam		P value:
( )	2 ( 2.8 )	3 ( 4.4 )	( )	NS

Number ( % )

# other adverse events

	Zolpidem	Triazolam		P value:
( )	5 ( 7 )	2 ( 2.9 )	( )	NS

Number ( % )

# total

	Zolpidem	Triazolam		P value:
( )	15 ( 21.1 )	15 ( 22 )	( )	NS

Number ( % )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 33.6  
Range: NR  
SD: 10.4  
**Gender:** 12 ( 55 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 22  
Number Withdrawn: 0  
Lost to fu: 2  
Analyzed: 20

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 (myoclones, kinaesthesia 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.

**Comments:**

**Intervention:**  
**Run-in :** 3  
**Wash out :** No  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	10	2 week	0 / 0
Triazolam	0.25 mg	12	2 week	0 / 2

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

**Adverse Events:**

withdrawals

# total withdrawals

Zolpidem	Triazolam			P value:
0 ( 0 )	2 ( 16.7 )	( )	( )	

Number ( % )

# withdrawals due to AEs

Zolpidem	Triazolam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )

overall AEs

# no. of adverse events reported by patients

Zolpidem	Triazolam			P value:
1 ( )	1 ( )	( )	( )	NR

Number ( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Singh                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                      **Country:** Canada                      **Funding:** Rhone-Poulenc Pharma Inc.

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 39.6  
 Range: 19-64  
 SD: 1.5  
**Gender:** 32 ( 53 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: 61  
 Enrolled: 60  
 Number Withdrawn: 3  
 Lost to fu: 0  
 Analyzed: 57

**Eligibility criteria:**  
 NR

**Exclusion criteria:**  
 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.

**Comments:**

Two patients were taking a benzodiazepine hypnotic medication at time of recruitment and they both fulfilled the inclusion criteria after a 4-day minimum washout period. The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?)

**Intervention:** Run-in : 4  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg		24 day	0 / 0
Zopiclone	11.2 mg		24 day	1 / 2
Flurazepam	30 mg		24 day	0 / 1

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Singh                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990                      **Country:** Canada                      **Funding:** Rhone-Poulenc Pharma Inc.

**Adverse Events:**

withdrawals

# total

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	2 ( )	1 ( )	( )	
Number ( )				

# due to AEs

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	1 ( )	0 ( )	( )	
Number ( )				

overall AEs

# taste perversion

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
7 ( )	10 ( )	7 ( )	( )	NR
Number ( )				

# drowsiness

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	1 ( )	9 ( )	( )	<0.05
Number ( )				

# headache

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	5 ( )	4 ( )	( )	NS
Number ( )				

# taste perversion- moderate and severe

Zopiclone 7.5mg	Zopiclone 11.25mg	Flurazepam 30mg		P value:
0 ( )	8 ( )	0 ( )	( )	
Number ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Stip	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 42.6  
Range:  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 60  
Number Withdrawn: 2  
Lost to fu: 8  
Analyzed: 50

**Eligibility criteria:**

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.

**Exclusion criteria:**  
NR

**Comments:**

Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week. Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	19	21 day	0 / 0
Temazepam	30 mg	16	21 day	0 / 1
Placebo	NA mg	15	21 day	0 / 1

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Stip	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Temazepam	Placebo		P value:
0 ( )	1 ( )	1 ( )	( )	
Number ( )				

# withdrawals due to AEs

Zopiclone	Temazepam	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	
Number ( )				



Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Tamminen	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1987	<b>Country:</b> Finland	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 47  
Range: 26-71  
SD:  
**Gender:** 72 ( 77 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 130  
Enrolled: 94  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 94

**Eligibility criteria:**

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.

**Exclusion criteria:**

Known hypersensitivity to benzodiazepines, major psychiatric disorders, somatic disorders directly causeing 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.

**Comments:**

Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

**Intervention:**

**Run-in :** 7  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	52	42 day	3 / 3
Nitrazepam	5 mg	46	42 day	1 / 1

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Tamminen                      **Trial type:** Active                      **Quality rating:** Poor  
**Year:** 1987                              **Country:** Finland                      **Funding:** Not reported

**Adverse Events:**

somatic complaint check list (higher score=more severe)- change from bas

# anxiety	Zopiclone	Nitrazepam			P value:
	3.8 ( <0.06 )	-6.8 ( <0.00 )	( )	( )	<0.05
Score ( p vs baseline )					
# sweating	Zopiclone	Nitrazepam			P value:
	5.7 ( <0.00 )	-7.1 ( <0.05 )	( )	( )	NS
Score ( p vs baseline )					
# nausea	Zopiclone	Nitrazepam			P value:
	4.3 ( NS )	-3.2 ( NS )	( )	( )	<0.05
Score ( p vs baseline )					
# loss of appetite	Zopiclone	Nitrazepam			P value:
	0 ( NS )	-6.5 ( <0.05 )	( )	( )	NS
Score ( p vs baseline )					
# restlessness	Zopiclone	Nitrazepam			P value:
	2.2 ( NS )	-5.9 ( <0.05 )	( )	( )	NS
Score ( p vs baseline )					
# physical tiredness	Zopiclone	Nitrazepam			P value:
	-3.5 ( <0.00 )	-10.3 ( <0.00 )	( )	( )	NS
Score ( p vs baseline )					
# dizziness	Zopiclone	Nitrazepam			P value:
	3.5 ( NS )	-7.8 ( <0.00 )	( )	( )	<0.05
Score ( p vs baseline )					

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Tamminen      **Trial type:** Active      **Quality rating:** Poor  
**Year:** 1987      **Country:** Finland      **Funding:** Not reported

# indigestion	Zopiclone	Nitrazepam			P value:
	8.8 ( <0.05 )	-10 ( <0.01 )	( )	( )	<0.05
	Score ( p vs baseline )				
<u>reported by patients</u>					
# number of events reported	Zopiclone	Nitrazepam			P value:
	24 ( )	13 ( )	( )	( )	
	Number ( )				
# number of patients experiencing unwanted effects	Zopiclone	Nitrazepam			P value:
	52 ( )	46 ( )	( )	( )	
	Number ( )				
<u>global evaluation</u>					
# safety score (1=poor; 5=excellent)	Zopiclone	Nitrazepam			P value:
	3.4 ( )	3.5 ( )	( )	( )	NS
	Score ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** NR

**Age:** 53  
 Range: 28-69  
 SD:  
**Gender:** 39 ( 71 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: 60  
 Enrolled: 55  
 Number Withdrawn: 2  
 Lost to fu: 0  
 Analyzed: 53

**Eligibility criteria:**

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

**Exclusion criteria:**

1. Patients taking a non-benzodiazapine hypnotic prior to the studym 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 benzodiazapine tranquilizers 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

**Comments:**

**Intervention:** Run-in : 2  
 Wash out : 7  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	53	5 day	1 / 1
Temazepam	20 mg	53	5 day	1 / 1

## Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

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**Adverse Events:**Reported by patients

# Bad headache

Zopiclone	Temazepam	Placebo		P value:
8 ( )	12 ( )	14 ( )	( )	NR
% ( )				

# Very severe perspiration

Zopiclone	Temazepam	Placebo		P value:
8 ( )	18 ( )	10 ( )	( )	NR
% ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** van der Kleijn      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1989      **Country:** Nijmegen      **Funding:** Rhone-Poulenc Pharma

Oponion of the patient about day-time status

# Well/normal	Zopiclone	Temazepam	Placebo		P value:
	30 ( 57 )	35 ( 66 )	27 ( 51 )	( )	NR
Number ( % )					
# Sleepy/dull/tired	Zopiclone	Temazepam	Placebo		P value:
	7 ( 13 )	6 ( 11 )	12 ( 23 )	( )	NR
Number ( % )					
# Headache	Zopiclone	Temazepam	Placebo		P value:
	3 ( 6 )	3 ( 6 )	1 ( 2 )	( )	NR
Number ( % )					
# Irritable/unstable	Zopiclone	Temazepam	Placebo		P value:
	4 ( 8 )	4 ( 8 )	6 ( 11 )	( )	NR
Number ( % )					
# Trembling/palpitation	Zopiclone	Temazepam	Placebo		P value:
	2 ( 4 )	4 ( 8 )	2 ( 4 )	( )	NR
Number ( % )					
# Difficulties to concentrate	Zopiclone	Temazepam	Placebo		P value:
	2 ( 4 )	0 ( 0 )	0 ( 0 )	( )	NR
Number ( % )					
# Depressive	Zopiclone	Temazepam	Placebo		P value:
	3 ( 6 )	1 ( 2 )	2 ( 4 )	( )	
% ( )					
# Unknown	Zopiclone	Temazepam	Placebo		P value:
	2 ( 4 )	0 ( 0 )	3 ( 6 )	( )	
% ( )					

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>van der Kleijn</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>Nijmegen</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

withdrawals

# Total withdrawals

Zopiclone	Temazepam			P value:
1 ( )	1 ( )	( )	( )	NR
Number ( )				

# withdrawals due to Aes

Zopiclone	Temazepam			P value:
1 ( )	1 ( )	( )	( )	NR
Number ( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Voshaar                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** Netherlands                      **Funding:** Sanfi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 46.1  
 Range:  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 221  
 Number Withdrawn: 9  
 Lost to fu: 5  
 Analyzed: 159

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

**Intervention:** Run-in : NR  
 Wash out : 4  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	74	28 day	N / NR
Temazepam	20 mg	85	28 day	N / NR



Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** Voshaar                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** Netherlands                      **Funding:** Sanfi-Synthelabo

---

**Adverse Events:**

withdrawals

# total withdrawals- not reported

				P value:
( )	( )	( )	( )	
( )	( )			

# withdrawals due to AEs- not reported

				P value:
( )	( )	( )	( )	
( )	( )			

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Walsh	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1998a	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 21-65  
SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 589  
Enrolled: 306  
Number Withdrawn: 28  
Lost to fu: 0  
Analyzed: 278

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

**Intervention:**

**Run-in :** 7  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	102	14 day	5 / 11
Trazodone	50 mg	100	14 day	5 / 10
Placebo	NA mg	104	14 day	2 / 7

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Walsh                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1998a                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Adverse Events:**

reported by patients

# total number of events

Zolpidem	Trazodone			P value:
78 ( 76.5 )	75 ( 75 )	( )	( )	NS
Number ( % )				

# headache (highest incidence)

Zolpidem	Trazodone	Placebo		P value:
24 ( )	30 ( )	19 ( )	( )	
% ( )				

# somnolence (highest incidence)

Zolpidem	Trazodone	Placebo		P value:
16 ( )	23 ( )	8 ( )	( )	
% ( )				

withdrawals

# total withdrawals

Zolpidem	Trazodone	Placebo		P value:
11 ( )	10 ( )	7 ( )	( )	
( )				

# withdrawals due to AEs

Zolpidem	Trazodone	Placebo		P value:
5 ( )	5 ( )	2 ( )	( )	
( )				

Evidence Table 6. Active controlled trials (Adults): Adverse Events

**Author:** Walsh\_                      **Trial type:** Active                      **Quality rating:** Good  
**Year:** 1998b                      **Country:** US                      **Funding:** Wyeth Ayerst

**Design:**

**Study design**

DB  
 Parallel

**Setting**

**Eligibility criteria:**

Patients with a DSM-III-R 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).

**Comments:**

day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

**Intervention:**

**Run-in :** 3  
**Wash out :** 2  
**Allow other medication :** NR

**Age:**

40.3  
 Range: 18-60  
 SD:

**Gender:**

77 ( 58 % ) Female

**Ethnicity:**

NR

Number Screened: 673  
 Eligible: 456  
 Enrolled: 132

Number Withdrawn: 7  
 Lost to fu: 0  
 Analyzed: 125

**Exclusion criteria:**

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 zaleplone, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	34	14 day	1 / 3
Zaleplon	10 mg	33	33 day	0 / 1
Triazolam	0.25 mg	31	14 day	0 / 0
Placebo	NA mg	34	14 day	0 / 3

Evidence Table 6. Active controlled trials (Adults): Adverse Events

Author: Walsh\_ Trial type: Active Quality rating: Good  
 Year: 1998b Country: US Funding: Wyeth Ayerst

Adverse Events:

Treatmet emergent adverse effects

# Overall number of reports

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	P value:
13 ( 38 )	12 ( 35 )	14 ( 42 )	17 ( 55 )	NS

Number ( % )

# Nausea

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	P value:
0 ( <0.04 )	0 ( <0.04 )	1 ( NR )	4 ( NA )	

Number ( p vs triazolam )

# headache- the most common adverse event

Placebo	Zaleplon 5mg	Zaleplon 10mg	Triazolam	P value:
5 ( 15 )	5 ( 15 )	6 ( 18 )	7 ( 23 )	

Number ( % )

withdrawals

# total withdrawals

Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo	P value:
3 ( )	1 ( )	0 ( )	3 ( )	

Number ( )

# withdrawals due to AEs

Zaleplon 5mg	Zaleplon 10mg	Triazolam	Placebo	P value:
1 ( )	0 ( )	0 ( )	0 ( )	

Number ( )

Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b> Walsh__	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst Research

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 42  
Range: 22-49  
SD:  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: 73  
Eligible: 39  
Enrolled: 30  
Number Withdrawn: 2  
Lost to fu: 0  
Analyzed: 22

**Eligibility criteria:**

Men and women with sleep maintenance insomnia, 18 to 60 years of age.

**Exclusion criteria:**

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, previous 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.

**Comments:**

The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were analyzed, 11 men; mean age, 42 y; range, 22-49.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10 mg	22	2 day	/
Flurazepam	30 mg	22	2 day	/
Placebo	NA mg	22	2 day	/

**Evidence Table 6. Active controlled trials (Adults): Adverse Events**

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<b>Author:</b> Walsh__	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst Research

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**Adverse Events:**

Evidence Table 6. Active controlled trials (Adults): Adverse Events

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<b>Author:</b>	Ware	<b>Trial type:</b>	Active	<b>Quality rating:</b>	Fair
<b>Year:</b>	1997	<b>Country:</b>	US	<b>Funding:</b>	Lorex Pharmaceuticals

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 21-55  
SD:  
**Gender:** 64 ( 58 % ) Female  
**Ethnicity:** 69% white

Number Screened: 358  
Eligible: NR  
Enrolled: 110  
Number Withdrawn: 11  
Lost to fu: NR  
Analyzed: 99

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

**Intervention:**

**Run-in :** 2  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	37	28 day	3 / NR
Triazolam	0.5 mg	30	28 day	4 / NR
Placebo	NA mg	35	28 day	0 / NR



Evidence Table 6. Active controlled trials (Adults): Adverse Events

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**Author:** Ware                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

---

**Adverse Events:**

withdrawals

# withdrawals due to Aes

Zolpidem	Triazolam	Placebo		P value:
3 ( 8.1 )	4 ( 11.1 )	0 ( 0 )	( )	
Number ( % )				

# total withdrawals

Zolpidem	Triazolam	Placebo		P value:
NR ( )	NR ( )	NR ( )	( )	
Number ( )				

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Wheatley</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1985</b>	<b>Country:</b>	<b>NR</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** NR

**Age:** 53.2  
Range: 25-82  
SD: 2.1  
**Gender:** 22 ( 61 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 36  
Number Withdrawn: 2  
Lost to fu: 0  
Analyzed: 36

**Eligibility criteria:**

Patients aged 18 years and over suffering from difficulty in sleeping, provided that symptoms had been present for at least one week.

**Exclusion criteria:**

NR

**Comments:**

zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

**Intervention:**

**Run-in :** 3  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	36	7 day	2 / 2
Temazepam	20 mg	36	7 day	0 / 0

### Evidence Table 6. Active controlled trials (Adults): Adverse Events

<b>Author:</b>	<b>Wheatley</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1985</b>	<b>Country:</b>	<b>NR</b>	<b>Funding:</b>	<b>Not reported</b>

**Adverse Events:**

Reported by patients

# Overall AEs, no. of patients

Zopiclone	Temazepam			P value:
10 ( 28 )	9 ( 25 )	( )	( )	NR

Number ( % )

# Daytime drowsiness

Zopiclone	Temazepam			P value:
3 ( )	2 ( )	( )	( )	NR

Number ( )

withdrawals

# total withdrawals

Zopiclone	Temazepam			P value:
2 ( )	0 ( )	( )	( )	

Number ( )

# withdrawals due to Aes

Zopiclone	Temazepam			P value:
2 ( )	0 ( )	( )	( )	

Number ( )

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Bergener                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1989                              **Country:** German                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** NR

**Age:** NR  
 Range: 64-80  
 SD:  
**Gender:** 36 ( 86 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 42  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 42

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

**Intervention:**

**Run-in :** 4  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	20	21 day	2 / 8
Flurazepam	30 mg	22	21 day	5 / 8

Evidence Table 7. Active controlled trials (Elderly): Efficacy

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<b>Author:</b> Bergener	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1989	<b>Country:</b> German	<b>Funding:</b> Not reported

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**Outcome Measurement:**

- # Sleep Disorder Intensity Scale (SDIS)
- # Visual Analogue Self-rating scales afternoon - VIS-A
- # Visual Analogue Self-rating scales morning - VIS-M

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep Disorder Intensity Scale (SDIS)

**Results**

SDIS (6=best sleep; 30=worst sleep)

# Day 33

Zopiclone	Flurazepam		P value
NR ( 17 )	NR ( 10 )	( )	( )

Score ( estimate from the figure )

## Evidence Table 7. Active controlled trials (Elderly): Efficacy

<b>Author:</b> Elie_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990a	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 76.0  
Range: 60-90  
SD: 1.3  
**Gender:** 33 ( 75 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 44  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 44

**Eligibility criteria:**

Age between 60 and 90 years, living in residential homes and suffering from chronic insomnia.

**Exclusion criteria:**

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.

**Comments:**

Elderly patients living in nursing homes.

**Intervention:** Run-in : 7  
Wash out : 4  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	5-7. mg	15	21 day	0 / 0
Triazolam	0.12 mg	14	21 day	0 / 0
Placebo	NA mg	15	21 day	0 / 0

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Elie\_                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990a                      **Country:** Canada                      **Funding:** Not reported

**Outcome Measurement:**

# Post-sleep questionnaire, administered by a research nurse

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- Sleep latency
  - Sleep soundness
  - Sleep quality
  - Status of wakefulness upon arising
  - Hangover

**Results**

Post-sleep questionnaire

# sleep latency, mean score

Zopiclone	Triazolam			P value
6.7 ( <0.05 )	6.8 ( <0.05 )	( )	( )	
Score ( p vs placebo )				

# sleep soundness, mean score

Zopiclone	Triazolam			P value
6.8 ( <0.01 )	6.4 ( <0.08 )	( )	( )	
Score ( p vs placebo )				

# quality of sleep, mean score

Zopiclone	Triazolam			P value
10.8 ( <0.08 )	11.0 ( <0.08 )	( )	( )	NS
Score ( p vs placebo )				

# morning wake-up, mean score

Zopiclone	Triazolam			P value
10.5 ( NS )	10.5 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# hangover, mean score

Zopiclone	Triazolam			P value
16.6 ( NS )	16.7 ( NS )	( )	( )	NS
Score ( p vs placebo )				

### Evidence Table 7. Active controlled trials (Elderly): Efficacy

<b>Author:</b>	<b>Klimm</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Community practic

**Age:** 73.2  
 Range: >65  
 SD: 1.54  
**Gender:** 59 ( 80 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 74  
 Number Withdrawn: 2  
 Lost to fu: 2  
 Analyzed: 72

**Eligibility criteria:**

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 (Syndrom Kurztest) was to be within normal range for their age.

**Exclusion criteria:**

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.

**Comments:**

no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensives, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

**Intervention:** Run-in : 7  
 Wash out : 7  
 Allow other medication : medication for concomitant disease were continued

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	36	7 day	0 / 1
Nitrazepam	5 mg	36	7 day	1 / 1



### Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Klimm                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                      **Country:** France                      **Funding:** Not reported

**Outcome Measurement:**

- # diary: analogue scales
- # Spiegel sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep onset latency
  - quality of sleep
  - feeling upon awakening
  - duration of sleep
  - awakenings during the night
  - dreams

**Results**

diary: analogue scales

# sleep onset latency- change from placebo baseline

Zopiclone	Nitrazepam			P value
-18.2 ( <0.04 )	-15.6 ( NS )	( )	( )	NS
Score ( p vs baseline )				

# quality of sleep- change from placebo baseline

Zopiclone	Nitrazepam			P value
24 ( <0.006 )	23.1 ( <0.002 )	( )	( )	NS
Score ( p vs baseline )				

# feeling on awakening- change from placebo baseline

Zopiclone	Nitrazepam			P value
-5.7 ( NS )	6.8 ( NS )	( )	( )	NS
Score ( p vs baseline )				

# feeling on awakening- on day 9 and day 11

Zopiclone	Nitrazepam			P value
better ( )	NR ( )	( )	( )	<0.02
Score ( )				

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Klimm                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1987                      **Country:** France                      **Funding:** Not reported

Spiegel sleep questionnaire

# sleep onset latency

Zopiclone	Nitrazepam			P value
NR ( 0.003 )	NR ( 0.009 )	( )	( )	NS

Score ( p vs placebo )

# quality of sleep

Zopiclone	Nitrazepam			P value
NR ( 0.003 )	NR ( 0.007 )	( )	( )	NS

Score ( p vs placebo )

# duration of sleep

Zopiclone	Nitrazepam			P value
NR ( 0.003 )	NR ( 0.005 )	( )	( )	NS

Score ( p vs placebo )

# awakenings at night

Zopiclone	Nitrazepam			P value
NR ( 0.004 )	NR ( 0.009 )	( )	( )	NS

Score ( p vs placebo )

# dreams

Zopiclone	Nitrazepam			P value
NR ( 0.003 )	NR ( 0.01 )	( )	( )	NS

Score ( p vs placebo )

# condition in the morning

Zopiclone	Nitrazepam			P value
NR ( 0.003 )	NR ( 0.002 )	( )	( )	NS

Score ( p vs placebo )

# general evaluation

Zopiclone	Nitrazepam			P value
NR ( 0.0004 )	NR ( 0.005 )	( )	( )	NS

Score ( p vs placebo )

# sleep onset latency on day 12

Zopiclone	Nitrazepam			P value
NR ( )	better ( )	( )	( )	<0.001

Score ( )

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                              **Country:** US                              **Funding:** Lornex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 69  
 Range: 59-85  
 SD:  
**Gender:** 211 ( 63 % ) Female  
**Ethnicity:** 93% white

Number Screened: NR  
 Eligible: 457  
 Enrolled: 335  
 Number Withdrawn: 40  
 Lost to fu: 0  
 Analyzed: 335

**Eligibility criteria:**

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:**

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 or myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.

**Comments:**

**Intervention:** Run-in : 7  
 Wash out : 4  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	82	28 day	2 / 6
Triazolam	0.12 mg	85	28 day	5 / 14
Temazepam	15 mg	84	28 day	5 / 10
Placebo	NA mg	84	28 day	6 / 10

### Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Leppik      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1997      **Country:** US      **Funding:** Lornex Pharmaceuticals

**Outcome Measurement:**

- # morning questionnaire
- # Global Impression of therapy

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep duration
  - ease of falling asleep
  - no. of awakenings
  - wake time after sleep onset
  - quality of sleep
  - morning sleepiness
  - ability to concentrate

**Results**

morning questionnaire

# sleep latency at week 4

Zolpidem	Triazolam	Temazepam	Placebo	P value
40.5 ( <0.05 )	47.7 ( NS )	38.0 ( <0.05 )	57.9 ( NA )	
minutes ( p vs placebo )				

# sleep latency at week 1 and week 3

Zolpidem	Triazolam			P value
shorter ( )	multiple d ( )	( )	( )	<0.05
minutes ( )				

# sleep latency at week 1 and week 3

Zolpidem	Temazepam			P value
multiple d ( )	multiple d ( )	( )	( )	NS
minutes ( )				

# sleep duration at week 4

Zolpidem	Triazolam	Temazepam	Placebo	P value
362.8 ( NS )	359.7 ( NS )	375.3 ( NS )	363 ( NA )	
minutes ( p vs placebo )				

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                              **Country:** US                              **Funding:** Lornex Pharmaceuticals

# tolerance to treatment

Zolpidem	Triazolam	Temazepam	Placebo	P value
multiple d ( NS )	multiple d ( NS )	multiple ( NS )	multiple ( NA )	
minutes ( p vs placebo )				

Global Impression of therapy

# sleep better

Zolpidem	Temazepam			P value
NR, better ( <0.05 )	NR, bette ( <0.05 )	( )	( )	
Score ( p vs placebo )				

# sleep latency

Zolpidem	Temazepam			P value
NR, better ( <0.05 )	NR, bette ( <0.05 )	( )	( )	
Score ( p vs placebo )				

# medication strength

Zolpidem	Temazepam			P value
NR, better ( <0.05 )	NR, bette ( <0.05 )	( )	( )	
Score ( p vs placebo )				

# overall feeling

Zolpidem	Temazepam			P value
NR, better ( <0.05 )	NR, bette ( <0.05 )	( )	( )	
Score ( p vs placebo )				

## Evidence Table 7. Active controlled trials (Elderly): Efficacy

<b>Author:</b>	<b>Roger</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 81.1  
Range: 58-98  
SD:  
**Gender:** 164 ( 74 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 221  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 205

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Inpatients at geriatric wards.

**Intervention:**

**Run-in :** 3  
**Wash out :** 7

**Allow other medication :** a rescue hypnotic (nitrazepam 5mg) was given at night by the attending nurse on specific patient request in cases of inefficiency

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	70	21 day	0 / 7
Zolpidem	10 mg	74	21 day	0 / 1
Triazolam	0.25 mg	77	21 day	2 / 5

### Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Roger                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** France                      **Funding:** Not reported

**Outcome Measurement:**

- # questionnaire
- # Clinical Global Impression (CGI)

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep onset
  - total sleep time
  - number of nocturnal awakenings
  - total duration of nocturnal awakenings
  - time of awakening
  - feeling of too early awakening
  - quality of sleep
  - quality of awakening

**Results**

questionnaire

# % of patients falling asleep well at day 24, change from baseline	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	55.9 ( <0.01 )	47.9 ( <0.01 )	51.9 ( <0.01 )	( )	
% ( p vs baseline )					
# % of patients falling asleep well at day 31, change from baseline	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	34.6 ( <0.01 )	19.8 ( <0.01 )	18.6 ( <0.01 )	( )	
% ( p vs baseline )					
# % of patients falling asleep in <30 minutes at day 24, change from baseline	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	35 ( <0.01 )	35 ( <0.01 )	35 ( <0.01 )	( )	
% ( p vs baseline )					
# mean total sleep time at day 24, change from baseline	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	1.6 ( NR )	1.9 ( NR )	1.9 ( NR )	( )	
hours ( p vs baseline )					

Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Roger                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** France                      **Funding:** Not reported

	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
# % of patients with >2 awakenings per night at day 24, change from baseline	-36.8 ( <0.001 )	-28.8 ( <0.001 )	-29.8 ( <0.00 )	( )	
Number ( p vs baseline )					
# % of patients with a total nocturnal waking time >1 hours	55.9 ( 17.6 )	47.9 ( 11.0 )	55.8 ( 15.6 )	( )	P value
day 3 ( day 24 )					
# overall sleep quality at day 24, change from baseline (higher score=better)	35.5 ( <0.001 )	34.4 ( <0.001 )	33.6 ( <0.00 )	( )	P value
Score ( p vs baseline )					
# % of patients who reported too early awakening at day 24, change from baseline	-35 ( <0.001 )	-38 ( <0.001 )	-35 ( <0.00 )	( )	P value
% ( p vs baseline )					
<u>Clinical Global Impression (CGI)</u>					
# total mean score- safety and efficacy	2.54 ( )	2.43 ( )	2.51 ( )	( )	NS
Score ( )					



Evidence Table 7. Active controlled trials (Elderly): Efficacy

<b>Author:</b>	<b>Venter</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1986</b>	<b>Country:</b>	<b>South Africa</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 76.8  
Range: 60-96  
SD:  
**Gender:** 31 ( 76 % ) Female  
**Ethnicity:** NR

Number Screened: 58  
Eligible: 41  
Enrolled: 41  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 41

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

22 patients were already receiving another hypnotic drug; the investigators decided a washout period in these patients would be undesirable. It was therefore decided that this group of patients should discontinue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study.  
Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

**Intervention:**

**Run-in :** 7  
**Wash out :** 0  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	0.33 mg	20	17 day	0 / 0
Triazolam	8.25 mg	21	17 day	0 / 0

### Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Venter                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1986                              **Country:** South Africa                      **Funding:** Not reported

**Outcome Measurement:**

# Pre- and during-treatment questionnaires

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- Difficulty in falling asleep, 3 points, 1: diff
- Sleep duration (hr)
- Sleep quality
- Night awakenings (no. of times)
- Early morning awakenings (no. of times)
- Daytime sleep
- Sleep satisfaction
- Daytime sleep

**Results**

Pre- and during-treatment questionnaires

# Difficulty in falling sleep - day 7  
(1=none/very little; 2=some; 3=a lot)

Zopiclone	Triazolam			P value
1.21 ( )	1.62 ( )	( )	( )	0.03
Score ( )				

# Sleep duration (hr) - day 7

Zopiclone	Triazolam			P value
7.4 ( )	7.5 ( )	( )	( )	0.05
No. hours ( )				

# Night awakenings - day 7

Zopiclone	Triazolam			P value
1 ( )	1.7 ( )	( )	( )	0.06
Frequency ( )				

# Sleep quality, Early morning awakenings, Mental alertness on rising, Sleep satisfaction- day 7

Zopiclone	Triazolam			P value
NR ( )	NR ( )	( )	( )	NS
( )				

## Evidence Table 7. Active controlled trials (Elderly): Efficacy

**Author:** Venter      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1986      **Country:** South Africa      **Funding:** Not reported

# Daytime sleep - day 7, compare to mean	Zopiclone	Triazolam			P value
	-8 ( )	9 ( )	( )	( )	0.07
	Minutes ( )				
# Daytime sleep - day 17 (no. of patients)	Zopiclone	Triazolam			P value
	2 ( )	5 ( )	( )	( )	NR
	Number ( )				
# Night awakenings - day 17	Zopiclone	Triazolam			P value
	NR ( )	1 ( )	( )	( )	0.06
	Frequency ( )				
# Daytime sleep - day 17, compare to mean	Zopiclone	Triazolam			P value
	-8 ( )	4 ( )	( )	( )	NS
	Minutes ( )				

Evidence Table 8. Active controlled trials (Elderly): Rebound Insomnia

<b>Author:</b> Elie_	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990a	<b>Country:</b> Canada	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 76.0  
Range: 60-90  
SD: 1.3  
**Gender:** 33 ( 75 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 44  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 44

**Eligibility criteria:**

Age between 60 and 90 years, living in residential homes and suffering from chronic insomnia.

**Exclusion criteria:**

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.

**Comments:**

Elderly patients living in nursing homes.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zopiclone	5-7. mg	15	21 day	0	0
Triazolam	0.12 mg	14	21 day	0	0
Placebo	NA mg	15	21 day	0	0

**Rebound:**

Post-sleep questionnaire

# rebound: no. of items above show withdrawal effects

Zopiclone	Triazolam			P value
0 ( )	3 ( )	( )	( )	
Number ( )				

Evidence Table 8. Active controlled trials (Elderly): Rebound Insomnia

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lornex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 69  
 Range: 59-85  
 SD:  
**Gender:** 211 ( 63 % ) Female  
**Ethnicity:** 93% white  
 Number Screened: NR  
 Eligible: 457  
 Enrolled: 335  
 Number Withdrawn: 40  
 Lost to fu: 0  
 Analyzed: 335

**Eligibility criteria:**

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:**

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 or myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	82	28 day	2 / 6
Triazolam	0.12 mg	85	28 day	5 / 14
Temazepam	15 mg	84	28 day	5 / 10
Placebo	NA mg	84	28 day	6 / 10

**Rebound:**

morning questionnaire

# rebound: ease of falling sleep

Triazolam				P value
worse ( <0.05 )	( )	( )	( )	
Score ( p vs baseline )				

Evidence Table 8. Active controlled trials (Elderly): Rebound Insomnia

<b>Author:</b> Leppik	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1997	<b>Country:</b> US	<b>Funding:</b> Lornex Pharmaceuticals

# rebound: sleep quality

Zolpidem	Triazolam	Temazepam		P value
worse ( NR )	worse ( NR )	worse ( NR )	( )	
Score ( p vs baseline )				

### Evidence Table 8. Active controlled trials (Elderly): Rebound Insomnia

<b>Author:</b>	<b>Roger</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 81.1  
Range: 58-98  
SD:  
**Gender:** 164 ( 74 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 221  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 205

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Inpatients at geriatric wards.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	5 mg	70	21 day	0	7
Zolpidem	10 mg	74	21 day	0	1
Triazolam	0.25 mg	77	21 day	2	5

**Rebound:**

questionnaire

# rebound: % of patients falling asleep in <30 minutes at day 31, change from baseline	Zolpidem 5mg	Zolpidem 10mg	Triazolam	P value
	18 ( 0.001 )	28 ( <0.00 )	9 ( 0.06 )	
	% ( p vs baseline )			
# rebound: % of patients with a total nocturnal waking time >1 hours	Zolpidem 5mg	Zolpidem 10mg	Triazolam	P value
	55.9 ( 13.6 )	47.9 ( 29.6 )	55.8 ( 26.4 )	
	day 3 ( day 31 )			

Evidence Table 8. Active controlled trials (Elderly): Rebound Insomnia

<b>Author:</b>	<b>Roger</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

# rebound: feel well rested in the morning, change from baseline (higher score=better)	Zaleplon 5mg	Zolpidem 10mg	Triazolam		P value
	17.2 ( 0.05 )	23.9 ( 0.05 )	10.5 ( NA )	( )	
	Score ( p vs triazolam )				



### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Bergener                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1989                              **Country:** German                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** NR

**Age:** NR  
 Range: 64-80  
 SD:  
**Gender:** 36 ( 86 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 42  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 42

**Eligibility criteria:**

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.

**Exclusion criteria:**

Patients with a history of a delirium or a predeliumm 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

**Comments:**

**Intervention:** Run-in : 4  
 Wash out : 7  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	20	21 day	2 / 8
Flurazepam	30 mg	22	21 day	5 / 8

**Adverse Events:**

Withdrawals

# number of patients

Zopiclone	Flurazepam			P value:
8 ( 40 )	8 ( 36.3 )	( )	( )	NS

Number ( % )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Bergener                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1989                              **Country:** German                      **Funding:** Not reported

# withdrawals due to AEs

Zopiclone	Flurazepam			P value:
2 ( 10 )	5 ( 22.7 )	( )	( )	NS

Number ( % )

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Elie\_                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990a                      **Country:** Canada                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 76.0  
 Range: 60-90  
 SD: 1.3  
**Gender:** 33 ( 75 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 44  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 44

**Eligibility criteria:**

Age between 60 and 90 years, living in residential homes and suffering from chronic insomnia.

**Exclusion criteria:**

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.

**Comments:**

Elderly patients living in nursing homes.

**Intervention:**

**Run-in :** 7  
**Wash out :** 4  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	5-7. mg	15	21 day	0 / 0
Triazolam	0.12 mg	14	21 day	0 / 0
Placebo	NA mg	15	21 day	0 / 0

**Adverse Events:**

reported by patients

# reduction of dreams

Zopiclone	Triazolam			P value:
5 ( <0.02 )	3 ( NS )	( )	( )	

Number ( p vs placebo )

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Elie\_                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1990a                      **Country:** Canada                      **Funding:** Not reported

# bitter taste	Zopiclone	Triazolam			P value:
	5 ( <0.06 )	0 ( NS )	( )	( )	
Number ( p vs placebo )					

withdrawals

# total withdrawals	Zopiclone	Trazodone	Placebo		P value:
	0 ( )	0 ( )	0 ( )	( )	
Number ( )					

# withdrawals due to AEs	Zopiclone	Trazodone	Placebo		P value:
	0 ( )	0 ( )	0 ( )	( )	
Number ( )					

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

<b>Author:</b> Klimm	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1987	<b>Country:</b> France	<b>Funding:</b> Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Community practic

**Age:** 73.2  
 Range: >65  
 SD: 1.54  
**Gender:** 59 ( 80 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 74  
 Number Withdrawn: 2  
 Lost to fu: 2  
 Analyzed: 72

**Eligibility criteria:**

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 (Syndrom Kurztest) was to be within normal range for their age.

**Exclusion criteria:**

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.

**Comments:**

no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensives, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

**Intervention:** **Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** medication for concomitant disease were continued

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	36	7 day	0 / 1
Nitrazepam	5 mg	36	7 day	1 / 1

**Adverse Events:**

reported by patients

# bitter taste

Zopiclone	Nitrazepam			P value:
1 ( )	0 ( )	( )	( )	
Number ( )				

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

<b>Author:</b>	<b>Klimm</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

# dizziness	Zopiclone	Nitrazepam			P value:
	1 ( )	0 ( )	( )	( )	
Number ( )					
# confusion	Zopiclone	Nitrazepam			P value:
	0 ( )	1 ( )	( )	( )	
Number ( )					
# fatigue	Zopiclone	Nitrazepam			P value:
	0 ( )	1 ( )	( )	( )	
Number ( )					
# complaints in answer to the standardized question on tolerance	Zopiclone	Nitrazepam			P value:
	less ( NS )	more ( <0.00 )	( )	( )	
Number ( p vs baseline )					
<u>withdrawals</u>					
# total withdrawals	Zopiclone	Nitrazepam			P value:
	1 ( )	1 ( )	( )	( )	
Number ( )					
# withdrawals due to AEs	Zopiclone	Nitrazepam			P value:
	0 ( )	1 ( )	( )	( )	
Number ( )					

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lornex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 69  
 Range: 59-85  
 SD:  
**Gender:** 211 ( 63 % ) Female  
**Ethnicity:** 93% white

Number Screened: NR  
 Eligible: 457  
 Enrolled: 335  
 Number Withdrawn: 40  
 Lost to fu: 0  
 Analyzed: 335

**Eligibility criteria:**

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:**

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.

**Comments:**

**Intervention:** Run-in : 7  
 Wash out : 4  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	82	28 day	2 / 6
Triazolam	0.12 mg	85	28 day	5 / 14
Temazepam	15 mg	84	28 day	5 / 10
Placebo	NA mg	84	28 day	6 / 10

**Adverse Events:**

overall adverse events

# overall incidence rates

Zolpidem	Triazolam	Temazepam	Placebo	P value:
52 ( 63 )	54 ( 64 )	56 ( 67 )	47 ( 56 )	

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                      **Country:** US                      **Funding:** Lornex Pharmaceuticals

	Number ( % )				
	Zolpidem	Triazolam	Temazepam	Placebo	P value:
# headache	15 ( 18.3 )	22 ( 25.9 )	18 ( 21.4 )	16 ( 19 )	
	Number ( % )				
# drowsiness	4 ( 4.9 )	7 ( 8.2 )	8 ( 9.5 )	3 ( 3.6 )	
	Number ( % )				
# myalgia	8 ( 9.8 )	7 ( 8.2 )	8 ( 9.5 )	9 ( 10.7 )	
	Number ( % )				
# nausea	6 ( 7.3 )	6 ( 7.1 )	4 ( 4.8 )	6 ( 7.1 )	
	Number ( % )				
# upper resp infection	6 ( 7.3 )	2 ( 2.4 )	7 ( 8.3 )	7 ( 8.3 )	
	Number ( % )				
# dyspepsia	5 ( 6.1 )	3 ( 3.5 )	5 ( 6.0 )	7 ( 8.3 )	
	Number ( % )				
# nervousness	2 ( 2.4 )	7 ( 8.2 )	3 ( 3.6 )	4 ( 4.8 )	
	Number ( % )				



### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Leppik                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1997                              **Country:** US                              **Funding:** Lornex Pharmaceuticals

# arthralgia	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	4 ( 4.9 )	5 ( 5.9 )	0 ( 0 )	3 ( 3.6 )	
Number ( % )					
# fatigue	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	1 ( 1.2 )	2 ( 2.4 )	5 ( 6.0 )	1 ( 1.2 )	
Number ( % )					
<u>withdrawals</u>					
# total withdrawals	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	6 ( )	14 ( )	10 ( )	10 ( )	
Number ( )					
# withdrawals due to AEs	Zolpidem	Triazolam	Temazepam	Placebo	P value:
	2 ( )	5 ( )	5 ( )	6 ( )	
Number ( )					

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

<b>Author:</b>	<b>Roger</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 81.1  
Range: 58-98  
SD:  
**Gender:** 164 ( 74 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 221  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 205

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Inpatients at geriatric wards.

**Intervention:**

**Run-in :** 3  
**Wash out :** 7  
**Allow other medication :** a rescue hypnotic (nitrazepam 5mg) was given at night by the attending nurse on specific patient request in cases of inefficiency

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	70	21 day	0 / 7
Zolpidem	10 mg	74	21 day	0 / 1
Triazolam	0.25 mg	77	21 day	2 / 5

**Adverse Events:**

overall report

# no. patients experiencing adverse events

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
11 ( 16 )	8 ( 11 )	16 ( 21 )	( )	
Number ( % )				

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Roger                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** France                      **Funding:** Not reported

# nightmares- the most common adverse effect	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	2 ( )	3 ( )	2 ( )	( )	
Number ( )					
<u>withdrawals</u>					
# total withdrawals	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	7 ( )	1 ( )	5 ( )	( )	
Number ( )					
# withdrawals due to AEs	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	0 ( )	0 ( )	2 ( )	( )	
Number ( )					

### Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Venter                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1986                              **Country:** South Africa                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 76.8  
 Range: 60-96  
 SD:  
**Gender:** 31 ( 76 % ) Female  
**Ethnicity:** NR

Number Screened: 58  
 Eligible: 41  
 Enrolled: 41  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 41

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

22 patients were already receiving another hypnotic drug; the investigators decided a washout period in these patients would be undesirable. It was therefore decided that this group of patients should discontinue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study. Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

**Intervention:**

**Run-in :** 7  
**Wash out :** 0  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	0.33 mg	20	17 day	0 / 0
Triazolam	8.25 mg	21	17 day	0 / 0

**Adverse Events:**

Reported by the patients

# total number of patient

Zopiclone	Triazolam			P value:
7 ( 35 )	8 ( 38 )	( )	( )	NR

Number ( % )

Evidence Table 9. Active controlled trials (Elderly): Adverse Events

**Author:** Venter                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1986                              **Country:** South Africa                      **Funding:** Not reported

# number of patient reporting AEs on day 7 and day 9

Zopiclone	Triazolam			P value:
more ( )	NR ( )	( )	( )	0.013
Number ( )				

Reported by the patients: CNS AEs

# depression, tearfulness, drowsiness, dizziness, agitation, nightmares, confusion, and disturbed sleep

Zopiclone	Triazolam			P value:
3 ( )	7 ( )	( )	( )	NR
Number ( )				

Reported by the patients: Gastrointestinal AEs

# Bad taste

Zopiclone	Triazolam			P value:
6 ( )	2 ( )	( )	( )	NR
Number ( )				

Reported by the patients: Other AEs

# muscular pain, angina pectoris episodes, and shortness of breath

Zopiclone	Triazolam			P value:
3 ( )	1 ( )	( )	( )	NR
Number ( )				

withdrawals

# total withdrawals

Zopiclone	Triazolam			P value:
0 ( )	0 ( )	( )	( )	
Number ( )				

# withdrawals due to AEs

Zopiclone	Triazolam			P value:
0 ( )	0 ( )	( )	( )	
Number ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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**Author:** Agnoli                      **Trial type:** Active                      **Subgroup:** Anxiety                      **Quality rating:** Poor  
**Year:** 1989                      **Country:** Rome, Foggia, Italy                      **Funding:** Not reported

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**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** NR

**Age:** 38.2  
 Range:  
 SD: 2.1  
**Gender:** 12 ( 60 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 20  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 20

**Eligibility criteria:**

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.

**Exclusion criteria:**

Presence of concomitant general illness; renal or hepatic failure; effectiveness of placebo administration; and pregnancy.

**Comments:**

Poor quality: insufficient information to assess.  
 Patients with generalized anxiety disorder.

**Intervention:**

**Run-in :** 3  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	1 day	/
Nitrazepam	5 mg	12	1 day	/

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Agnoli                      **Trial type:** Active                      **Subgroup:** Anxiety                      **Quality rating:** Poor  
**Year:** 1989                      **Country:** Rome, Foggia, Italy                      **Funding:** Not reported

**Outcome Measurement:**

- # Hamilton Rating Scale for Anxiety (HRSA)
- # Toulouse-Pieron Attention Test (TPAT)
- # Time-signed semiquantitative scale

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- anxiety levels
  - time of sleep induction
  - hours of sleep
  - number of nocturnal arousals
  - quality of sleep
  - quality of daytime arousal

**Results**

Hamilton Rating Scale for Anxiety (HRSA)

# after the 1st and 2nd weeks of treatment (less score = better)

Nitrazepam					P value
-	( )	( )	( )	( )	<0.05
Score	( )	( )	( )	( )	

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Agnoli      **Trial type:** Active      **Subgroup:** Anxiety      **Quality rating:** Poor  
**Year:** 1989      **Country:** Rome, Foggia, Italy      **Funding:** Not reported

Toulouse-Pieron Attention Test

# reduction of omitted items on the 7th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# reduction of omitted items on the 14th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.05
	Number ( )				
# reduction of errors items on the 7th day (more reduction=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# times of excution (shorter=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				

Time-signed semiquantitative scale

# time of sleep induction (shorter=better)	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.001
	Number ( )				
# quality of daytime arousal	Nitrazepam				P value
	- ( )	( )	( )	( )	<0.01
	Number ( )				
# number of nocturnal arousals, the quality of sleep, the duration of sleep	Nitrazepam				P value
	NR ( )	( )	( )	( )	NS
	Number ( )				



### Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b>	<b>Ansoms</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>alcoholism</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1991</b>	<b>Country:</b>	<b>US</b>			<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 43.9  
Range: 20-55  
SD:  
**Gender:** 17 ( 33 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: 54  
Enrolled: 52  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 52

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

**Intervention:**

**Run-in :** 2  
**Wash out :** NR  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	27	5 day	0 / 0
Lormetazepam	1 mg	25	5 day	0 / 0

### Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Ansoms      **Trial type:** Active      **Subgroup:** alcoholism      **Quality rating:** Fair  
**Year:** 1991      **Country:** US      **Funding:** Not reported

**Outcome Measurement:**

- # Spiegel Sleep Questionnaire
- # Visual Analogue Scale
- # Investigator-completed scale (1=excellent, 2=good, 3=fair, 4=poor)

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- Efficacy (Spiegel Sleep Questionnaire)
- Behavior and mood on waking up
- Overall evaluation of efficacy and tolerabilit

**Results**

Efficacy (Spiegel Sleep Questionnaire)

# Improvement from baseline to end of treatment on time to fall asleep

Zopiclone	Lormetazepam			P value
NS ( )	0.013 ( )	( )	( )	

p-value ( )

# Improvement from baseline to end of treatment on quality of sleep

Zopiclone	Lormetazepam			P value
NS ( )	0.065 ( )	( )	( )	

p-value ( )

# Improvement from baseline to end of treatment on duration of sleep

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

# Improvement from baseline to end of treatment on nocturnal awakenings

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

# Improvement from baseline to end of treatment on dreams

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

# Improvement from baseline to end of treatment on morning disposition

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	

p-value ( )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Ansoms      **Trial type:** Active      **Subgroup:** alcoholism      **Quality rating:** Fair  
**Year:** 1991      **Country:** US      **Funding:** Not reported

# Improvement from baseline to end of treatment on general evaluation

Zopiclone	Lormetazepam			P value
NS ( )	NS ( )	( )	( )	
p-value ( )				

Overall evaluation of efficacy and tolerability

# Physician's overall efficacy assessment after treatment ("excellent or good")

Zopiclone	Lormetazepam			P value
44 ( )	48 ( )	( )	( )	NS
(%) ( )				

Behavior and mood on waking up

# No differences between treatments on any of 18 items based on Norris mood rating scale

0				P value
( )	( )	( )	( )	
( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Bozin-Juracic      **Trial type:** Active      **Subgroup:** shiftworker      **Quality rating:** Fair  
**Year:** 1995      **Country:** Croatia      **Funding:** May and Becker and Rhone-

**Design:**

**Study design** NR  
 NR  
 Crossover

**Setting** Single Center

**Age:** NR  
 Range: 24-58  
 SD:  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: 32  
 Enrolled: 29  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 29

**Eligibility criteria:**

A group of workers employed in a security company were recruited to the study as subjects

**Exclusion criteria:**  
 NR

**Comments:**

Not clear if randomized.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	29	7 day	0 / 0
Nitrazepam	5 mg	29	7 day	0 / 0
Placebo	NA mg	29	7 day	0 / 0

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b> Bozin-Juracic	<b>Trial type:</b> Active	<b>Subgroup:</b> shiftworker	<b>Quality rating:</b> Fair
<b>Year:</b> 1995	<b>Country:</b> Croatia	<b>Funding:</b> May and Becker and Rhone-	

**Outcome Measurement:**

# sleep questionnaire using visual-analogue scale

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- time in bed
- length of sleep episode
- total sleep time
- sleep efficacy
- sleep latency
- sleep quality
- no. of awakenings
- spontaneous final awakenings

**Results**

sleep questionnaire using visual-analogue scale

# mean total length of main sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	295 ( )	285 ( )	270 ( )	( )	NR
	minutes ( )				
# mean sleep efficacy of main sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	88 ( )	87 ( )	82 ( )	( )	NR
	% ( )				
# mean sleep efficacy of all day sleep (estimate from the figure)	Zopiclone	Nitrazepam	Placebo		P value
	88 ( )	87 ( )	82 ( )	( )	NR
	% ( )				
# 10 items of main sleep characteristics	Zopiclone	Nitrazepam	Placebo		P value
	NR ( )	NR ( )	NR ( )	( )	NS
	Score ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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**Author:** Bozin-Juracic      **Trial type:** Active      **Subgroup:** shiftworker      **Quality rating:** Fair  
**Year:** 1995      **Country:** Croatia      **Funding:** May and Becker and Rhone-

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# 5 items of all day sleep characteristics	Zopiclone	Nitrazepam	Placebo		P value
	NR ( )	NR ( )	NR ( )	( )	NS
	Score ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b>	<b>Fontaine</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>psychiatric</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>			<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 42.9  
Range: 26-58  
SD: 1.1  
**Gender:** 40 ( 53 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 75  
Number Withdrawn: 21  
Lost to fu: 0  
Analyzed: 75

**Eligibility criteria:**

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:**

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).

**Comments:**

Subgroup: generalized anxiety disorder

**Intervention:**

**Run-in :** 7  
**Wash out :** 21  
**Allow other medication :** no psychotropic medications

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	30	28 day	4 / 8
Triazolam	0.5 mg	30	28 day	3 / 8
Placebo	NA mg	15	28 day	0 / 5

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Fontaine      **Trial type:** Active      **Subgroup:** psychiatric      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Rhone-Poulenc Pharma

**Outcome Measurement:**

- # sleep inventory
- # Hamilton Rating Scale (HAM)
- # Clinical Global Impression (CGI)

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep induction
  - sleep soundness
  - duration of sleep
  - morning awakening
  - hangover effect

**Results**

sleep inventory

# sleep induction time

Zopiclone	Triazolam			P value
3.5 ( <0.01 )	3.5 ( <0.05 )	( )	( )	NS
Score ( p vs placebo )				

# sleep induction cluster

Zopiclone	Triazolam			P value
14.7 ( <0.05 )	14.1 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# duration of sleep

Zopiclone	Triazolam			P value
2.9 ( NS )	2.9 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# sleep soundness

Zopiclone	Triazolam			P value
11.0 ( <0.05 )	10.5 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# global sleep index

Zopiclone	Triazolam			P value
35.7 ( NS )	34.6 ( NS )	( )	( )	NS
Score ( p vs placebo )				



Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Fontaine      **Trial type:** Active      **Subgroup:** psychiatric      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Rhone-Poulenc Pharma

# morning awakening

Zopiclone	Triazolam			P value
7.3 ( NS )	6.7 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# hangover

Zopiclone	Triazolam			P value
6.8 ( NS )	6.3 ( NS )	( )	( )	NS
Score ( p vs placebo )				

Hamilton Rating Scale (HAM)

# somatic anxiety

Zopiclone	Triazolam			P value
8.8 ( NS )	12.0 ( NS )	( )	( )	<0.01
Score ( p vs placebo )				

# psychic anxiety

Zopiclone	Triazolam			P value
9.3 ( NS )	10.8 ( NS )	( )	( )	NS
Score ( p vs placebo )				

# total score

Zopiclone	Triazolam			P value
18.2 ( NS )	22.4 ( NS )	( )	( )	<0.01
Score ( p vs placebo )				

# daytime anxiety

Zopiclone	Triazolam			P value
5 ( 17 )	10 ( 33 )	( )	( )	0.16
Number ( % )				

Clinical Global Impression (CGI)

# overall

Zopiclone	Triazolam			P value
NR ( sig. bet )	NR ( sig. bet )	( )	( )	NR
Score ( p vs placebo )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b>	<b>Li Pi Shan</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>Stroke (inpatient)</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b> Not reported			

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 56.6  
Range: 20-78  
SD:  
**Gender:** 8 ( 44 % ) Female  
**Ethnicity:** NR  
Number Screened: 44  
Eligible: 27  
Enrolled: 18  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 18

**Eligibility criteria:**

Each patient with a diagnosis of either stroke or brain injury was consecutively recruited for eligibility.

**Exclusion criteria:**

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.

**Comments:**

Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1.  
Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** Concomitant use of medication were maintained throughout the trial

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	3.75 mg	18	As needed for 7 day	0 / 0
Lorazepam	0.5- mg	18	As needed for 7 day	0 / 0

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Li Pi Shan      **Trial type:** Active      **Subgroup:** Stroke (inpatient)      **Quality rating:** Fair  
**Year:** 2004      **Country:** Canada      **Funding:** Not reported

**Outcome Measurement:**

- # recorded by nurses
- # sleep questionnaire
- # Mini mentalstate examination score

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- total time of sleep
  - quality of sleep
  - depth of sleep
  - feeling of rest
  - daytime drowsiness
  - lethargy
  - fatigue

**Results**

recorded by nurses

# total time of sleep

Zopiclone	Lorazepam			P value
7.23 ( 0.63 )	7.49 ( 0.77 )	( )	( )	0.09
hours ( SD )				

# alertness (higer score=better)

Zopiclone	Lorazepam			P value
4 ( 3.5-4 )	4 ( 3.5-4 )	( )	( )	0.6
Score ( Range )				

# feeling of being refreshed (higer score=better)

Zopiclone	Lorazepam			P value
3.5 ( 3-4 )	4 ( 3-4 )	( )	( )	0.79
Score ( Range )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Li Pi Shan      **Trial type:** Active      **Subgroup:** Stroke (inpatient)      **Quality rating:** Fair  
**Year:** 2004      **Country:** Canada      **Funding:** Not reported

sleep questionnaire

# quality of sleep (higher score=better)

Zopiclone	Lorazepam			P value
8 ( 5-9 )	8.5 ( 7.5-10 )	( )	( )	0.17

Score ( Range )

# depth of sleep (higher score=better)

Zopiclone	Lorazepam			P value
8 ( 6-10 )	8 ( 7-10 )	( )	( )	0.21

Score ( Range )

# feeling of being refreshed (higher score=better)

Zopiclone	Lorazepam			P value
8 ( 6.5-10 )	8 ( 6.5-9.5 )	( )	( )	0.52

Score ( Range )

# alertness (higher score=better)

Zopiclone	Lorazepam			P value
9 ( 6.5-10 )	9 ( 8-10 )	( )	( )	0.6

Score ( Range )

# tiredness (higher score=better)

Zopiclone	Lorazepam			P value
8 ( 5.5-8.5 )	7.5 ( 5-10 )	( )	( )	0.29

Score ( Range )

Mini mentalstate examination score

# total score

Zopiclone	Lorazepam			P value
28 ( 27-30 )	27 ( 25-29 )	( )	( )	0.054

Score ( Range )

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b>	<b>Pagot</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>psychiatric</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>			<b>Funding:</b>	<b>Not reported</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 48  
Range:  
SD:  
**Gender:** 58 ( 61 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 95  
Number Withdrawn: 33  
Lost to fu: 0  
Analyzed: 62

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** 4  
**Wash out :** 30  
**Allow other medication :** no other hypnotic drugs

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	20 mg	47	86 day	1 / 15
Triazolam	0.5 mg	48	86 day	2 / 18

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Pagot                      **Trial type:** Active                      **Subgroup:** psychiatric                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** France                      **Funding:** Not reported

**Outcome Measurement:**

- # global assessment by the investigator
- # therapeutic efficacy by patients
- # Hamilton Rating Scale for anxiety

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- duration of sleep
  - number of nocturnal awakenings
  - time awake during the night
  - subjective status on awakening
  - therapeutic efficacy
  - anxiety

**Results**

therapeutic efficacy by patients

# therapeutic effects at day 30- good and excellent

Zolpidem	Triazolam			P value
32 ( 75 )	32 ( 75 )	( )	( )	NS
Number ( % )				

# therapeutic effects at day 60- good and excellent

Zolpidem	Triazolam			P value
33 ( 87 )	31 ( 84 )	( )	( )	NS
Number ( % )				

# therapeutic effects at day 90- good and excellent

Zolpidem	Triazolam			P value
32 ( 91 )	29 ( 85 )	( )	( )	NS
Number ( % )				

# quality of sleep at day 60

Zolpidem	Triazolam			P value
74 ( )	65 ( )	( )	( )	NR
% ( )				

# quality of sleep at day 90

Zolpidem	Triazolam			P value
81 ( )	73 ( )	( )	( )	NR
% ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Pagot      **Trial type:** Active      **Subgroup:** psychiatric      **Quality rating:** Fair  
**Year:** 1993      **Country:** France      **Funding:** Not reported

# overall rating

Zolpidem	Triazolam			P value
38.4 ( 78.6 )	36.3 ( 76.6 )	( )	( )	NR
day 0 ( day 90 )				

# status on awakening and alertness, number of patients

Zolpidem	Triazolam			P value
28 ( 44 )	40 ( 42 )	( )	( )	NR
day 4 ( day 90 )				

global assessment by the investigator

# sleep latency at day 90, change from baseline

Zolpidem	Triazolam			P value
-1.9 ( <0.001 )	-1.9 ( <0.001 )	( )	( )	NS
Score ( p vs baseline )				

# mean sleep time at day 90, change from baseline

Zolpidem	Triazolam			P value
2.72 ( <0.001 )	2.26 ( <0.001 )	( )	( )	NS
hours ( p vs baseline )				

# number of nocturnal awakenings at day 60, change from baseline

Zolpidem	Triazolam			P value
-1.7 ( 0.02 )	-1 ( 0.02 )	( )	( )	<0.05
Number ( p vs baseline )				

# duration of nocturnal awakenings at day 60

Zolpidem	Triazolam			P value
18 ( 0.02 )	14 ( 0.02 )	( )	( )	<0.05
minutes ( p vs baseline )				

Hamilton Rating Scale for anxiety

# total score

Zolpidem	Triazolam			P value
multiple d ( )	multiple d ( )	( )	( )	NS
Score ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

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**Author:** Schwartz                      **Trial type:** Active                      **Subgroup:** psychiatric (inpati                      **Quality rating:** Poor  
**Year:** 2004                              **Country:** US    **Funding:** Not reported

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**Design:**

**Study design** RCT  
 Open  
 Parallel  
**Setting** Single Center

**Age:** NR  
 Range: 18-65  
 SD:  
**Gender:** 8 ( 50 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 16  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 16

**Eligibility criteria:**  
 inpatient psychiatric care

**Exclusion criteria:**  
 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.

**Comments:**  
 Psychiatric inpatients

**Intervention:** Run-in : NR  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10-2 mg	7	AsN	1 / 1
Trazadone	50-1 mg	9	AsN	1 / 1



Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Schwartz      **Trial type:** Active      **Subgroup:** psychiatric (inpati      **Quality rating:** Poor  
**Year:** 2004      **Country:** US      **Funding:** Not reported

**Outcome Measurement:**

- # Epworth sleepiness scale (ESS)
- # analogue sleep quality scale
- # inpatient, nurse-recorded sleep log

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleepiness
  - sleep duration

**Results**

Epworth sleepiness scale (ESS)

# median at study entry-matching

Zaleplon	Trazodone			P value
7 ( )	9 ( )	( )	( )	0.885
Score ( )				

# media change from baseline efficacy and tolerability

Zaleplon	Trazodone			P value
-1 ( )	1 ( )	( )	( )	0.23
Score ( )				

inpatient, nurse-recorded sleep log

# sleep- median at study entry-matching

Zaleplon	Trazodone			P value
3 ( )	3 ( )	( )	( )	0.894
hours ( )				

# sleep- median change from baseline efficacy and tolerability

Zaleplon	Trazodone			P value
0 ( )	3 ( )	( )	( )	0.181
hours ( )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

<b>Author:</b>	<b>Steens</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>COPD</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b> Lorex Pharmaceuticals			

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Multicenter

**Age:** 58.2  
Range:  
SD: 5.5  
**Gender:** 9 ( 38 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 24  
Number Withdrawn: 0  
Lost to fu: 0  
Analyzed: 24

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, known 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.

**Comments:**

One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** no other hypnotics

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	24	1 day	0 / 0
Zolpidem	10 mg	24	1 day	0 / 0
Triazolam	0.25 mg	24	1 day	0 / 0
Placebo	NA mg	24	1 day	0 / 0

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Steens                      **Trial type:** Active                      **Subgroup:** COPD                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** Canada                      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # evening questionnaire
- # polysomnography
- # morning questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep quality
  - total wake time
  - awakening
  - microarousal
  - total sleep time
  - wake time during sleep period

**Results**

overall measures

# total sleep time

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
384.82 (<0.05 )	397.12 ( NS )	413.79 ( NA )	( )	
minutes ( p vs triazolam )				

# total wake time

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
93.09 (<0.05 )	82.37 ( NS )	66.10 ( NA )	( )	
minutes ( p vs triazolam )				

# sleep efficacy

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
79.74 (<0.05 )	82.35 ( NS )	85.83 ( NA )	( )	
% ( p vs triazolam )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Steens                      **Trial type:** Active                      **Subgroup:** COPD                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** Canada                      **Funding:** Lorex Pharmaceuticals

maintenance measures

# awakenings (no./hours of sleep)	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	4.70 (<0.05 )	4.07 ( NS )	3.68 ( NA )	( )	
	Number ( p vs triazolam )				
# microarousals (no./hour of sleep)	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	14.08 ( NS )	12.57 ( NS )	13.23 ( NA )	( )	
	Number ( p vs triazolam )				
# Arousals/total sleep time (no./hour)	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	18.69 ( NS )	16.46 ( NS )	16.72 ( NA )	( )	
	Number ( p vs triazolam )				
# wake time during sleep	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
	55.57 ( NS )	50.69 ( NS )	40.47 ( NA )	( )	
	Number ( p vs triazolam )				

Evidence Table 10. Active controlled trials (Other Subgroups): Efficacy

**Author:** Steens      **Trial type:** Active      **Subgroup:** COPD      **Quality rating:** Fair  
**Year:** 1993      **Country:** Canada      **Funding:** Lorex Pharmaceuticals

subjective assessment of sleep

# sleep latency

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
38.7 ( NS )	30.22 ( NS )	25.52 ( NA )	( )	
minutes ( p vs triazolam )				

# ease of falling sleep (lower score=better)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
46.48 ( <0.05 )	30.09 ( NS )	20.96 ( NA )	( )	
Score ( p vs triazolam )				

# no. of awakenings

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.74 ( NS )	2.17 ( NS )	1.61 ( NA )	( )	
minutes ( p vs triazolam )				

# duration of night waking

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
103.04 ( NS )	16.78 ( NS )	43.83 ( NA )	( )	
minutes ( p vs triazolam )				

# sleep duration

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
333.26 ( <0.05 )	388.22 ( NS )	411.17 ( NA )	( )	
minutes ( p vs triazolam )				

# feeling of sleep (1=excellent, 4=poor)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.61 ( <0.05 )	2.13 ( NS )	1.87 ( NA )	( )	
minutes ( p vs triazolam )				

# sleepy in the morning (higher score=better)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
55.04 ( NS )	65.44 ( NS )	66.52 ( NA )	( )	
minutes ( p vs triazolam )				

# concentration in the morning (1=excellent, 4=poor)

Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value
2.30 ( NS )	2.26 ( NS )	2.13 ( NA )	( )	
minutes ( p vs triazolam )				

Evidence Table 11. Active controlled trials (Other Subgroups): Rebound Insomnia

<b>Author:</b> Pagot	<b>Trial type:</b> Active	<b>Subgroup:</b> psychiatric	<b>Quality rating:</b> Fair
<b>Year:</b> 1993	<b>Country:</b> France	<b>Funding:</b> Not reported	

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 48  
Range:  
SD:  
**Gender:** 58 ( 61 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 95  
Number Withdrawn: 33  
Lost to fu: 0  
Analyzed: 62

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	20 mg	47	86 day	1 / 15
Triazolam	0.5 mg	48	86 day	2 / 18

**Rebound:**

therapeutic efficacy by patients

# rebound: therapeutic effects at day 120- good and excellent

Zolpidem	Triazolam			P value
33 ( 89 )	34 ( 83 )	( )	( )	NS
Number ( % )				

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Agnoli                      **Trial type:** Active                      **Subgroup:** Anxiety                      **Quality rating:** Poor  
**Year:** 1989                      **Country:** Rome, Foggia, Italy                      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** NR

**Age:** 38.2  
 Range:  
 SD: 2.1  
**Gender:** 12 ( 60 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 20  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 20

**Eligibility criteria:**

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.

**Exclusion criteria:**

Presence of concomitant general illness; renal or hepatic failure; effectiveness of placebo administration; and pregnancy.

**Comments:**

Poor quality: insufficient information to assess.  
 Patients with generalized anxiety disorder.

**Intervention:**

**Run-in :** 3  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	12	1 day	/
Nitrazepam	5 mg	12	1 day	/

**Adverse Events:**

epigestralgia

# 1st week

Zopiclone	Nitrazepam			P value:
1 ( )	1 ( )	( )	( )	NR
Number ( )				

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

---

**Author:** Agnoli                      **Trial type:** Active                      **Subgroup:** Anxiety                      **Quality rating:** Poor  
**Year:** 1989                              **Country:** Rome, Foggia, Italy                      **Funding:** Not reported

---

daytime sedation

# 1st week

Zopiclone	Nitrazepam			P value:
0 ( )	6 ( )	( )	( )	NR
Number ( )				

# 2dn week

Zopiclone	Nitrazepam			P value:
0 ( )	14 ( )	( )	( )	NR
Number ( )				

# prolonged into the wash-out period between treatment

Zopiclone	Nitrazepam			P value:
0 ( )	3 ( )	( )	( )	NR
Number ( )				

restlessness

# 1st week

Zopiclone	Nitrazepam			P value:
0 ( )	1 ( )	( )	( )	NR
Number ( )				



### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Ansoms      **Trial type:** Active      **Subgroup:** alcoholism      **Quality rating:** Fair  
**Year:** 1991      **Country:** US      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 43.9  
 Range: 20-55  
 SD:  
**Gender:** 17 ( 33 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: 54  
 Enrolled: 52  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 52

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

**Intervention:** Run-in : 2  
 Wash out : NR  
 Allow other medication : No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	27	5 day	0 / 0
Lormetazepam	1 mg	25	5 day	0 / 0

**Adverse Events:**

Overall safety

# Physician's overall safety assessment ("excellent" or "good")

	Zopiclone	Lormetazepam		P value:
( )	93 ( )	76 ( )	( )	NR

% ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Ansoms      **Trial type:** Active      **Subgroup:** alcoholism      **Quality rating:** Fair  
**Year:** 1991      **Country:** US      **Funding:** Not reported

withdrawals

# total withdrawals not reported

				P value:
( )	( )	( )	( )	
( )				

# withdrawals due to AEs not reported

				P value:
( )	( )	( )	( )	
( )				

Overall AEs

# Overall AEs

	Zopiclone	Lormetazepam		P value:
( )	26 ( )	28 ( )	( )	NS
%	( )			

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Bozin-Juracic      **Trial type:** Active      **Subgroup:** shiftworker      **Quality rating:** Fair  
**Year:** 1995      **Country:** Croatia      **Funding:** May and Becker and Rhone-

**Design:**

**Study design** NR  
 NR  
 Crossover  
**Setting** Single Center

**Age:** NR  
 Range: 24-58  
 SD:

**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: 32  
 Enrolled: 29  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 29

**Eligibility criteria:**

A group of workers employed in a security company were recruited to the study as subjects

**Exclusion criteria:**

NR

**Comments:**

Not clear if randomized.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	29	7 day	0 / 0
Nitrazepam	5 mg	29	7 day	0 / 0
Placebo	NA mg	29	7 day	0 / 0

**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Nitrazepam	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

# withdrawals due to AEs

Zopiclone	Nitrazepam	Placebo		P value:
0 ( )	0 ( )	0 ( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

<b>Author:</b>	<b>Fontaine</b>	<b>Trial type:</b>	<b>Active</b>	<b>Subgroup:</b>	<b>psychiatric</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b> Rhone-Poulenc Pharma			

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 42.9  
Range: 26-58  
SD: 1.1  
**Gender:** 40 ( 53 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 75  
Number Withdrawn: 21  
Lost to fu: 0  
Analyzed: 75

**Eligibility criteria:**

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:**

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).

**Comments:**

Subgroup: generalized anxiety disorder

**Intervention:**

**Run-in :** 7  
**Wash out :** 21  
**Allow other medication :** no psychotropic medications

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	30	28 day	4 / 8
Triazolam	0.5 mg	30	28 day	3 / 8
Placebo	NA mg	15	28 day	0 / 5

**Adverse Events:**

Hopkins Symptoms Checklist (SCL-90)

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Fontaine      **Trial type:** Active      **Subgroup:** psychiatric      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Rhone-Poulenc Pharma

# drowsiness	Zopiclone	Triazolam	Placebo		P value:
	3 ( )	5 ( )	4 ( )	( )	NS
Number ( )					
# ataxia	Zopiclone	Triazolam	Placebo		P value:
	2 ( )	3 ( )	1 ( )	( )	NS
Number ( )					
# headache	Zopiclone	Triazolam	Placebo		P value:
	6 ( )	3 ( )	3 ( )	( )	NS
Number ( )					
# taste perversion	Zopiclone	Triazolam	Placebo		P value:
	17 ( )	3 ( )	1 ( )	( )	<0.001
Number ( )					
# nausea	Zopiclone	Triazolam	Placebo		P value:
	2 ( )	3 ( )	4 ( )	( )	NS
Number ( )					
# dry mouth	Zopiclone	Triazolam	Placebo		P value:
	7 ( )	1 ( )	1 ( )	( )	<0.05
Number ( )					

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Fontaine      **Trial type:** Active      **Subgroup:** psychiatric      **Quality rating:** Fair  
**Year:** 1990      **Country:** Canada      **Funding:** Rhone-Poulenc Pharma

withdrawals

# total withdrawals

Zopiclone	Triazolam	Placebo		P value:
8 ( )	8 ( )	5 ( )	( )	
Number ( )				

# withdrawals due to AEs

Zopiclone	Triazolam	Placebo		P value:
4 ( )	3 ( )	0 ( )	( )	
Number ( )				

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Li Pi Shan      **Trial type:** Active      **Subgroup:** Stroke (inpatient)      **Quality rating:** Fair  
**Year:** 2004      **Country:** Canada      **Funding:** Not reported

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** 56.6  
 Range: 20-78  
 SD:  
**Gender:** 8 ( 44 % ) Female  
**Ethnicity:** NR  
 Number Screened: 44  
 Eligible: 27  
 Enrolled: 18  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 18

**Eligibility criteria:**

Each patient with a diagnosis of either stroke or brain injury was consecutively recruited for eligibility.

**Exclusion criteria:**

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.

**Comments:**

Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1.  
 Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** Concomitant use of medication were maintained throughout the trial

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	3.75 mg	18	As needed for 7 day	0 / 0
Lorazepam	0.5- mg	18	As needed for 7 day	0 / 0

**Adverse Events:**

withdrawals

# total withdrawals

Zopiclone	Lorazepam			P value:
0 ( )	0 ( )	( )	( )	
Number ( )				

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Li Pi Shan      **Trial type:** Active      **Subgroup:** Stroke (inpatient)      **Quality rating:** Fair  
**Year:** 2004      **Country:** Canada      **Funding:** Not reported

# withdrawals due to AEs

Zopiclone	Lorazepam			P value:
0 ( )	0 ( )	( )	( )	

Number ( )



### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

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**Author:** Pagot                                      **Trial type:** Active                                      **Subgroup:** psychiatric                                      **Quality rating:** Fair  
**Year:** 1993    **Country:** France    **Funding:** Not reported

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**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 48  
 Range:  
 SD:  
**Gender:** 58 ( 61 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 95  
 Number Withdrawn: 33  
 Lost to fu: 0  
 Analyzed: 62

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**      **Run-in :**            4  
                               **Wash out :**        30  
                               **Allow other medication :**    no other hypnotic drugs

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	20 mg	47	86 day	1 / 15	
Triazolam	0.5 mg	48	86 day	2 / 18	

**Adverse Events:**

withdrawals

# total withdrawals

Zolpidem 20mg	Triazolam 0.5mg			P value:
15 ( )	18 ( )	( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Pagot                      **Trial type:** Active                      **Subgroup:** psychiatric                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** France                      **Funding:** Not reported

# withdrawals due to AEs

Zolpidem 20mg	Triazolam 0.5mg			P value:
1 ( )	2 ( )	( )	( )	

Number ( )

Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Schwartz      **Trial type:** Active      **Subgroup:** psychiatric (inpati      **Quality rating:** Poor  
**Year:** 2004      **Country:** US      **Funding:** Not reported

**Design:**

**Study design** RCT  
 Open  
 Parallel  
**Setting** Single Center

**Age:** NR  
 Range: 18-65  
 SD:  
**Gender:** 8 ( 50 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 16  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 16

**Eligibility criteria:**  
 inpatient psychiatric care

**Exclusion criteria:**  
 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.

**Comments:**  
 Psychiatric inpatients

**Intervention:** Run-in : NR  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	10-2 mg	7	AsN	1 / 1
Trazadone	50-1 mg	9	AsN	1 / 1

**Adverse Events:**

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Steens                      **Trial type:** Active                      **Subgroup:** COPD                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** Canada                      **Funding:** Lorex Pharmaceuticals

# total withdrawals	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	0 ( )	0 ( )	0 ( )	( )	
	Number ( )				
# withdrawals due to AEs	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	0 ( )	0 ( )	0 ( )	( )	
	Number ( )				
<u>Lab data- respiratory events</u>					
# reduction of SaO2	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	0 ( )	2 ( )	2 ( )	( )	
	Number ( )				
# apnea-hypopnea	Zolpidem 5mg	Zolpidem 10mg	Triazolam		P value:
	1 ( )	2 ( )	1 ( )	( )	
	Number ( )				

### Evidence Table 12. Active controlled trials (Other Subgroups): Adverse Events

**Author:** Steens                      **Trial type:** Active                      **Subgroup:** COPD                      **Quality rating:** Fair  
**Year:** 1993                      **Country:** Canada                      **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Multicenter

**Age:** 58.2  
 Range:  
 SD: 5.5  
**Gender:** 9 ( 38 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 24  
 Number Withdrawn: 0  
 Lost to fu: 0  
 Analyzed: 24

**Eligibility criteria:**

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.

**Exclusion criteria:**

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, known 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.

**Comments:**

One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

**Intervention:**

**Run-in :** 0  
**Wash out :** 0  
**Allow other medication :** no other hypnotics

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	5 mg	24	1 day	0 / 0
Zolpidem	10 mg	24	1 day	0 / 0
Triazolam	0.25 mg	24	1 day	0 / 0
Placebo	NA mg	24	1 day	0 / 0

**Adverse Events:**

withdrawals

### Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Allain</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 51.9  
 Range: 32-84  
 SD: 16.7  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 37  
 Number Withdrawn: 18  
 Lost to fu: NR  
 Analyzed: 37

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 woemn; liver or respiratory failure, myasthenia, or epilepsy.

**Comments:**

**Intervention:** Run-in : 3  
 Wash out : 3  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	18	21 day	1 / 1
Placebo	NA mg	19	21 day	17 / 17

### Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Allain                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1998                      **Country:** France                      **Funding:** NR

---

**Outcome Measurement:**

- # clinical global impression
- # sleep questionnaire
- # sleep diary

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - number of nocturnal awakenings
  - total sleep time
  - sleep quality
  - nightmares
  - wakefulness
  - daytime alertness
  - anxiety
  - mood
  - energy

**Results**

clinical global impression

# overall no different except day 21, where zolpidem was more effective, p<0.007

Zolpidem	Placebo			P value
NR ( )	NR ( )	( )	( )	NS
Mean ( )	( )			

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Allain                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1998                      **Country:** France                      **Funding:** NR

sleep questionnaire

# daytime alertness

Zolpidem	Placebo			P value
NR ( )	NR ( )	( )	( )	NS

Mean ( )

# total sleep time (hr) at day 7

Zolpidem	Placebo			P value
6.13 ( )	6.40 ( )	( )	( )	NR

Mean ( )

# total sleep time (hr) at day 28

Zolpidem	Placebo			P value
NR ( )	NR ( )	( )	( )	NS

Mean ( )

# less nightmare

Zolpidem	Placebo			P value
93 ( )	less ( )	( )	( )	<0.04

% ( )

sleep diary

# number of awakenings

Zolpidem	Placebo			P value
better ( )	NR ( )	( )	( )	<0.0001

( )

# anxiety

Zolpidem	Placebo			P value
better ( )	NR ( )	( )	( )	<0.0003

( )

# amount of sleep

Zolpidem	Placebo			P value
better ( )	NR ( )	( )	( )	<0.0001

( )

# energy

Zolpidem	Placebo			P value
better ( )	NR ( )	( )	( )	<0.01

( )



Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Allain\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** France                      **Funding:** Sanofi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 46.1  
 Range: 25-64  
 SD: 10.5  
**Gender:** 188 ( 77 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 245  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 245

**Eligibility criteria:**

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterised 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 characterised 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.

**Exclusion criteria:**

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 if they had desynchronisation type 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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more than 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

**Comments:**

Zolpidem was administrated as needed, not every night.

**Intervention:** Run-in : 3-7  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	124	28 day	1 / 3
Placebo	NA mg	121	28 day	1 / 7

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Allain\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 2001      **Country:** France      **Funding:** Sanofi-Synthelabo

**Outcome Measurement:**

- # sleep diary
- # clinical global impression
- # SF-36 healthy survey

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep duration
  - quality of sleep
  - drowsiness during the day
  - anxious during the day
  - sadness during the day
  - duration of daytime sleep
  - sleep-onset latency
  - number of nocturnal awakenings
  - wake time after sleep onset

**Results**

sleep diary

# total sleep time (min), change from baseline, all condition	Zolpidem	Placebo			P value
	74.6 ( 77.7 )	63.2 ( 69.9 )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min), change from baseline, with pill	Zolpidem	Placebo			P value
	82.7 ( 80.1 )	62.8 ( 77.2 )	( )	( )	<0.05
	Mean ( SD )				
# sleep quality (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	14.1 ( 17.4 )	20.6 ( 22.3 )	( )	( )	0.01
	Mean ( SD )				
# daytime drowsiness (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	-1.8 ( 12.6 )	-5.3 ( 14.9 )	( )	( )	0.048
	Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

Author:	Allain_	Trial type:	Placebo	Quality rating:	Fair
Year:	2001	Country:	France	Funding:	Sanofi-Synthelabo
# anxiety during the day (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	-1.5 ( 16.2 )	-2.9 ( 19.7 )	( )	( )	0.55
	Mean ( SD )				
# sadness during the day (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	-0.6 ( 15.4 )	-2.8 ( 17.7 )	( )	( )	0.30
	Mean ( SD )				
# vitality in the morning (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	9.1 ( 16.2 )	9.6 ( 21.3 )	( )	( )	0.83
	Mean ( SD )				
# lucidity in the morning (1=worse; 100=better), change from baseline	Zolpidem	Placebo			P value
	2.9 ( 16.2 )	2.3 ( 18.4 )	( )	( )	0.77
	Mean ( SD )				
# sleep onset latency (min), change from baseline	Zolpidem	Placebo			P value
	-23 ( 38.7 )	-18.8 ( 35.4 )	( )	( )	<0.05
	Mean ( SD )				
# wake time after sleep onset (min), change from baseline	Zolpidem	Placebo			P value
	-32.8 ( 37.7 )	-31.4 ( 37.1 )	( )	( )	NR
	Mean ( SD )				
# number of nocturnal awakenings, change from baseline	Zolpidem	Placebo			P value
	-1.2 ( NR )	-1.2 ( NR )	( )	( )	<0.05
	Mean ( SD )				
# daytime sleep duration (min), change from baseline	Zolpidem	Placebo			P value
	-2.6 ( 19.6 )	-0.9 ( 15.1 )	( )	( )	NR
	Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Allain\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 2001      **Country:** France      **Funding:** Sanofi-Synthelabo

clinical global impression

# severity of illness- not ill to mildly ill

Zolpidem	Placebo			P value
69 ( 55.6 )	46 ( 38.7 )	( )	( )	0.002

Number ( % )

# global impression- much or very much improved

Zolpidem	Placebo			P value
67 ( 54 )	29 ( 24 )	( )	( )	<0.0001

Number ( % )

# efficacy index- when efficacy outseighs safety )

Zolpidem	Placebo			P value
108 ( 87 )	84 ( 71 )	( )	( )	0.0004

Number ( % )

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Allain\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 2001      **Country:** France      **Funding:** Sanofi-Synthelabo

SF-36 healthy survey

# physical function, change from baseline	Zolpidem	Placebo			P value
	2.5 ( 17.3 )	2.7 ( 4.6 )	( )	( )	NS
	Mean ( SD )				
# role limitations due to physical problem, change from baseline	Zolpidem	Placebo			P value
	7.5 ( 29 )	4.9 ( 32.5 )	( )	( )	NS
	Mean ( SD )				
# bodily pain, change from baseline	Zolpidem	Placebo			P value
	4.7 ( 21 )	3.7 ( 22.4 )	( )	( )	NS
	Mean ( SD )				
# general health perception, change from baseline	Zolpidem	Placebo			P value
	3.4 ( 12.4 )	2.5 ( 12.5 )	( )	( )	NS
	Mean ( SD )				
# vitality, change from baseline	Zolpidem	Placebo			P value
	6.5 ( 16.6 )	5.7 ( 14 )	( )	( )	NS
	Mean ( SD )				
# social functioning, change from baseline	Zolpidem	Placebo			P value
	6.1 ( 22.4 )	2.8 ( 21.6 )	( )	( )	NS
	Mean ( SD )				
# role limitations due to emotional problems, change from baseline	Zolpidem	Placebo			P value
	7.9 ( 39.1 )	-0.3 ( 33.9 )	( )	( )	NS
	Mean ( SD )				
# general mental health, change from baseline	Zolpidem	Placebo			P value
	5.9 ( 16.8 )	5.1 ( 14.5 )	( )	( )	NS
	Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Chadoir</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	<b>NR (May &amp; Baker provided m</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 50  
Range: 35-65  
SD: NR  
**Gender:** 18 ( 72 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 30  
Enrolled: 25  
Number Withdrawn: 5  
Lost to fu: 0  
Analyzed: 25

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	25	7 day	2 / 2
Placebo	NA mg	25	7 day	3 / 3

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Chaudoir      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1983      **Country:** UK      **Funding:** NR (May & Baker provided m

**Outcome Measurement:**

- # sleep questionnaire
- # interview by investigator

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - number of awakenings
  - sleep quality
  - feeling after waking

**Results**

daily sleep questionnaire

# feelings after waking (VAS - mm),  
0=very badly; 100=very well

Zopiclone	Placebo			P value
59 ( 4.4 )	59 ( 4.2 )	( )	( )	NS
Mean ( SD	)			

# sleep onset latency (min)

Zopiclone	Placebo			P value
31.1 ( 4.0 )	49.1 ( 4.5 )	( )	( )	<0.001
Mean ( SD	)			

# number of night awakenings

Zopiclone	Placebo			P value
1.5 ( 0.2 )	2.1 ( 0.3 )	( )	( )	<0.05
Mean ( SD	)			

# sleep quality (VAS - mm), 0=very  
badly; 100=very well

Zopiclone	Placebo			P value
67 ( 4.0 )	51 ( 3.5 )	( )	( )	<0.05
Mean ( SD	)			

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Chaudoir      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1983      **Country:** UK      **Funding:** NR (May & Baker provided m

weekly assessment

# sleep onset latency (min)	Zopiclone	Placebo			P value
	28.6 ( 3.9 )	45.2 ( 5.5 )	( )	( )	<0.05
	Mean ( SD )				
# number of night awakenings	Zopiclone	Placebo			P value
	1.6 ( 0.3 )	2.1 ( 0.3 )	( )	( )	NS
	Mean ( SD )				
# sleep quality (VAS mm), 0=very badly; 100=very well	Zopiclone	Placebo			P value
	63 ( 4.8 )	48 ( 5.0 )	( )	( )	<0.01
	Mean ( SD )				
# feelings after awakening (VAS mm), 0=very badly; 100=very well	Zopiclone	Placebo			P value
	67 ( 4.9 )	67 ( 4.7 )	( )	( )	NS
	Mean ( SD )				
# percentage of patients with early awakenings (%)	Zopiclone	Placebo			P value
	44 ( )	56 ( )	( )	( )	NS
	Mean ( )				
# mood rating scales (mm) - factor I alertness	Zopiclone	Placebo			P value
	59 ( 3.6 )	59 ( 4.2 )	( )	( )	NS
	Mean ( SD )				
# mood rating scales (mm) - factor II contentedness	Zopiclone	Placebo			P value
	61 ( 4.5 )	63 ( 3.9 )	( )	( )	NS
	Mean ( SD )				
# mood rating scales (mm) - factor III calmness	Zopiclone	Placebo			P value
	57 ( 3.7 )	59 ( 4.7 )	( )	( )	NS
	Mean ( SD )				



### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dockhorn                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1996                              **Country:** US                              **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 32.7  
 Range: 20-55  
 SD: NR  
**Gender:** 80 ( 58 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 138  
 Number Withdrawn: 9  
 Lost to fu: 2  
 Analyzed: 136

**Eligibility criteria:**

Healthy patients who had experienced acute insomnia (3-9 nights) due 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)

**Exclusion criteria:**

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 hypnotic. Patients who normally slept on an unusual schedule (e.g., shift workers) and women who were lactating or at risk on pregnancy were excluded

**Comments:**

**Intervention:** Run-in : NR  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	68	7-10 day	1 / 3
Placebo	NA mg	68	7-10 day	2 / 6

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dockhorn      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1996      **Country:** US      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # morning questionnaire
- # clinical global impression scale

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep latency
  - total sleep time
  - ease of falling asleep
  - number og awakenings
  - wake time after sleep onset
  - quality of sleep
  - ability to concentrate in the morning
  - morning sleepiness

**Results**

morning questionnaire

# sleep latency (min), day 3-10

Zolpidem	Placebo			P value
43.2 ( 6.9 )	64.0 ( 7.7 )	( )	( )	0.001
Mean ( SD )				

# total sleep time (min), day 3-10

Zolpidem	Placebo			P value
422.2 ( 11 )	389 ( 10.1 )	( )	( )	0.054
Mean ( SD )				

# ease of falling asleep (0=very easy; 100= not all easy), day 3-10

Zolpidem	Placebo			P value
34.8 ( 2.2 )	45.2 ( 2.3 )	( )	( )	0.004
Mean ( SD )				

# number of awakenings, day 3-10

Zolpidem	Placebo			P value
0.8 ( 0.1 )	1.2 ( 0.1 )	( )	( )	0.014
Mean ( SD )				

## Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dockhorn      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1996      **Country:** US      **Funding:** Lorex Pharmaceuticals

# wake time after sleep onset (min), day 3-10	Zolpidem	Placebo			P value
	18.1 ( 3.4 )	34.6 ( 4.8 )	( )	( )	0.008
	Mean ( SD )				
# quality of sleep (1=excellent; 4=poor), day 3-10	Zolpidem	Placebo			P value
	2.2 ( 0.1 )	2.5 ( 0.01 )	( )	( )	0.007
	Mean ( SD )				
# ability to concentrate (1=excellent; 4=poor), day 3-10	Zolpidem	Placebo			P value
	2.3 ( 0.1 )	2.4 ( 0.1 )	( )	( )	0.358
	Mean ( SD )				
# morning sleepiness (0=very sleepy; 100=not at all sleepy), day 3-10	Zolpidem	Placebo			P value
	53.6 ( 2.2 )	52.1 ( 2.3 )	( )	( )	0.762
	Mean ( SD )				

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dockhorn      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1996      **Country:** US      **Funding:** Lorex Pharmaceuticals

clinical global impression scale

# quality of sleep- excellent or good	Zolpidem	Placebo			P value
	78 ( )	42 ( )	( )	( )	<0.001
	% ( )				
# change in sleep- improved a lot or somewhat	Zolpidem	Placebo			P value
	84 ( )	48 ( )	( )	( )	<0.001
	% ( )				
# change in time to fall asleep	Zolpidem	Placebo			P value
	81 ( )	42 ( )	( )	( )	<0.001
	% ( )				
# change in amount of sleep	Zolpidem	Placebo			P value
	79 ( )	43 ( )	( )	( )	<0.001
	% ( )				
# strength of medication- just right	Zolpidem	Placebo			P value
	62 ( )	28 ( )	( )	( )	<0.001
	% ( )				
# change during posttreatment days- much or somewhat better	Zolpidem	Placebo			P value
	75 ( )	40 ( )	( )	( )	0.002
	% ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dorsey                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                      **Country:** US                      **Funding:** Sanofi-Synthelabo

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 50.8  
 Range: 39-60  
 SD: 4.5  
**Gender:** 141 ( 100 % ) Female  
**Ethnicity:** NR  
 Number Screened: 242  
 Eligible: 141  
 Enrolled: 141  
 Number Withdrawn: 16  
 Lost to fu: 3  
 Analyzed: 141

**Eligibility criteria:**

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:**

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, barbituates, 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.

**Comments:**

**Intervention:**      **Run-in :** 6-14  
                              **Wash out :** NR  
                              **Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5

### Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Dorsey                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                      **Country:** US                      **Funding:** Sanofi-Synthelabo

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**Outcome Measurement:**

- # patients global impression rating
- # sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - number of awakenings
  - wake time after sleep onset
  - sleep duration
  - quality of sleep

**Results**

patients global impression rating

# average summary score (lower score=better sleep)

Zolpidem	Placebo			P value
5.53 ( )	6.71 ( )	( )	( )	
Mean ( )				

# number of patients with better sleep

Zolpidem	Placebo			P value
76.8 ( )	43.8 ( )	( )	( )	<0.001
% ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Dorsey                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sanofi-Synthelabo

sleep questionnaire

# change in sleep duration (min), 4 weeks average	Zolpidem	Placebo			P value
	56.5 ( )	20.5 ( )	( )	( )	<0.01
Mean ( )					
# wake after sleep onset (min), 4 weeks average	Zolpidem	Placebo			P value
	29.75 ( )	52.75 ( )	( )	( )	<0.05
Mean ( )					
# number of awakenings, 4 weeks average	Zolpidem	Placebo			P value
	1.4 ( )	2 ( )	( )	( )	<0.05
Mean ( )					
# sleep latency (min), 4 weeks average	Zolpidem	Placebo			P value
	31.25 ( )	34.25 ( )	( )	( )	NS
Mean ( )					
# sleep-related difficulty with daytime functioning	Zolpidem	Placebo			P value
	2.1 ( )	2.2 ( )	( )	( )	<0.05
Mean ( )					
# quality of life	Zolpidem	Placebo			P value
	NR ( )	NR ( )	( )	( )	NS
Mean ( )					

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Goldenberg</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>UK, France</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 25-60  
SD: NR  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 524  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 458

**Eligibility criteria:**

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 wakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.

**Exclusion criteria:**

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 of pregnancy. Nursing mothers, and those performing skilled tasks, shiftwork 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.

**Comments:**

Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	44 day	N / NR



### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Goldenberg      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1994      **Country:** UK, France      **Funding:** NR

**Outcome Measurement:**

- # psychological general well being index (PGWBI)
- # sleep evaluation questionnaire (SEQ)
- # Leeds sleep evaluation questionnaire (LSEQ)

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- quality of sleep
  - quality of waking up
  - feeling of well being during the day
  - physician's overall evaluation

**Results**

Sleep efficiency at endpoint

# quality of sleep

Zopiclone	Placebo			P value
1.9 ( 1.1 )	1.3 ( 1.2 )	( )	( )	<0.0001
Mean ( SD	)			

# quality of waking up

Zopiclone	Placebo			P value
1.5 ( 1.2 )	1.0 ( 1.1 )	( )	( )	<0.0001
Mean ( SD	)			

# feeling of well being during the day

Zopiclone	Placebo			P value
1.3 ( 1.1 )	0.8 ( 1.1 )	( )	( )	<0.0001
Mean ( SD	)			

# physician's overall evaluation:  
average, good or excellent

Zopiclone	Placebo			P value
187 ( 92.5 )	125 ( 66.9 )	( )	( )	<0.0001
Number ( %	)			

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Goldenberg      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1994      **Country:** UK, France      **Funding:** NR

Quality of life - change from baseline

# PGWBI	Zopiclone	Placebo			P value
	11.8 ( )	9.1 ( )	( )	( )	NS
	Score ( )				
# SEQ	Zolpidem	Placebo			P value
	14.6 ( )	2.7 ( )	( )	( )	<0.0001
	Score ( )				
# Activity	Zopiclone	Placebo			P value
	20 ( )	9.9 ( )	( )	( )	<0.0001
	Score ( )				
# Social	Zolpidem	Placebo			P value
	13.1 ( )	5.7 ( )	( )	( )	<0.01
	Score ( )				
# Profession	Zopiclone	Placebo			P value
	23.3 ( )	12.9 ( )	( )	( )	<0.01
	Score ( )				
# Global	Zopiclone	Placebo			P value
	10.8 ( )	5.7 ( )	( )	( )	NS
	Score ( )				

### Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Hedner                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000                      **Country:** Europe                      **Funding:**

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**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 72.5  
 Range: 59-95  
 SD: NR  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 437  
 Number Withdrawn: 22  
 Lost to fu: NR  
 Analyzed: 422

**Eligibility criteria:**

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 characterised 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.

**Exclusion criteria:**

Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled.

**Comments:**

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	139	14 day	10 / 10
Zaleplon	10 mg	145	14 day	5 / 5
Placebo	NA mg	138	14 day	7 / 7

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Hedner                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000                      **Country:** Europe                      **Funding:**

**Outcome Measurement:**

# sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep duration
  - number of awakenings
  - sleep quality

**Results**

sleep questionnaire

# subjective sleep latency (min), week 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	43 (<0.001 )	40 (<0.001 )	60 ( NA )	( )	
	Median ( p vs placebo )				
# subjective sleep latency (min), week 2	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	40 (<0.001 )	37 (<0.001 )	50 ( NA )	( )	
	Median ( p vs placebo )				
# subjective total sleep time (min), week 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	342 ( NS )	342.9 (<0.05 )	346.1 ( NA )	( )	
	Median ( p vs placebo )				
# subjective total sleep time (min), week 2	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	351.7 ( NS )	351.4 ( NS )	342.9 ( NA )	( )	
	Median ( p vs placebo )				
# subjective number of awakenings, week 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	2 ( NS )	2 (<0.05 )	2 ( NA )	( )	
	Median ( p vs placebo )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Hedner                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000                      **Country:** Europe                      **Funding:**

# subjective number of awakenings, week 2	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	2 ( NS )	1 ( NS )	2 ( NA )	( )	
Median ( p vs placebo )					
# subjective sleep quality, week 1 (score). 1=excellent; 7=extremely poor	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	3.8 ( <0.01 )	3.8 ( <0.01 )	3.9 ( NA )	( )	
Mean ( p vs placebo )					
# subjective sleep quality, week 2 (score). 1=excellent; 7=extremely poor	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	3.7 ( <0.05 )	3.7 ( <0.05 )	3.8 ( NA )	( )	
Mean ( p vs placebo )					
# subjective sleep quality, improvement in sleep quality- week 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	48 ( NS )	55 ( <0.000 )	36 ( NA )	( )	
% ( p vs placebo )					
# subjective sleep quality, improvement in sleep quality- week 2	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	53 ( NS )	63 ( <0.000 )	36 ( NA )	( )	
% ( p vs placebo )					

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Herrmann                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1993                              **Country:** France                      **Funding:** NR

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** NR  
 Range: 25-65  
 SD: NR  
**Gender:** 9 ( 43 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: 25  
 Enrolled: 21  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 21

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Herrmann      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1993      **Country:** France      **Funding:** NR

**Outcome Measurement:**

- # polysomnography
- # sleep questionnaire

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep efficiency
  - sleep latency
  - total sleep time
  - number of awakenings
  - wake after sleep onset

**Results**

polysomnography

# sleep efficiency (%), day 21 treatment

Zolpidem	Placebo			P value
86.2 ( 2 )	78.3 ( 5 )	( )	( )	<0.05
Mean ( SD )				

# total sleep time (min), day 21 treatment

Zolpidem	Placebo			P value
381.3 ( 10 )	360.3 ( 23 )	( )	( )	NS
Mean ( SD )				

# sleep onset latency (min), day 21 treatment

Zolpidem	Placebo			P value
28 ( 7 )	41.7 ( 15 )	( )	( )	NS
Mean ( SD )				

# time awake (min), day 21 treatment

Zolpidem	Placebo			P value
34.7 ( 7 )	60 ( 12 )	( )	( )	NS
Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Herrmann      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1993      **Country:** France      **Funding:** NR

sleep questionnaire

# sleep onset latency (min), day 15-21 treatment	Zolpidem	Placebo			P value
	40.5 ( 10 )	72.8 ( 10 )	( )	( )	<0.05
	Mean ( SD )				
# total sleep time (min), day 15-21 treatment	Zolpidem	Placebo			P value
	372.7 ( 12 )	327.4 ( 22 )	( )	( )	NS
	Mean ( SD )				
# no. of awakenings, day 15-21 treatment	Zolpidem	Placebo			P value
	1.8 ( 0.4 )	2.3 ( 0.4 )	( )	( )	NS
	Mean ( SD )				
# calm/restless, fresh/fatigued, relaxed/anxious, lying down during the day	Zolpidem	Placebo			P value
	multi-data ( multi-d )	multi-data ( multi-d )	( )	( )	NS
	Mean ( SD )				



Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Hindmarch                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1995                                  **Country:** UK                                  **Funding:**

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 42.9  
 Range: 25-60  
 SD: 8.9  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 458  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 458

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	42 day	N / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Hindmarch      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1995      **Country:** UK      **Funding:**

**Outcome Measurement:**

# questionnaire

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- quality of sleep
  - quality of waking up
  - daytime feeling of well being

**Results**

questionnaire

# psychological general well-being index (PGWBI), change from baseline, day 14	Zolpidem	Placebo			P value
	11.8 ( )	9.1 ( )	( )	( )	NS
Mean ( )					
# sleep evaluation questionnaire (SEQ), change from baseline, day 14	Zolpidem	Placebo			P value
	14.6 ( )	2.7 ( )	( )	( )	<0.0001
Mean ( )					
# activity, change from baseline, day 14	Zolpidem	Placebo			P value
	20 ( )	9.9 ( )	( )	( )	<0.0001
Mean ( )					
# social, change from baseline, day 14	Zolpidem	Placebo			P value
	13.4 ( )	5.7 ( )	( )	( )	<0.01
Mean ( )					
# profession, change from baseline, day 14	Zolpidem	Placebo			P value
	23.3 ( )	12.9 ( )	( )	( )	<0.01
Mean ( )					
# global, change from baseline, day 14	Zolpidem	Placebo			P value
	10.8 ( )	5.7 ( )	( )	( )	NS
Mean ( )					

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Hindmarch      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1995      **Country:** UK      **Funding:**

# psychological general well-being index (PGWBI), change from baseline, endpoint	Zolpidem	Placebo			P value
	15.2 ( )	12.9 ( )	( )	( )	NS
Mean ( )					
# sleep evaluation questionnaire (SEQ), change from baseline, endpoint	Zolpidem	Placebo			P value
	20.9 ( )	12.5 ( )	( )	( )	<0.0001
Mean ( )					
# activity, change from baseline, endpoint	Zolpidem	Placebo			P value
	21.6 ( )	14.2 ( )	( )	( )	<0.0001
Mean ( )					
# social, change from baseline, endpoint	Zolpidem	Placebo			P value
	14.9 ( )	9.1 ( )	( )	( )	<0.01
Mean ( )					
# profession, change from baseline, endpoint	Zolpidem	Placebo			P value
	24.5 ( )	18.7 ( )	( )	( )	NS
Mean ( )					
# global, change from baseline, endpoint	Zolpidem	Placebo			P value
	13.8 ( )	8.9 ( )	( )	( )	NS
Mean ( )					
# physician's overall evaluation of treatment efficacy as "excellent" or "good" at endpoint	Zolpidem	Placebo			P value
	76.7 ( )	51.4 ( )	( )	( )	
% ( )					

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Krystal                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2003                              **Country:** US                              **Funding:** Sepracor

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 44  
 Range: 21-69  
 SD: 11.3  
**Gender:** 195 ( 25 % ) Female  
**Ethnicity:** 80% caucasian  
 13.2% african  
 american  
 7.9% other

Number Screened: 1194  
 Eligible: 791  
 Enrolled: 788  
 Number Withdrawn: 320  
 Lost to fu: 60  
 Analyzed: 788

**Eligibility criteria:**

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.

**Exclusion criteria:**  
 NR

**Comments:**

**Intervention:**      **Run-in :** NR  
                             **Wash out :** 5-7  
                             **Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	3 mg	593	180 day	76 / 235
Placebo	NA mg	195	180 day	14 / 85

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Krystal                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2003                              **Country:** US                              **Funding:** Sepracor

**Outcome Measurement:**

# telephone interview

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep latency
  - wake time after sleep onset
  - total sleep time
  - number of awakenings
  - number of nights during the week
  - sleep quality
  - daytime ability to function
  - daytime alertness
  - sense of physical well-being

**Results**

telephone interview

# sleep latency, month 6

Eszopiclone	Placebo			P value
47.0 ( 50.6 )	63.1 ( 57.9 )	( )	( )	<0.001
Mean ( SD )				

# wake after sleep onset, month 6

Eszopiclone	Placebo			P value
44.2 ( 74.2 )	48.2 ( 59.4 )	( )	( )	0.0032
Mean ( SD )				

# number of awakenings, month 6

Eszopiclone	Placebo			P value
1.9 ( 1.5 )	2.6 ( 2.7 )	( )	( )	<0.0001
Mean ( SD )				

# number of night awakenings per week, month 6

Eszopiclone	Placebo			P value
3.9 ( 2.5 )	4.7 ( 2.4 )	( )	( )	0.0001
Mean ( SD )				

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Krystal                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2003                              **Country:** US                              **Funding:** Sepracor

# total sleep time, month 6	Eszopiclone	Placebo			P value
	378.3 ( 72.3 )	339.3 ( 77.1 )	( )	( )	<0.001
	Mean ( SD )				
# sleep quality, month 6	Eszopiclone	Placebo			P value
	6.4 ( 1.8 )	5.5 ( 1.8 )	( )	( )	<0.0001
	Mean ( SD )				
# daytime ability to function, month 6	Eszopiclone	Placebo			P value
	6.8 ( 1.7 )	6.2 ( 1.8 )	( )	( )	<0.0001
	Mean ( SD )				
# daytime alertness, month 6	Eszopiclone	Placebo			P value
	6.5 ( 1.7 )	5.9 ( 1.7 )	( )	( )	<.0001
	Mean ( SD )				
# sense of physical well-being, month 6	Eszopiclone	Placebo			P value
	6.7 ( 1.7 )	6.1 ( 1.8 )	( )	( )	0.0002
	Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Lahmeyer</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1997</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Roche Pharmaceuticals</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 44.9  
Range: 19-61  
SD: 11.6  
**Gender:** 81 ( 56 % ) Female  
**Ethnicity:** 92% caucasian  
6% black  
<1% hispanic  
1% asian  
Number Screened: 178  
Eligible: 33  
Enrolled: 145  
Number Withdrawn: 27  
Lost to fu: 0  
Analyzed: 118

**Eligibility criteria:**

Patients had to have a history of a minimum of 3 months of disturbed sleep, characterised by a typical sleep duration of between 4 and 6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints.

**Exclusion criteria:**

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 shortacting 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 nights 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.

**Comments:**

**Intervention:**

**Run-in :** 3  
**Wash out :** 4  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	45	31 day	4 / 8
Zolpidem	15 mg	46	31 day	3 / 9
Placebo	NA mg	54	31 day	0 / 10

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Lahmeyer      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1997      **Country:** US      **Funding:** Orex Pharmaceuticals

**Outcome Measurement:**

- # morning questionnaire
- # clinical global impression

**Efficacy Outcome List:**

- Primary outcome**
- sleep duration
  - sleep latency
  - ease of falling asleep
  - number of awakenings
  - wake after sleep onset
  - quality of sleep
  - morning sleepiness
  - ability to concentrate

**Results**

morning questionnaire - 4 weeks average

# sleep latency (min), change from baseline - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	-30 ( )	-33.5 ( )	-9 ( )	( )	
Mean ( )					
# total sleep time (min) - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	379 ( )	381 ( )	346 ( )	( )	
Mean ( )					
# number of awakenings - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	1.3 ( )	1.3 ( )	1.9 ( )	( )	
Mean ( )					
# sleep quality (1=excellent; 4=poor) - 4 weeks average	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
	2.4 ( )	2.4 ( )	2.8 ( )	( )	
Mean ( )					



Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Lahmeyer      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1997      **Country:** US      **Funding:** Orex Pharmaceuticals

morning questionnaire - at week 4

# sleep latency (min), change from baseline - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
-31 ( <0.05 )	-31 ( NS )	-16 ( NA )	( )	

Mean ( p vs placebo )

# total sleep time (min) - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
390 ( NS )	385 ( NS )	360 ( NA )	( )	

Mean ( p vs placebo )

# number of awakenings - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
1.4 ( NS )	1.2 ( NS )	1.7 ( NA )	( )	

Mean ( p vs placebo )

# sleep quality (1=excellent; 4=poor) - at week 4

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.4 ( NS )	2.4 ( NS )	2.6 ( NA )	( )	

Mean ( p vs placebo )

morning questionnaire - post-treatment

# sleep latency (min), change from baseline - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
-10 ( NS )	-11 ( NS )	-25 ( NA )	( )	

Mean ( p vs placebo )

# total sleep time (min) - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
354 ( NS )	332 ( NS )	359 ( NA )	( )	

Mean ( p vs placebo )

# number of awakenings - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
1.7 ( NS )	1.9 ( NS )	1.9 ( NA )	( )	

Mean ( p vs placebo )

# sleep quality (1=excellent; 4=poor) - post-treatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.8 ( NS )	2.9 ( NS )	2.8 ( NA )	( )	

Mean ( p vs placebo )

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Lahmeyer      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1997      **Country:** US      **Funding:** Orex Pharmaceuticals

clinical global impression

# medication helped me - fall asleep faster

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
84 ( <0.05 )	78 ( <0.05 )	51 ( NA )	( )	
% ( p vs placebo )				

# medication helped me - sleep longer

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
78 ( <0.05 )	76 ( NS )	51 ( NA )	( )	
% ( p vs placebo )				

# medication helped me - get a better night's sleep

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
84 ( ,0.05 )	84 ( <0.05 )	49 ( NA )	( )	
% ( p vs placebo )				

# medication strength - too strong

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
0 ( NS )	0 ( NS )	0 ( NA )	( )	
% ( p vs placebo )				

# medication strength - strong enough

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
71 ( <0.05 )	72 ( <0.05 )	44 ( NA )	( )	
% ( p vs placebo )				

# medication strength - too weak

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
29 ( NS )	28 ( NS )	56 ( NA )	( )	
% ( p vs placebo )				

### Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Monchesky      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1986      **Country:** Canada      **Funding:** NR

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**Design:**

**Study design** RCT  
 DB  
 Crossover  
**Setting** Single Center

**Age:** NR  
 Range: 23-69  
 SD: NR  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 99  
 Number Withdrawn: 0  
 Lost to fu: 2  
 Analyzed: 91

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Zopiclone 7.5mg for run-in and wash-out periods.  
 Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** No use of neuroleptics, sedatives, analgesics, or antidepressants

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	91	7 day	N / NR
Placebo	NA mg	91	7 day	N / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monchesky      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1986      **Country:** Canada      **Funding:** NR

**Outcome Measurement:**

# sleep questionnaire

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- sleepiness during the day
- sleep latency
- sleep duration
- number of awakenings

**Results**

sleep questionnaire

# duration of sleep (min), treatment day 7	Zolpidem	Placebo			P value
	384.8 ( )	307.4 ( )	( )	( )	NR
	Mean ( )				
# number of awakenings, treatment day 7	Zolpidem	Placebo			P value
	1.8 ( )	3.5 ( )	( )	( )	NR
	Mean ( )				
# quality of sleep, treatment day 7	Zolpidem	Placebo			P value
	4.15 ( )	3.15 ( )	( )	( )	NR
	Mean ( )				
# soundness of sleep, treatment day 7	Zolpidem	Placebo			P value
	3.8 ( )	2.75 ( )	( )	( )	NR
	Mean ( )				
# morning state of rest, treatment day 7	Zolpidem	Placebo			P value
	2.85 ( )	1.95 ( )	( )	( )	NR
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monchesky      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1986      **Country:** Canada      **Funding:** NR

# sleepiness during the day, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.3 ( )	2.9 ( )	( )	( )	NR
Mean ( )					
# sleep induction time (min), treatment day 14 (switch)	Zolpidem	Placebo			P value
	53.8 ( )	119.3 ( )	( )	( )	NR
Mean ( )					
# duration of sleep (min), treatment day 14 (switch)	Zolpidem	Placebo			P value
	376.7 ( )	299.5 ( )	( )	( )	NR
Mean ( )					
# number of awakenings, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.0 ( )	2.45 ( )	( )	( )	NR
Mean ( )					
# quality of sleep, treatment day 14 (switch)	Zolpidem	Placebo			P value
	4.35 ( )	2.95 ( )	( )	( )	NR
Mean ( )					
# soundness of sleep, treatment day 14 (switch)	Zolpidem	Placebo			P value
	4.0 ( )	2.4 ( )	( )	( )	NR
Mean ( )					
# morning state of rest, treatment day 14 (switch)	Zolpidem	Placebo			P value
	2.9 ( )	2.15 ( )	( )	( )	NR
Mean ( )					
# sleepiness during the day, treatment day 7	Zolpidem	Placebo			P value
	2.3 ( )	2.65 ( )	( )	( )	NR
Mean ( )					

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monchesky      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1986      **Country:** Canada      **Funding:** NR

# sleep induction time (min), treatment day 7

Zolpidem	Placebo			P value
51.85 ( )	89.9 ( )	( )	( )	NR
Mean ( )	( )			

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 44.25  
 Range: NR  
 SD: 4.8  
**Gender:** 10 ( 83 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 12  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 12

**Eligibility criteria:**

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 waketime >20 minutes; number of nocturnal awakenings >3.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**  
**Run-in :** 2  
**Wash out :** 3  
**Allow other medication :** No

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	6	27 day	N / NR
Placebo	NA mg	6	27 day	N / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monti                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1996                      **Country:** Uruguay                      **Funding:** NR

**Outcome Measurement:**

- # polysomnography
- # questionnaire

**Efficacy Outcome List:**

- Primary outcome**    **Outcome:**
- sleep latency
  - number of awakenings
  - total wake time
  - wake time after sleep onset
  - total sleep time
  - sleep efficiency
  - movement time

**Results**

polysomnography

# stage 2 sleep latency (min), nights 29-30	Zolpidem	Placebo			P value
	23.6 ( 7.1 )	35.1 ( 5.6 )	( )	( )	NS
Mean ( SD )					
# total number of awakenings, nights 29-30	Zolpidem	Placebo			P value
	24.8 ( 4.3 )	25.5 ( 5.7 )	( )	( )	NS
Mean ( SD )					
# total wake time (min), nights 29-30	Zolpidem	Placebo			P value
	53.8 ( 6.9 )	104.8 ( 21.8 )	( )	( )	<0.05
Mean ( SD )					
# wake time after sleep onset (min), nights 29-30	Zolpidem	Placebo			P value
	26.3 ( 7.0 )	85.3 ( 24.2 )	( )	( )	NS
Mean ( SD )					
# total sleep time (min), nights 29-30	Zolpidem	Placebo			P value
	419.3 ( 7.1 )	370.9 ( 21.2 )	( )	( )	<0.05
Mean ( SD )					



Evidence Table 13. Placebo controlled trials: Efficacy

Author:	<b>Monti</b>	Trial type:	<b>Placebo</b>	Quality rating:	<b>Fair</b>
Year:	<b>1996</b>	Country:	<b>Uruguay</b>	Funding:	<b>NR</b>
# sleep efficiency (%), nights 29-30	Zolpidem	Placebo			P value
	87.3 ( 1.5 )	77.3 ( 4.4 )	( )	( )	NS
Mean ( SD )					
# movement time, nights 29-30	Zolpidem	Placebo			P value
	6.9 ( 2.6 )	4.3 ( 1.2 )	( )	( )	NS
Mean ( SD )					
<u>questionnaire</u>					
# sleep latency (lower score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.0 ( 0.4 )	1.8 ( 0.5 )	( )	( )	NS
Mean ( SD )					
# sleep duration (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.3 ( 0.3 )	2.5 ( 0.4 )	( )	( )	NS
Mean ( SD )					
# number of awakenings (lower score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	2.6 ( 0.3 )	1.9 ( 0.3 )	( )	( )	NS
Mean ( SD )					
# disturbed sleep (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	73.1 ( 8.7 )	48.5 ( 8.3 )	( )	( )	<0.01
Mean ( SD )					
# daytime alertness (higher score indicates more positive response), night 29-30	Zolpidem	Placebo			P value
	69.0 ( 9.5 )	44.2 ( 8.4 )	( )	( )	NS
Mean ( SD )					

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Monti_</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 51.9  
Range: NR  
SD: 3.6  
**Gender:** 12 ( 100 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 12  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 12

**Eligibility criteria:**

Patients aged between 27 and 59 years, with chronic primary insomina according to the DSM-IV participated in the study.

**Exclusion criteria:**

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 swere pregnanct women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with cliniclally significant diviations 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.

**Comments:**

**Intervention:**  
**Run-in :** 3  
**Wash out :** 3  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	6	15 day	N / NR
Placebo	NA mg	6	15 day	N / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monti\_      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 2000      **Country:** Uruguay      **Funding:** NR

**Outcome Measurement:**

- # Interview
- # polygraphic sleep record

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep latency
  - number of awakenings
  - wake time after sleep onset
  - total sleep time
  - sleep efficiency

**Results**

polygraphic sleep record

# total sleep time (min) - night 17-18

Zolpidem	Placebo			P value
361.2 ( 25.8 )	264.4 ( 33.3 )	( )	( )	<0.02
Mean ( SD )				

# sleep efficiency (%) - night 4-5

Zolpidem	Placebo			P value
79.9 ( 1.6 )	61.9 ( 5 )	( )	( )	<0.006
Mean ( SD )				

# sleep efficiency (%) - night 17-18

Zolpidem	Placebo			P value
75.4 ( 5.4 )	55.1 ( 6.9 )	( )	( )	<0.01
Mean ( SD )				

# stage 2 sleep latency - night 4-5

Zolpidem	Placebo			P value
26.1 ( 4.5 )	67.4 ( 14.9 )	( )	( )	<0.02
Mean ( SD )				

# stage 2 sleep latency - night 17-18

Zolpidem	Placebo			P value
29.2 ( 6.8 )	48.3 ( 6.9 )	( )	( )	NS
Mean ( SD )				

### Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Monti_</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>NR</b>

	Zolpidem	Placebo			P value
# total number of awakenings - night 4-5	29.4 ( 5.1 )	32.2 ( 3.8 )	( )	( )	NS
	Mean ( SD )				
# total number of awakenings - night 17-18	26.9 ( 2.2 )	26.5 ( 4.9 )	( )	( )	NS
	Mean ( SD )				
# waking time after sleep onset (min) - night 4-5	75.1 ( 7.9 )	137.5 ( 29.2 )	( )	( )	<0.03
	Mean ( SD )				
# waking time after sleep onset (min) - night 17-18	95.7 ( 23.3 )	173.3 ( 35.4 )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min) - night 4-5	378.8 ( 8.2 )	279.3 ( 24.2 )	( )	( )	<0.01
	Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Monti\_      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 2000      **Country:** Uruguay      **Funding:** NR

interview

# sleep latency (min) - night 4-5

Zolpidem	Placebo			P value
34.6 ( 8.2 )	228.0 ( 80.8 )	( )	( )	<0.01
Mean ( SD )				

# sleep latency (min) - night 17-18

Zolpidem	Placebo			P value
49.5 ( 8.2 )	154.0 ( 52.1 )	( )	( )	<0.01
Mean ( SD )				

# sleep duration (min) - night 4-5

Zolpidem	Placebo			P value
384.0 ( 29.1 )	180.0 ( 61.3 )	( )	( )	NS
Mean ( SD )				

# sleep duration (min) - night 17-18

Zolpidem	Placebo			P value
342.0 ( 40.5 )	225.0 ( 55.3 )	( )	( )	NS
Mean ( SD )				

# disturbed sleep - night 4-5 (1=agree; 100=disagree)

Zolpidem	Placebo			P value
78.4 ( 6.2 )	46.4 ( 12.9 )	( )	( )	NS
Mean ( SD )				

# disturbed sleep - night 17-18 (1=agree; 100=disagree)

Zolpidem	Placebo			P value
74.6 ( 8.4 )	40.1 ( 14.8 )	( )	( )	NS
Mean ( SD )				

# alert in the morning - night 4-5 (1=agree; 100=disagree)

Zolpidem	Placebo			P value
20.8 ( 6.3 )	57.5 ( 16.1 )	( )	( )	NS
Mean ( SD )				

# alert in the morning - night 17-18 (1=agree; 100=disagree)

Zolpidem	Placebo			P value
30.3 ( 10.6 )	65.9 ( 12.1 )	( )	( )	NS
Mean ( SD )				

### Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Perlis</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Lorex Pharmaceuticals</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 40.8  
Range: 18-64  
SD: 12.7  
**Gender:** 141 ( 71 % ) Female  
**Ethnicity:** 70% euro-american  
Number Screened: 322  
Eligible: 277  
Enrolled: 199  
Number Withdrawn: 10  
Lost to fu: 3  
Analyzed: 192

**Eligibility criteria:**

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:**

Exclusion criteria included presene 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; postiive urine screen for medication that could interfere with the assessment of study medication; history of drug addiciton, alcoholism, or drug abuse; and histroy 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.

**Comments:**

Patients were instructed to "take the medication when you think you need it, at bedtime, for a total of between 3 and 5 capsules per week". They were also told to take only 1 pill per night and not to use the study medication to treat early awakenings.

**Intervention:**

**Run-in :** 6-14  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	98	84 day	7 / 7
Placebo	NA mg	101	84 day	3 / 3

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Perlis                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # sleep diaries
- # global outcome measure

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - number of awakenings
  - wake after sleep onset
  - total sleep time

**Results**

sleep diaries

# sleep latency (min), without pill

Zolpidem	Placebo			P value
NR ( NR )	NR ( NR )	( )	( )	NS
Mean ( SD	)			

# sleep latency (min), all condition significant at week 10 only

Zolpidem	Placebo			P value
NR ( NR )	NR ( NR )	( )	( )	NS
Mean ( SD	)			

# number of awakenings, with pill

Zolpidem	Placebo			P value
1.03 ( 0.92 )	1.64 ( 1.33 )	( )	( )	<0.05
Mean ( SD	)			

# number of awakenings, without pill

Zolpidem	Placebo			P value
NR ( NR )	NR ( NR )	( )	( )	NS
Mean ( SD	)			

# number of awakenings, all condition, significant at week 2 and 12 only

Zolpidem	Placebo			P value
1.38 ( 1.00 )	1.69 ( 1.28 )	( )	( )	NS
Mean ( SD	)			

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Perlis      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 2004      **Country:** US      **Funding:** Lorex Pharmaceuticals

# wake after sleep onset (min), with pill	Zolpidem	Placebo			P value
	32.6 ( 43.5 )	55.4 ( 56.1 )	( )	( )	<0.05
	Mean ( SD )				
# wake after sleep onset (min), without pill	Zolpidem	Placebo			P value
	NR ( NR )	NR ( NR )	( )	( )	NS
	Mean ( SD )				
# wake after sleep onset (min), all condition, significant at week 2 only	Zolpidem	Placebo			P value
	NR ( NR )	NR ( NR )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min), with pill	Zolpidem	Placebo			P value
	417 ( 64.4 )	359.8 ( 77.1 )	( )	( )	<0.05
	Mean ( SD )				
# total sleep time (min), without pill	Zolpidem	Placebo			P value
	NR ( NR )	NR ( NR )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min), all condition	Zolpidem	Placebo			P value
	394.1 ( 60.1 )	355.6 ( 69.6 )	( )	( )	<0.05
	Mean ( SD )				
# sleep latency (min), with pill	Zolpidem	Placebo			P value
	38.4 ( 33.1 )	55.1 ( 52.3 )	( )	( )	<0.05
	Mean ( SD )				
<u>global outcome measure</u>					
# IGR scale	Zolpidem	Placebo			P value
	6 ( 0.12 )	4.5 ( 0.14 )	( )	( )	<0.001
	Mean ( SD )				



Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2005                      **Country:** US                      **Funding:**

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 72.3  
 Range: 64-85  
 SD: 4.9  
**Gender:** 133 ( 58 % ) Female  
**Ethnicity:** 89.4% caucasian  
 2.2% black  
 1.3% hispanic  
 Number Screened: 353  
 Eligible: NR  
 Enrolled: 231  
 Number Withdrawn: 21  
 Lost to fu: NR  
 Analyzed: 231

**Eligibility criteria:**

Men and women between the ges of 65 and 85 years who met the DSM-IV for primary insomnia and who reprted sleeping 6.5 hours per night or less and took more than 30 minutes to fall asleep each night for at least 1 month

**Exclusion criteria:**

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 excluded.

**Comments:**

**Intervention:**    **Run-in :** 3-14  
                          **Wash out :** NR  
                          **Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	1 mg	72	14 day	1 / NR
Eszopiclone	2 mg	79	14 day	2 / NR
Placebo	NA mg	80	14 day	5 / NR

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2005                              **Country:** US                              **Funding:**

**Outcome Measurement:**

- # morning questionnaire
- # evening questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - total sleep time
  - wake time after sleep onset
  - number of awakenings
  - sleep quality
  - sleep depth
  - daytime alertness
  - ability to function
  - sense of physical well-being
  - number of naps taken
  - length of naps

**Results**

morning questionnaire

# number of awakenings - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
2 ( NS )	1.7 ( NS )	1.9 ( NA )	( )	
Mean ( p vs placebo )				

# sleep quality (0=poor; 10=excellent) - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.6 ( NS )	7.2 ( 0.0006 )	6.3 ( NA )	( )	
Mean ( p vs placebo )				

# sleep depth (0=very light; 10=very deep) - average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.5 ( NS )	7.1 ( 0.0015 )	6.2 ( NA )	( )	
Mean ( p vs placebo )				

### Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b> Scharf	<b>Trial type:</b> Placebo			<b>Quality rating:</b> Fair	
<b>Year:</b> 2005	<b>Country:</b> US			<b>Funding:</b>	

# sleep latency (min) - average	Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
	53.6 ( <0.05 )	50 ( 0.0034 )	85.5 ( NA )	( )	
	Mean ( p vs placebo )				
# total sleep time (min) - average	Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
	349.8 ( NS )	372.3 ( 0.0003 )	328.2 ( NA )	( )	
	Mean ( p vs placebo )				
# wake after sleep onset (min) - average	Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
	72.6 ( NS )	58.5 ( 0.423 )	74.1 ( NA )	( )	
	Mean ( p vs placebo )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2005                              **Country:** US                              **Funding:**

evening questionnaire

# daytime alertness (0=drowsy; 10=alert), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.1 ( NS )	7.3 ( 0.0223 )	6.8 ( NA )	( )	

Mean ( p vs placebo )

# physical well-being (0=poor; 10=excellent), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.5 ( NS )	7.7 ( 0.0474 )	7.2 ( NA )	( )	

Mean ( p vs placebo )

# morning sleepiness (0=very sleepy; 10=not at all sleepy), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
6.9 ( NS )	7.2 ( 0.054 )	6.6 ( NA )	( )	

Mean ( p vs placebo )

# daily ability to function (0=poor; 10=excellent), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
7.4 ( NS )	7.6 ( 0.0579 )	7.2 ( NA )	( )	

Mean ( p vs placebo )

# number of naps taken, total

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
5.0 ( NS )	4.3 ( 0.0276 )	5.9 ( NA )	( )	

Mean ( p vs placebo )

# duration per nap (min), average

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value
47.7 ( <0.05 )	52.7 ( 0.0113 )	59.2 ( NA )	( )	

Mean ( p vs placebo )

### Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b> Scharf_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 1994	<b>Country:</b> US	<b>Funding:</b> NR

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 38  
Range: 22-60  
SD: NR  
**Gender:** 48 ( 64 % ) Female  
**Ethnicity:** 73.3% white  
26.7% non-white

Number Screened: 178  
Eligible: 75  
Enrolled: 75  
Number Withdrawn:  
Lost to fu:  
Analyzed:

**Eligibility criteria:**

After giving informed consent, outpatient insomniacs, aged 21 to 60 years, were screened to rule out significant medical or psychiatric disorders and to ensure that they were in good health. Patients were not have used any investigational drug within 30 days of the start of the study. In addition, patients were required to have chronic insomnia defined as a history of the following for at least 3 months preceding screening: usual reported sleep duration between 4 and 6 hours, usual reported sleep latency of at least 30 minutes, and daytime complaints associated with disturbed sleep. The first night of placebo screening period served as a laboratory adaptation night and to rule out patients with sleep apnea or periodic limb movements during sleep. During the next 3 nightns, patients had to meet the following criteria: total sleep time of 240 to 420 minutes (4 to 7 hours) in a 480-minute recording on at least 2 or the 3 screening nights, and a latency to persistant sleep of > 20 minutes on each of these 2 nights. "Persistent sleep" was defined as the first continuous 20 epochs of a non-wake state.

**Exclusion criteria:**

**Comments:**

**Intervention:** Run-in : 11  
Wash out : 2  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	26	35 day	0 / 4
Zolpidem	15 mg	25	35 day	2 / 3
Placebo	NA mg	24	35 day	0 / 1

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1994      **Country:** US      **Funding:** NR

**Outcome Measurement:**

- # polysomnography
- # morning questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep efficiency
  - total sleep time
  - sleep quality
  - ease of falling sleep

**Results**

polysomnography

# sleep latency (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
25.8 ( 0.063 )	28.1 ( p<0.05 )	48 ( NA )	( )	
Mean ( p vs placebo )				

# sleep efficiency (%), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
87.9 ( 0.063 )	87.3 ( p<0.05 )	80.7 ( NA )	( )	
Mean ( p vs placebo )				

# sleep latency (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
47.1 ( NS )	47.7 ( NS )	48.0 ( NA )	( )	
Mean ( p vs placebo )				

# sleep efficiency (%), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
83.1 ( NS )	79.9 ( NS )	81.9 ( NA )	( )	
Mean ( p vs placebo )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1994      **Country:** US      **Funding:** NR

morning questionnaire

# sleep latency (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
38.4 ( NS )	31.7 ( <0.05 )	56.6 ( NA )	( )	

Mean ( p vs placebo )

# ease of falling sleep (0=very easy; 100=not easy), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
50.7 ( NS )	35.7 ( <0.05 )	48.4 ( NA )	( )	

Mean ( p vs placebo )

# sleep quality (1=excellent; 4=poor), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.5 ( NS )	2.5 ( NS )	2.6 ( NA )	( )	

Mean ( p vs placebo )

# total sleep time (min), week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
369 ( NS )	394 ( NS )	356 ( NA )	( )	

Mean ( p vs placebo )

# sleep latency (min), posttreatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
62.3 ( NS )	78.2 ( NS )	47.5 ( NA )	( )	

Mean ( p vs placebo )

# ease of falling sleep (0=very easy; 100=not easy), posttreatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
63.7 ( NS )	64.0 ( <0.05 )	44.4 ( NA )	( )	

Mean ( p vs placebo )

# sleep quality (1=excellent; 4=poor), posttreatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
2.9 ( <0.05 )	3.1 ( <0.05 )	2.6 ( NA )	( )	

Mean ( p vs placebo )

# total sleep time (min), posttreatment

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
333 ( NS )	341 ( NS )	333 ( NA )	( )	

Mean ( p vs placebo )

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Scharf\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1994      **Country:** US      **Funding:** NR

# tolerance assessment, change from week 2 to week 6

Zolpidem 10mg	Zolpidem 15mg	Placebo		P value
multi-data ( NS )	multi-data ( NS )	multi-dat ( NA )	( )	
Mean ( p vs placebo )				



Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Terzano                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1992                              **Country:** Italy                              **Funding:** Partially supported by Italian

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 49.6  
 Range: 40-60  
 SD: 5.1  
**Gender:** 8 ( 67 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 12  
 Number Withdrawn: NR  
 Lost to fu: NR  
 Analyzed: 12

**Eligibility criteria:**

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.

**Exclusion criteria:**

patients had nocturnal myoclonus or sleep apnea syndrome

**Comments:**

**Intervention:** Run-in : 14  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	0	1 day	N / NA
Placebo	NA mg	0	1 day	N / NA

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Terzano                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1992                              **Country:** Italy                              **Funding:** Partially supported by Italian

**Outcome Measurement:**

# polysomnography

**Efficacy Outcome List:**

**Primary outcome**

**Outcome:**

- sleep latency
- wake after sleep onset
- total sleep time

**Results**

polysomnography

# sleep latency (min)

Zolpidem	Placebo			P value
8.1 ( 7.1 )	14.5 ( 14 )	( )	( )	NR
Mean ( SD )				

# wake after sleep onset (min)

Zolpidem	Placebo			P value
16 ( )	41 ( )	( )	( )	NR
Mean ( )				

# total sleep time (min)

Zolpidem	Placebo			P value
420 ( 49.7 )	402 ( 37.9 )	( )	( )	NR
Mean ( SD )				

Evidence Table 13. Placebo controlled trials: Efficacy

<b>Author:</b>	<b>Walsh</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000a</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 67.5  
Range: 60-79  
SD: NR  
**Gender:** 17 ( 35 % ) Female  
**Ethnicity:** NR  
Number Screened: 311  
Eligible: 54  
Enrolled: 48  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 48

**Eligibility criteria:**

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 tiem between 180 and 360 minutes.

**Exclusion criteria:**

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 medicaiton 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.

**Comments:**

**Intervention:**  
**Run-in :** 5-12  
**Wash out :** 5-12  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	2 mg	12	2 day	N / NR
Zaleplon	5 mg	12	2 day	N / NR
Zaleplon	10 mg	12	2 day	N / NR
Placebo	NA mg	12	2 day	N / NR

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Walsh                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 2000a                      **Country:** US                      **Funding:**

**Outcome Measurement:**

- # polysomnography
- # questionnaire

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - sleep duration
  - number of awakenings

**Results**

polysomnography

# PSG latency to persistent sleep (min)

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
30.4 ( 0.015 )	26.0 ( <0.001 )	21.8 ( <0.00 )	47.7 ( NA )	
Mean ( p vs placebo )				

# PSG total sleep time (min)

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
359.3 ( 0.239 )	363.9 ( 0.003 )	362.8 ( 0.03 )	351.2 ( NA )	
Mean ( p vs placebo )				

# PSG no. of awakenings

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
21.6 ( 0.872 )	21.9 ( 0.623 )	22.1 ( 0.969 )	21.6 ( NA )	
Mean ( p vs placebo )				

## Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Walsh                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 2000a                      **Country:** US                      **Funding:**

questionnaire

# subjective sleep latency (min)

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
55.2 ( 0.654 )	42.0 ( 0.017 )	34.4 ( <0.00)	58.3 ( NA )	

Mean ( p vs placebo )

# subjective total sleep time (min)

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
335.8 ( 0.776 )	343.2 ( 0.140 )	351.6 ( 0.011)	327.9 ( NA )	

Mean ( p vs placebo )

# subjective no. of awakenings

Zaleplon 2mg	Zaleplon 5mg	Zaleplon 10mg	Placebo	P value
3.4 ( 0.671 )	3.1 ( 0.906 )	2.8 ( 0.045)	3.3 ( NA )	

Mean ( p vs placebo )

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Walsh\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000b, 2002                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 44.1  
 Range: 21-65  
 SD: 1.2  
**Gender:** 115 ( 71 % ) Female  
**Ethnicity:** 83.4% caucasian  
 16.6% other

Number Screened: 365  
 Eligible: 163  
 Enrolled: 163  
 Number Withdrawn: 29  
 Lost to fu: 5  
 Analyzed: NR

**Eligibility criteria:**

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or totla sleep time (TST) < 6.5 hours, and insomina-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; betime and risetime 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 fuction within 7 to 25 days (depending on half life), or an investigational drug within 30 days. 10) smoking < 10 cigarettes per day.

**Exclusion criteria:**  
 NR

**Comments:**

Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

**Intervention:**    **Run-in :**        7  
                          **Wash out :**      7  
                          **Allow other medication :**    NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	82	56 day	4 / 18
Placebo	NA mg	81	56 day	1 / 10

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Walsh\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 2000b, 2002      **Country:** US      **Funding:** Lorex Pharmaceuticals

**Outcome Measurement:**

- # morning questionnaire
- # SF-36

**Efficacy Outcome List:**

- Primary outcome Outcome:**
- sleep latency
  - total sleep time
  - number of awakenings
  - sleep quality

**Results**

morning questionnaire

# sleep latency (min), all condition, 8 weeks average	Zolpidem	Placebo			P value
	12.39 ( )	19.55 ( )	( )	( )	NS
	Mean ( )				
# sleep latency (min), with pill, 8 weeks average	Zolpidem	Placebo			P value
	36.7 ( )	50.4 ( )	( )	( )	<0.05
	Mean ( )				
# total sleep time (min), with pill, 8 weeks average	Zolpidem	Placebo			P value
	415.4 ( )	364.1 ( )	( )	( )	<0.05
	Mean ( )				
# number of awakenings, with pill, 8 weeks average	Zolpidem	Placebo			P value
	1.1 ( )	1.8 ( )	( )	( )	<0.05
	Mean ( )				
# sleep quality (1=excellent; 4=poor), with pill, 8 weeks average	Zolpidem	Placebo			P value
	2.1 ( )	2.5 ( )	( )	( )	<0.05
	Mean ( )				

Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Walsh\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000b, 2002                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

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SF-36

# quality of life

Zolpidem	Placebo			P value
multi-data ( )	multi-data ( )	( )	( )	NS
Mean ( )	( )			



### Evidence Table 13. Placebo controlled trials: Efficacy

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<b>Author:</b> Zammit	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sepracor

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**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 39.8  
Range: 21-64  
SD: 11.7  
**Gender:** 189 ( 61 % ) Female  
**Ethnicity:** 66.2% caucasians  
16.6% black  
13% hispanic  
4.2% other

Number Screened: NR  
Eligible: 669  
Enrolled: 308  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 308

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 2  
Wash out : 5-7  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	2 mg	104	44 day	3 / 7
Eszopiclone	3 mg	105	44 day	0 / 4
Placebo	NA mg	99	44 day	0 / 5

### Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Zammit                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sepracor

**Outcome Measurement:**

- # polysomnography
- # morning questionnaire
- # evening questionnaire

**Efficacy Outcome List:**

- Primary outcome**      **Outcome:**
- sleep latency
  - sleep duration
  - number of awakenings
  - wake time after sleep onset
  - quality of sleep
  - depth of sleep
  - daytime alertness
  - daytime ability to function
  - morning sleepiness

**Results**

polysomnography

# sleep latency (minute) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
15 ( <0.001 )	13.1 ( <0.001 )	29 ( NA )	( )	
Median ( p vs placebo )				

# sleep efficiency (%) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
88.1 ( <0.01 )	90.1 ( <0.001 )	85.7 ( NA )	( )	
Median ( p vs placebo )				

# wake time after sleep onset, WASO (min) - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
37.1 ( NS )	33.8 ( <0.01 )	44.1 ( NA )	( )	
Median ( p vs placebo )				

# number of awakenings, NAW - night 1, 15, 29 average

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.5 ( NS )	5.7 ( NS )	6.0 ( NA )	( )	
Median ( p vs placebo )				

Evidence Table 13. Placebo controlled trials: Efficacy

**Author:** Zammit                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sepracor

morning questionnaire

# sleep latency (min)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
30 ( <0.000 )	27.7 ( <0.000 )	46 ( NA )	( )	

Median ( p vs placebo )

# total sleep time (min)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
400 ( 0.0207 )	406 ( <0.000 )	366 ( NA )	( )	

Median ( p vs placebo )

# number of awakenings

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
2.7 ( 0.2956 )	2.4 ( 0.1720 )	3.0 ( NA )	( )	

Median ( p vs placebo )

# WASO (min)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
37.1 ( 0.6884 )	30.2 ( 0.0204 )	45 ( NA )	( )	

Median ( p vs placebo )

# quality of sleep (0=poor; 100=excellent)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
54.5 ( 0.0414 )	56.6 ( 0.0072 )	47.7 ( NA )	( )	

Median ( p vs placebo )

# depth of sleep (0=poor; 100=excellent)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
58.9 ( 0.0052 )	56.7 ( 0.0457 )	51.7 ( NA )	( )	

Median ( p vs placebo )

### Evidence Table 13. Placebo controlled trials: Efficacy

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**Author:** Zammit                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sepracor

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evening questionnaire

# daytime alertness (higher scores indicate improved function)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.66 ( 0.873 )	7.02 ( 0.059 )	6.67 ( NA )	( )	

Mean ( p vs placebo )

# daytime ability to function (higher scores indicate improved function)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
6.81 ( 0.901 )	7.15 ( 0.118 )	6.83 ( NA )	( )	

Mean ( p vs placebo )

# morning sleepiness (1=very sleepy; 100=not at all sleepy)

Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value
51.3 ( 0.256 )	50.8 ( 0.344 )	48.2 ( NA )	( )	

Mean ( p vs placebo )

### Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b> Hedner	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> Europe	<b>Funding:</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 72.5  
Range: 59-95  
SD: NR  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 437  
Number Withdrawn: 22  
Lost to fu: NR  
Analyzed: 422

**Eligibility criteria:**

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 characterised 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.

**Exclusion criteria:**

Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled.

**Comments:**

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	139	14 day	10 / 10
Zaleplon	10 mg	145	14 day	5 / 5
Placebo	NA mg	138	14 day	7 / 7

**Rebound:**

sleep questionnaire - rebound insomnia

# rebound: subjective sleep latency (min), withdrawal day 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	45 ( )	50 ( )	60 ( )	( )	
	Median ( )				
# rebound: subjective total sleep time (min), withdrawal day 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	330 ( )	300 ( )	330 ( )	( )	
	Median ( )				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

**Author:** Hedner                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000                      **Country:** Europe                      **Funding:**

# rebound: subjective number of awakenings, withdrawal day 1	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	2 ( )	2 ( )	2 ( )	( )	
	Median ( )				

incidence of rebound insomnia

# rebound insomnia: subjective sleep latency	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	11 ( 9 )	12 ( 9 )	7 ( 5 )	( )	
	Number ( % )				

# rebound insomnia: subjective total sleep time	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	14 ( 11 )	17 ( 13 )	6 ( 5 )	( )	
	Number ( % )				

# rebound insomnia: number of awakenings	Zaleplon 5mg	Zaleplon 10mg	Placebo		P value
	7 ( 6 )	4 ( 3 )	7 ( 6 )	( )	
	Number ( % )				

### Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b> Herrmann	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 1993	<b>Country:</b> France	<b>Funding:</b> NR

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** NR  
Range: 25-65  
SD: NR  
**Gender:** 9 ( 43 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: 25  
Enrolled: 21  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 21

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

**Rebound:**

polysomnography

# sleep efficiency (%), day 28 wistrawal, rebound	Zolpidem	Placebo			P value
	77.4 ( 4 )	68.9 ( 4 )	( )	( )	<0.05
	Mean ( SD	)			
# total sleep time (min), day 28 wistrawal, rebound	Zolpidem	Placebo			P value
	341.3 ( 12 )	298.3 ( 21 )	( )	( )	<0.05
	Mean ( SD	)			
# sleep onset latency (min), day 28 wistrawal, rebound	Zolpidem	Placebo			P value
	50.7 ( 11 )	36.3 ( 7 )	( )	( )	NS
	Mean ( SD	)			

### Evidence Table 14. Placebo controlled trials: Rebound Insomnia

**Author:** Herrmann      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1993      **Country:** France      **Funding:** NR

# time awake (min), day 28 wistrawal, rebound	Zolpidem	Placebo			P value
	53.7 ( 13 )	99.3 ( 17 )	( )	( )	<0.05
	Mean ( SD )				
<u>sleep questionnaire</u>					
# sleep onset latency (min), day 22-28 withdrawal, rebound	Zolpidem	Placebo			P value
	60.8 ( 14 )	70.8 ( 10 )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min), day 22-28 withdrawal, rebound	Zolpidem	Placebo			P value
	341.8 ( 18 )	310.9 ( 21 )	( )	( )	NS
	Mean ( SD )				
# no. of awakenings, day 22-28 withdrawal, rebound	Zolpidem	Placebo			P value
	2.4 ( 0.5 )	2.5 ( 0 )	( )	( )	NS
	Mean ( SD )				



Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 44.25  
Range: NR  
SD: 4.8  
**Gender:** 10 ( 83 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 12  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 12

**Eligibility criteria:**

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 waketime >20 minutes; number of nocturnal awakenings >3.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Zolpidem	10 mg	6	27 day	N / NR	
Placebo	NA mg	6	27 day	N / NR	

**Rebound:**

polysomnography

# stage 2 sleep latency (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	47.2 ( 11.1 )	32.3 ( 7.9 )	( )	( )	NS
	Mean ( SD	)			
# total number of awakenings, nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	28.7 ( 4.6 )	26.1 ( 3.7 )	( )	( )	NS
	Mean ( SD	)			
# total wake time (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	97.7 ( 15.8 )	115.9 ( 18.8 )	( )	( )	NS
	Mean ( SD	)			

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

**Author:** Monti                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1996                      **Country:** Uruguay                      **Funding:** NR

# wake time after sleep onset (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	54.9 ( 16.1 )	92.0 ( 16.3 )	( )	( )	NS
	Mean ( SD )				
# total sleep time (min), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	378.6 ( 15.3 )	361.2 ( 17.9 )	( )	( )	NS
	Mean ( SD )				
# sleep efficiency (%), nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	79.0 ( 3.7 )	75.3 ( 3.7 )	( )	( )	NS
	Mean ( SD )				
# movement time, nights 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	3.7 ( 0.8 )	2.9 ( 0.7 )	( )	( )	NS
	Mean ( SD )				
<u>questionnaire</u>					
# sleep latency (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.4 ( 0.4 )	1.9 ( 0.3 )	( )	( )	NS
	Mean ( SD )				
# sleep duration (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.1 ( 0.2 )	2.4 ( 0.3 )	( )	( )	NS
	Mean ( SD )				
# number of awakenings (lower score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	2.3 ( 0.4 )	2.6 ( 0.3 )	( )	( )	NS
	Mean ( SD )				
# disturbed sleep (higher score indicates more positive response), night 31-33, withdrawal, rebound	Zolpidem	Placebo			P value
	64.9 ( 8.2 )	63.7 ( 6.8 )	( )	( )	NS
	Mean ( SD )				

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>NR</b>

# daytime alertness (higher score indicates more positive response), night 31-33, withdrawal, rebound

Zolpidem	Placebo			P value
73.8 ( 7.0 )	54.1 ( 7.0 )	( )	( )	<0.05
Mean ( SD	)			

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b> Monti_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 2000	<b>Country:</b> Uruguay	<b>Funding:</b> NR

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 51.9  
Range: NR  
SD: 3.6  
**Gender:** 12 ( 100 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 12  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 12

**Eligibility criteria:**

Patients aged between 27 and 59 years, with chronic primary insomina according to the DSM-IV participated in the study.

**Exclusion criteria:**

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 swere pregnanct women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with cliniclally significant diviations 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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/ Total withdrawal
Zolpidem	10 mg	6	15 day	N / NR
Placebo	NA mg	6	15 day	N / NR

**Rebound:**

polygraphic sleep record

# total sleep time (min) - night 19-21, withdrawal, rebound

Zolpidem	Placebo			P value
334.6 ( 22 )	281.6 ( 33.2 )	( )	( )	NS
Mean ( SD	)			

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

**Author:** Monti\_                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 2000                      **Country:** Uruguay                      **Funding:** NR

# sleep efficiency (%) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	69.7 ( 4.6 )	58.6 ( 6.9 )	( )	( )	NS
Mean ( SD )					
# stage 2 sleep latency - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	55.7 ( 15.7 )	69.7 ( 12.5 )	( )	( )	NS
Mean ( SD )					
# total number of awakenings - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	25.4 ( 3.8 )	32.2 ( 5.9 )	( )	( )	NS
Mean ( SD )					
# waking time after sleep onset (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	75.1 ( 7.9 )	137.5 ( 29.2 )	( )	( )	NS
Mean ( SD )					
<u>interview</u>					
# sleep latency (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	94.3 ( 48.5 )	118.4 ( 34.2 )	( )	( )	NS
Mean ( SD )					
# sleep duration (min) - night 19-21, withdrawal, rebound	Zolpidem	Placebo			P value
	342.0 ( 47.5 )	207.4 ( 70.5 )	( )	( )	NS
Mean ( SD )					
# disturbed sleep - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem	Placebo			P value
	62.7 ( 11.4 )	56.8 ( 9.3 )	( )	( )	NS
Mean ( SD )					
# alert in the morning - night 19-21 (1=agree; 100=disagree), withdrawal, rebound	Zolpidem	Placebo			P value
	37.9 ( 9.5 )	61.5 ( 9.8 )	( )	( )	NS
Mean ( SD )					

### Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b> Zammit	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sepracor

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** 39.8  
Range: 21-64  
SD: 11.7  
**Gender:** 189 ( 61 % ) Female  
**Ethnicity:** 66.2% caucasians  
16.6% black  
13% hispanic  
4.2% other  
Number Screened: NR  
Eligible: 669  
Enrolled: 308  
Number Withdrawn: 16  
Lost to fu: 0  
Analyzed: 308

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:**

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Eszopiclone	2 mg	104	44 day	3	7
Eszopiclone	3 mg	105	44 day	0	4
Placebo	NA mg	99	44 day	0	5

**Rebound:**

polysomnography

# sleep latency (min), rebound insomnia, change vs baseline

Eszopiclone 2mg	Eszopiclone 3mg			P value
NR ( NS )	-8.5 ( <0.05 )	( )	( )	

Mean ( p vs baseline )

# sleep efficiency (%), rebound insomnia, change vs baseline

Eszopiclone 2mg	Eszopiclone 3mg			P value
-2.5 ( <0.05 )	3.7 ( <0.05 )	( )	( )	

Mean ( p vs baseline )

Evidence Table 14. Placebo controlled trials: Rebound Insomnia

<b>Author:</b>	<b>Zammit</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Sepracor</b>

# WASO (min), rebound insomnia, change vs baseline	Eszopiclone 2mg	Eszopiclone 3mg			P value
	7 ( <0.05 )	NR ( NS )	( )	( )	
	Mean ( p vs baseline	)			

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Allain                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1998                      **Country:** France                      **Funding:** NR

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 51.9  
 Range: 32-84  
 SD: 16.7  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
 Eligible: NR  
 Enrolled: 37  
 Number Withdrawn: 18  
 Lost to fu: NR  
 Analyzed: 37

**Eligibility criteria:**

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.

**Exclusion criteria:**

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 woemn; liver or respiratory failure, myasthenia, or epilepsy.

**Comments:**

**Intervention:** Run-in : 3  
 Wash out : 3  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	18	21 day	1 / 1
Placebo	NA mg	19	21 day	17 / 17



Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Allain                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1998                      **Country:** France                      **Funding:** NR

---

**Adverse Events:**

adverse events

# rebound insomnia

Zolpidem	Placebo			P value:
0 ( 0 )	15 ( 14 )	( )	( )	
Total ( Withdrawal )				

Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b> Allain_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2001	<b>Country:</b> France	<b>Funding:</b> Sanofi-Synthelabo

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 46.1  
Range: 25-64  
SD: 10.5  
**Gender:** 188 ( 77 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 245  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 245

**Eligibility criteria:**

Patients of either gender (aged 25 to 64 years) with DSM-IV diagnosis of primary insomnia, characterised 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 characterised 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.

**Exclusion criteria:**

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 if they had desynchronisation type 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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more than 15 days in the month prior to inclusion, were also excluded from the study, as were patients who consumed large quantities of caffeine.

**Comments:**

Zolpidem was administrated as needed, not every night.

**Intervention:**

**Run-in :** 3-7  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	124	28 day	1 / 3
Placebo	NA mg	121	28 day	1 / 7

### Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Allain\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2001                              **Country:** France                      **Funding:** Sanofi-Synthelabo

**Adverse Events:**

treatment-emergent adverse events

# overall

Zolpidem	Placebo			P value:
23 ( 19 )	18 ( 15 )	( )	( )	NS

Number ( % )

# anxiety

Zolpidem	Placebo			P value:
4 ( )	0 ( )	( )	( )	NR

% ( )

# headache

Zolpidem	Placebo			P value:
3.2 ( )	0 ( )	( )	( )	NR

% ( )

# rhinitis

Zolpidem	Placebo			P value:
0 ( )	3.3 ( )	( )	( )	NR

% ( )

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Chaudoir</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	<b>NR (May &amp; Baker provided m</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** 50  
Range: 35-65  
SD: NR  
**Gender:** 18 ( 72 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: 30  
Enrolled: 25  
Number Withdrawn: 5  
Lost to fu: 0  
Analyzed: 25

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	25	7 day	2 / 2
Placebo	NA mg	25	7 day	3 / 3

### Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Chaudoir                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1983                              **Country:** UK                              **Funding:** NR (May & Baker provided m

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**Adverse Events:**

40-item symptom check-list

# bitter taste (data NR)

Zopiclone	Placebo			P value:
more ( )	less ( )	( )	( )	NR

Number ( )

# overall adverse event

Zopiclone	Placebo			P value:
5 ( )	2 ( )	( )	( )	NR

Number ( )

# drowsiness/dizziness

Zopiclone	Placebo			P value:
2 ( )	1 ( )	( )	( )	NR

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Dockhorn                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1996                              **Country:** US                              **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 32.7  
 Range: 20-55  
 SD: NR  
**Gender:** 80 ( 58 % ) Female  
**Ethnicity:** NR  
 Number Screened: NR  
 Eligible: NR  
 Enrolled: 138  
 Number Withdrawn: 9  
 Lost to fu: 2  
 Analyzed: 136

**Eligibility criteria:**

Healthy patients who had experienced acute insomnia (3-9 nights) due 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)

**Exclusion criteria:**

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 hypnotic. Patients who normally slept on an unusual schedule (e.g., shift workers) and women who were lactating or at risk on pregnancy were excluded

**Comments:**

**Intervention:** Run-in : NR  
 Wash out : NR  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	68	7-10 day	1 / 3
Placebo	NA mg	68	7-10 day	2 / 6

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Dockhorn                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1996                              **Country:** US                              **Funding:** Lorex Pharmaceuticals

**Adverse Events:**

adverse events

# headache

Zolpidem	Placebo			P value:
31.9 ( )	24.6 ( )	( )	( )	

% ( )

# drowsiness

Zolpidem	Placebo			P value:
5.8 ( )	1.4 ( )	( )	( )	

% ( )

# diarrhea

Zolpidem	Placebo			P value:
4.3 ( )	0 ( )	( )	( )	

% ( )

# dizziness

Zolpidem	Placebo			P value:
4.3 ( )	0 ( )	( )	( )	

% ( )

# myalgia

Zolpidem	Placebo			P value:
1.4 ( )	4.3 ( )	( )	( )	

% ( )

# nausea

Zolpidem	Placebo			P value:
1.4 ( )	4.3 ( )	( )	( )	

% ( )

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Dorsey</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Sanofi-Synthelabo</b>

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 50.8  
 Range: 39-60  
 SD: 4.5  
**Gender:** 141 ( 100 % ) Female  
**Ethnicity:** NR  
 Number Screened: 242  
 Eligible: 141  
 Enrolled: 141  
 Number Withdrawn: 16  
 Lost to fu: 3  
 Analyzed: 141

**Eligibility criteria:**

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:**

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 urinate screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbituates, 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.

**Comments:**

**Intervention:**  
**Run-in :** 6-14  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	68	28 day	5 / 11
Placebo	NA mg	73	28 day	2 / 5



### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b> Dorsey	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sanofi-Synthelabo

**Adverse Events:**

overall

# headache	Zolpidem	Placebo			P value:
	36 ( 52.9 )	24 ( 32.9 )	( )	( )	0.08
Number ( % )					
# upper respiratory tract infection	Zolpidem	Placebo			P value:
	11 ( 16.2 )	5 ( 6.8 )	( )	( )	0.11
Number ( % )					
# drowsiness	Zolpidem	Placebo			P value:
	7 ( 10.3 )	1 ( 4 )	( )	( )	0.03
Number ( % )					
# dizziness	Zolpidem	Placebo			P value:
	6 ( 8.8 )	0 ( 0 )	( )	( )	0.01
Number ( % )					
# backache	Zolpidem	Placebo			P value:
	5 ( 7.4 )	0 ( 0 )	( )	( )	0.02
Number ( % )					
# irritability	Zolpidem	Placebo			P value:
	5 ( 7.4 )	2 ( 2.7 )	( )	( )	0.02
Number ( % )					

Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Goldenberg</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>UK, France</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** NR  
Range: 25-60  
SD: NR  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: NR  
Enrolled: 524  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 458

**Eligibility criteria:**

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 wakings; sleep onset latency of 30 minutes or more, or daily symptoms attributable to disturbed sleep.

**Exclusion criteria:**

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, shiftwork 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.

**Comments:**

Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

**Intervention:**

**Run-in :** NR  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	44 day	N / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Goldenberg      **Trial type:** Placebo      **Quality rating:** Poor  
**Year:** 1994      **Country:** UK, France      **Funding:** NR

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**Adverse Events:**

Adverse events

# overall reported

Zopiclone	Placebo			P value:
54 ( 20.6 )	30 ( 11.5 )	( )	( )	

Number ( % )

# dry mouth

Zopiclone	Placebo			P value:
10 ( )	5 ( )	( )	( )	

Number ( )

# bitter taste

Zopiclone	Placebo			P value:
11 ( )	0 ( )	( )	( )	

Number ( )

## Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Hedner</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>Europe</b>	<b>Funding:</b>	

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 72.5  
Range: 59-95  
SD: NR  
**Gender:** NR ( % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 437  
Number Withdrawn: 22  
Lost to fu: NR  
Analyzed: 422

**Eligibility criteria:**

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 characterised 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.

**Exclusion criteria:**

Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled.

**Comments:**

Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zaleplon	5 mg	139	14 day	10 / 10
Zaleplon	10 mg	145	14 day	5 / 5
Placebo	NA mg	138	14 day	7 / 7

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Hedner                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000                      **Country:** Europe                      **Funding:**

**Adverse Events:**

treatment-emergent adverse events

# overall

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value:
68 ( 48 )	59 ( 40 )	74 ( 51 )	( )	NS

Number ( % )

# withdrawals

Zaleplon 5mg	Zaleplon 10mg	Placebo		P value:
10 ( 7 )	5 ( 3 )	7 ( 5 )	( )	NS

Number ( % )

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Herrmann</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1993</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Single Center

**Age:** NR  
Range: 25-65  
SD: NR  
**Gender:** 9 ( 43 % ) Female  
**Ethnicity:** NR  
Number Screened: NR  
Eligible: 25  
Enrolled: 21  
Number Withdrawn: NR  
Lost to fu: NR  
Analyzed: 21

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 7  
Wash out : 7  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	11	14 day	N / NR
Placebo	NA mg	10	14 day	N / NR

### Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Herrmann                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1993                              **Country:** France                      **Funding:** NR

---

**Adverse Events:**

adverse events

# headache - during treatment

Zolpidem	Placebo			P value:
3 ( )	4 ( )	( )	( )	

Number ( )

# headache - withdrawal

Zolpidem	Placebo			P value:
2 ( )	1 ( )	( )	( )	

Number ( )

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Hindmarch</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1995</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	

<b>Design:</b>		<b>Age:</b>	42.9	Number Screened:	NR
<b>Study design</b>	RCT		Range: 25-60	Eligible:	NR
	DB		SD: 8.9	Enrolled:	458
	Parallel	<b>Gender:</b>	NR ( 0 % ) Female	Number Withdrawn:	NR
<b>Setting</b>	Multicenter	<b>Ethnicity:</b>	NR	Lost to fu:	NR
				Analyzed:	458
<b>Eligibility criteria:</b>		<b>Exclusion criteria:</b>			
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.			

**Comments:**

**Intervention:**

<b>Run-in :</b>	NR
<b>Wash out :</b>	NR
<b>Allow other medication :</b>	NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	231	48 day	N / NR
Placebo	NA mg	227	42 day	N / NR



Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Hindmarch      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1995      **Country:** UK      **Funding:**

**Adverse Events:**

adverse events

# overall drop out

Zolpidem	Placebo			P value:
30 ( 11.5 )	54 ( 20.6 )	( )	( )	NS

Number ( % )

# bitter taste

Zolpidem	Placebo			P value:
11 ( )	0 ( )	( )	( )	

Number ( )

# dry mouth

Zaleplon	Placebo			P value:
10 ( )	5 ( )	( )	( )	

Number ( )

### Evidence Table 15. Placebo controlled trials: Adverse Events

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<b>Author:</b> Krystal	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2003	<b>Country:</b> US	<b>Funding:</b> Sepracor

---

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 44  
Range: 21-69  
SD: 11.3  
**Gender:** 195 ( 25 % ) Female  
**Ethnicity:** 80% caucasian  
13.2% african  
american  
7.9% other

Number Screened: 1194  
Eligible: 791  
Enrolled: 788  
Number Withdrawn: 320  
Lost to fu: 60  
Analyzed: 788

**Eligibility criteria:**

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.

**Exclusion criteria:**  
NR

**Comments:**

**Intervention:** Run-in : NR  
Wash out : 5-7  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	3 mg	593	180 day	76 / 235
Placebo	NA mg	195	180 day	14 / 85

## Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Krystal                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2003                              **Country:** US                              **Funding:** Sepracor

**Adverse Events:**adverse events

# overall

Eszopiclone	Placebo			P value:
81.1 ( )	70.8 ( )	( )	( )	NR

% ( )

# abdominal pain

Eszopiclone	Placebo			P value:
48 ( 8.1 )	11 ( 5.6 )	( )	( )	NR

Number ( % )

# Accidental injury

Eszopiclone	Placebo			P value:
43 ( 7.3 )	11 ( 5.6 )	( )	( )	NR

Number ( % )

# asthenia

Eszopiclone	Placebo			P value:
26 ( 4.4 )	11 ( 5.6 )	( )	( )	NR

Number ( % )

# back pain

Eszopiclone	Placebo			P value:
45 ( 7.6 )	6 ( 3.1 )	( )	( )	NR

Number ( % )

# diarrhea

Eszopiclone	Placebo			P value:
45 ( 7.6 )	14 ( 7.2 )	( )	( )	NR

Number ( % )

# dizziness

Eszopiclone	Placebo			P value:
58 ( 9.8 )	6 ( 3.1 )	( )	( )	NR

Number ( % )

### Evidence Table 15. Placebo controlled trials: Adverse Events

Author:	<b>Krystal</b>	Trial type:	<b>Placebo</b>	Quality rating:	<b>Fair</b>
Year:	<b>2003</b>	Country:	<b>US</b>	Funding:	<b>Sepracor</b>
# dry mouth	Eszopiclone	Placebo			P value:
	39 ( 6.6 )	3 ( 1.5 )	( )	( )	NR
	Number ( % )				
# dyspepsia	Eszopiclone	Placebo			P value:
	41 ( 6.9 )	13 ( 6.7 )	( )	( )	NR
	Number ( % )				
# headache	Eszopiclone	Placebo			P value:
	116 ( 19.6 )	37 ( 19 )	( )	( )	NR
	Number ( % )				
# infection	Eszopiclone	Placebo			P value:
	94 ( 15.9 )	13 ( 6.7 )	( )	( )	NR
	Number ( % )				
# nausea	Eszopiclone	Placebo			P value:
	67 ( 11.3 )	11 ( 5.6 )	( )	( )	NR
	Number ( % )				
# pain	Eszopiclone	Placebo			P value:
	67 ( 11.3 )	12. ( 6.2 )	( )	( )	NR
	Number ( % )				
# pharyngitis	Eszopiclone	Placebo			P value:
	59 ( 9.9 )	10 ( 5.1 )	( )	( )	NR
	Number ( % )				
# rash	Eszopiclone	Placebo			P value:
	31 ( 5.2 )	6 ( 3.1 )	( )	( )	NR
	Number ( % )				

### Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Krystal                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2003                              **Country:** US                              **Funding:** Sepracor

# rhinitis	Eszopiclone	Placebo			P value:
	42 ( 7.1 )	9 ( 4.6 )	( )	( )	NR
Number ( % )					
# sinusitis	Eszopiclone	Placebo			P value:
	25 ( 4.2 )	11 ( 5.6 )	( )	( )	NR
Number ( % )					
# somnolence	Eszopiclone	Placebo			P value:
	54 ( 9.1 )	5 ( 2.6 )	( )	( )	NR
Number ( % )					
# unpleasant taste	Eszopiclone	Placebo			P value:
	155 ( 26.1 )	11 ( 5.6 )	( )	( )	NR
Number ( % )					

Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Lahmeyer</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1997</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Roche Pharmaceuticals</b>

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 44.9  
Range: 19-61  
SD: 11.6  
**Gender:** 81 ( 56 % ) Female  
**Ethnicity:** 92% caucasian  
6% black  
<1% hispanic  
1% asian  
Number Screened: 178  
Eligible: 33  
Enrolled: 145  
Number Withdrawn: 27  
Lost to fu: 0  
Analyzed: 118

**Eligibility criteria:**

Patients had to have a history of a minimum of 3 months of disturbed sleep, characterised by a typical sleep duration of between 4 and 6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints.

**Exclusion criteria:**

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 shortacting 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 nights 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.

**Comments:**

**Intervention:**  
**Run-in :** 3  
**Wash out :** 4  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	45	31 day	4 / 8
Zolpidem	15 mg	46	31 day	3 / 9
Placebo	NA mg	54	31 day	0 / 10

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Lahmeyer      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1997      **Country:** US      **Funding:** ?orex Pharmaceuticals

**Adverse Events:**

overall adverse events

# drowsiness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	11 ( )	12 ( )	6 ( )	( )	
	% ( )				
# dizziness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	5 ( )	7 ( )	4 ( )	( )	
	% ( )				
# pharyngitis	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	2 ( )	9 ( )	2 ( )	( )	
	% ( )				
# rhinitis	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	0 ( )	7 ( )	2 ( )	( )	
	% ( )				
# lethargy	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	7 ( )	2 ( )	0 ( )	( )	
	% ( )				
# overall	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	25 ( 57 )	30 ( 70 )	56 ( 43 )	( )	
	Number ( % )				
# CNS related	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	19 ( 28.3 )	15 ( 43.2 )	15 ( 34.8 )	( )	
	Number ( % )				

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Monchesky</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1986</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>NR</b>

**Design:**

**Study design** RCT  
DB  
Crossover  
**Setting** Single Center

**Age:** NR  
Range: 23-69  
SD: NR  
**Gender:** NR ( 0 % ) Female  
**Ethnicity:** NR

Number Screened: NR  
Eligible: NR  
Enrolled: 99  
Number Withdrawn: 0  
Lost to fu: 2  
Analyzed: 91

**Eligibility criteria:**

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.

**Exclusion criteria:**

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

**Comments:**

Zopiclone 7.5mg for run-in and wash-out periods.  
Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** No use of neuroleptics, sedatives, analgesics, or antidepressants

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zopiclone	7.5 mg	91	7 day	N / NR
Placebo	NA mg	91	7 day	N / NR



### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b>	<b>Monchesky</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1986</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>NR</b>

**Adverse Events:**

adverse events

# headache

Zopiclone	Placebo			P value:
11 ( )	11 ( )	( )	( )	

Number ( )

# dizziness

Zopiclone	Placebo			P value:
4 ( )	6 ( )	( )	( )	

Number ( )

# nausea

Zopiclone	Placebo			P value:
7 ( )	4 ( )	( )	( )	

Number ( )

# bad/bitter taste

Zopiclone	Placebo			P value:
4 ( )	3 ( )	( )	( )	

Number ( )

# back pain

Zopiclone	Placebo			P value:
1 ( )	3 ( )	( )	( )	

Number ( )

# stomach pain

Zopiclone	Placebo			P value:
3 ( )	2 ( )	( )	( )	

Number ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Scharf                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2005                      **Country:** US                      **Funding:**

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 72.3  
 Range: 64-85  
 SD: 4.9  
**Gender:** 133 ( 58 % ) Female  
**Ethnicity:** 89.4% caucasian  
 2.2% black  
 1.3% hispanic  
 Number Screened: 353  
 Eligible: NR  
 Enrolled: 231  
 Number Withdrawn: 21  
 Lost to fu: NR  
 Analyzed: 231

**Eligibility criteria:**

Men and women between the ges of 65 and 85 years who met the DSM-IV for primary insomnia and who repted sleeping 6.5 hours per night or less and took more than 30 minutes to fall asleep each night for at least 1 month

**Exclusion criteria:**

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 excluded.

**Comments:**

**Intervention:** **Run-in :** 3-14  
**Wash out :** NR  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Eszopiclone	1 mg	72	14 day	1 / NR
Eszopiclone	2 mg	79	14 day	2 / NR
Placebo	NA mg	80	14 day	5 / NR

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Scharf                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2005                      **Country:** US                      **Funding:**

**Adverse Events:**

adverse events

# overall

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
40 ( )	43 ( )	40 ( )	( )	

% ( )

# withdrawals due to adverse events

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
1.4 ( )	2.5 ( )	6.3 ( )	( )	

% ( )

# headache

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
15.3 ( )	15.2 ( )	15.0 ( )	( )	

% ( )

# unpleasant taste

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
8.3 ( )	11.4 ( )	1.3 ( )	( )	

% ( )

# somnolence

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
6.9 ( )	3.8 ( )	8.8 ( )	( )	

% ( )

# dyspepsia

Eszopiclone 1mg	Eszopiclone 2mg	Placebo		P value:
5.6 ( )	1.3 ( )	2.5 ( )	( )	

% ( )

Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b> Scharf_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 1994	<b>Country:</b> US	<b>Funding:</b> NR

**Design:**

**Study design** RCT  
DB  
Parallel  
**Setting** Multicenter

**Age:** 38  
Range: 22-60  
SD: NR  
**Gender:** 48 ( 64 % ) Female  
**Ethnicity:** 73.3% white  
26.7% non-white

Number Screened: 178  
Eligible: 75  
Enrolled: 75  
Number Withdrawn:  
Lost to fu:  
Analyzed:

**Eligibility criteria:**

After giving informed consent, outpatient insomniacs, aged 21 to 60 years, were screened to rule out significant medical or psychiatric disorders and to ensure that they were in good health. Patients were not have used any investigational drug within 30 days of the start of the study. In addition, patients were required to have chronic insomnia defined as a history of the following for at least 3 months preceding screening: usual reported sleep duration between 4 and 6 hours, usual reported sleep latency of at least 30 minutes, and daytime complaints associated with disturbed sleep. The first night of placebo screening period served as a laboratory adaptation night and to rule out patients with sleep apnea or periodic limb movements during sleep. During the next 3 nightns, patients had to meet the following criteria: total sleep time of 240 to 420 minutes (4 to 7 hours) in a 480-minute recording on at least 2 or the 3 screening nights, and a latency to persistant sleep of > 20 minutes on each of these 2 nights. "Persistent sleep" was defined as the first continuous 20 epochs of a non-wake state.

**Exclusion criteria:**

**Comments:**

**Intervention:** Run-in : 11  
Wash out : 2  
Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	26	35 day	0 / 4
Zolpidem	15 mg	25	35 day	2 / 3
Placebo	NA mg	24	35 day	0 / 1

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b> Scharf_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 1994	<b>Country:</b> US	<b>Funding:</b> NR

**Adverse Events:**

adverse events

# dry mouth	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	0 ( 0 )	2 ( 8 )	0 ( 0 )	( )	
Number ( % )					
# headache	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	2 ( 8 )	4 ( 16 )	7 ( 29 )	( )	
Number ( % )					
# drowsiness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	3 ( 12 )	5 ( 20 )	2 ( 8 )	( )	
Number ( % )					
# dizziness	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	3 ( 12 )	4 ( 16 )	0 ( 0 )	( )	
Number ( % )					
# lethargy	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	2 ( 8 )	1 ( 4 )	1 ( 4 )	( )	
Number ( % )					
# drugged	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	2 ( 8 )	1 ( 4 )	0 ( 0 )	( )	
Number ( % )					
# confusion	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	0 ( 0 )	2 ( 8 )	0 ( 0 )	( )	
Number ( % )					

Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Scharf\_      **Trial type:** Placebo      **Quality rating:** Fair  
**Year:** 1994      **Country:** US      **Funding:** NR

# nausea	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	1 ( 4 )	3 ( 12 )	1 ( 4 )	( )	
Number ( % )					
# dyspepsia	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	2 ( 8 )	2 ( 8 )	0 ( 0 )	( )	
Number ( % )					
# arthralgia	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	1 ( 4 )	0 ( 0 )	2 ( 8 )	( )	
Number ( % )					
# amnesia	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	1 ( 4 )	2 ( 8 )	0 ( 0 )	( )	
Number ( % )					
# rhinitis	Zolpidem 10mg	Zolpidem 15mg	Placebo		P value:
	0 ( 0 )	0 ( 0 )	2 ( 8 )	( )	
Number ( % )					

### Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Walsh\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000b, 2002                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Multicenter

**Age:** 44.1  
 Range: 21-65  
 SD: 1.2  
**Gender:** 115 ( 71 % ) Female  
**Ethnicity:** 83.4% caucasian  
 16.6% other

Number Screened: 365  
 Eligible: 163  
 Enrolled: 163  
 Number Withdrawn: 29  
 Lost to fu: 5  
 Analyzed: NR

**Eligibility criteria:**

1) DSM-IV diagnosis of primary insomnia 2) reported sleep latency (SL) > 45 minutes, or totla sleep time (TST) < 6.5 hours, and insomina-related daytime complaints on at least three of the seven baseline days 3) nightly time-in-bed between 6.5 and 9.0 hours; betime and risetime 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 fuction within 7 to 25 days (depending on half life), or an investigational drug within 30 days. 10) smoking < 10 cigarettes per day.

**Exclusion criteria:**  
 NR

**Comments:**

Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".

**Intervention:**

**Run-in :** 7  
**Wash out :** 7  
**Allow other medication :** NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/
				Total withdrawal
Zolpidem	10 mg	82	56 day	4 / 18
Placebo	NA mg	81	56 day	1 / 10

Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Walsh\_                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2000b, 2002                      **Country:** US                      **Funding:** Lorex Pharmaceuticals

---

**Adverse Events:**

adverse events

# overall

Zolpidem	Placebo			P value:
1 ( )	4 ( )	( )	( )	NS

Number ( )



Evidence Table 15. Placebo controlled trials: Adverse Events

**Author:** Zammit                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sepracor

**Design:**

**Study design** RCT  
 DB  
 Parallel  
**Setting** Single Center

**Age:** 39.8  
 Range: 21-64  
 SD: 11.7  
**Gender:** 189 ( 61 % ) Female  
**Ethnicity:** 66.2% caucasians  
 16.6% black  
 13% hispanic  
 4.2% other  
 Number Screened: NR  
 Eligible: 669  
 Enrolled: 308  
 Number Withdrawn: 16  
 Lost to fu: 0  
 Analyzed: 308

**Eligibility criteria:**

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.

**Exclusion criteria:**

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.

**Comments:**

**Intervention:** Run-in : 2  
 Wash out : 5-7  
 Allow other medication : NR

Drug name	dosage	N=	Duration	Withdrawals due to AEs/	
				Total withdrawal	
Eszopiclone	2 mg	104	44 day	3 / 7	
Eszopiclone	3 mg	105	44 day	0 / 4	
Placebo	NA mg	99	44 day	0 / 5	

### Evidence Table 15. Placebo controlled trials: Adverse Events

<b>Author:</b> Zammit	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sepracor

**Adverse Events:**

adverse events during treatment

# abnormal dreams	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 ( 2 )	3 ( 2.9 )	2 ( 1.9 )	( )	
	Number ( % )				
# nervousness	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 ( 2 )	5 ( 4.8 )	0 ( 0 )	( )	
	Number ( % )				
# back pain	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 ( 2 )	1 ( 1 )	4 ( 3.8 )	( )	
	Number ( % )				
# dizziness	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	4 ( 4 )	3 ( 2.9 )	5 ( 4.8 )	( )	
	Number ( % )				
# dry mouth	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	2 ( 2 )	5 ( 4.8 )	6 ( 5.7 )	( )	
	Number ( % )				
# headache	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	8 ( 8.1 )	13 ( 12.5 )	12 ( 11.4 )	( )	
	Number ( % )				
# somnolence	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	3 ( 3 )	8 ( 7.7 )	8 ( 7.6 )	( )	
	Number ( % )				

### Evidence Table 15. Placebo controlled trials: Adverse Events

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**Author:** Zammit                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 2004                              **Country:** US                              **Funding:** Sepracor

---

# unpleasant taste	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	3 ( 3 )	17 ( 16.3 )	35 ( 33.3 )	( )	
Number ( % )					
<u>adverse events after treatment discontinuation</u>					
# CNS related	Eszopiclone 2mg	Eszopiclone 3mg	Placebo		P value:
	11.5 ( NS )	15.2 ( NS )	18.2 ( NA )	( )	
% ( p vs placebo )					

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Agnoli</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>Rome, Foggia, Italy</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

- |   |                     |
|---|---------------------|
| 1. Randomization adequate?              | NR                  |
| 2. Allocation adequate?                 | NR                  |
| 3. Groups similar at baseline:          | NR                  |
| 4. Eligibility criteria specified       | Yes                 |
| 5. Outcome assessors masked             | Yes                 |
| 6. Care provider masked                 | NR                  |
| 7. Patients masked                      | Yes                 |
| 8. Reporting of Attrition               | No                  |
| Crossover                               | No                  |
| Adherence                               | No                  |
| Contamination                           | No                  |
| 9. Loss to follow-up differential/ high | No                  |
| If Yes, please report:                  |                     |
| 10. Intention-to-treat analysis:        | Unable to determine |
| 11. Postrandomization exclusions:       | Unable to determine |
| 12. Quality rating:                     | Poor                |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 20   |
| 2. Exclusion criteria:                | Presence of concomitant general illness; renal or hepatic failure; effectiveness of placebo administration; and pregnancy. |
| 3. Run-in:                            | 3  |
| Wash out:                             | NR   |
| 4. Class naive patients only          | Yes  |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Not reported   |
| 7. Relevance:                         | patients with gener  |

---

**Comment:** Poor quality: insufficient information to assess. Patients with generalized anxiety disorder.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Allain</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>NR</b>

---

**Internal validity**

- |                                   |                     |
|-----------------------------------|---------------------|
| 1. Randomization adequate?        | NR                  |
| 2. Allocation adequate?           | NR                  |
| 3. Groups similar at baseline:    | Yes                 |
| 4. Eligibility criteria specified | Yes                 |
| 5. Outcome assessors masked       | Yes                 |
| 6. Care provider masked           | Yes                 |
| 7. Patients masked                | Yes                 |
| 8. Reporting of Attrition         | No                  |
| Crossover                         | No                  |
| Adherence                         | No                  |
| Contamination                     | No                  |
| 9. Loss to follow-up              |                     |
| differential/ high                | NR                  |
| If Yes, please report:            |                     |
| 10. Intention-to-treat analysis:  | Unable to determine |
| 11. Postrandomization exclusions: | NR                  |
| 12. Quality rating:               | Fair                |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 37  |
| 2. Exclusion criteria:                |   |
|                                       | 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 woemn; liver or respiratory failure, myasthenia, or epilepsy. |
| 3. Run-in:                            | 3   |
| Wash out:                             | 3   |
| 4. Class naive patients only          | NR (all were  |
| 5. Controlled group standard of care: | NR  |
| 6. Funding:                           | NR  |
| 7. Relevance:                         | Patients discontinui  |

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Allain</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>NR</b>
<b>Internal validity</b>			<b>External validity</b>		
1. Randomization adequate?	Yes	1. Number Screened:	NR	Eligible:	NR
2. Allocation adequate?	NR	Enrolled:	53	2. Exclusion criteria:	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 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.
3. Groups similar at baseline:	Yes	3. Run-in:	No	4. Class naive patients only	No
4. Eligibility criteria specified	Yes	Wash out:	No	5. Controlled group standard of care:	Yes
5. Outcome assessors masked	Yes	4. Class naive patients only	No	6. Funding:	Sanofi-Synthelabo
6. Care provider masked	NR	5. Controlled group standard of care:	Yes	7. Relevance:	No (single dose)
7. Patients masked	Yes	6. Funding:	Sanofi-Synthelabo		
8. Reporting of Attrition	Yes				
Crossover	Yes				
Adherence	Yes				
Contamination	No				
9. Loss to follow-up differential/ high	No				
If Yes, please report:					
10. Intention-to-treat analysis:	Yes				
11. Postrandomization exclusions:	No				
12. Quality rating:	Fair				

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b> Allain_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2001	<b>Country:</b> France	<b>Funding:</b> Sanofi-Synthelabo

**Internal validity**

- |   |                     |
|---|---------------------|
| 1. Randomization adequate?                                | NR                  |
| 2. Allocation adequate?                                   | NR                  |
| 3. Groups similar at baseline:                            | Placebo group lower |
| 4. Eligibility criteria specified                         | Yes                 |
| 5. Outcome assessors masked                               | Yes                 |
| 6. Care provider masked                                   | NR                  |
| 7. Patients masked  | Yes                 |
| 8. Reporting of Attrition                                 | Yes                 |
| Crossover   | No                  |
| Adherence   | Yes                 |
| Contamination   | No                  |
| 9. Loss to follow-up differential/ high                   | Yes                 |
| If Yes, please report:                                    |                     |
| 7 placebo and 3 zolpidem withdrew, but report ITT results |                     |
| 10. Intention-to-treat analysis:                          | Yes                 |
| 11. Postrandomization exclusions:                         | No                  |
| 12. Quality rating:                                       | Fair                |

**External validity**

- |  |                   |
|--|-------------------|
| 1. Number Screened:  | NR                |
| Eligible:  | NR                |
| Enrolled:  | 245               |
| 2. Exclusion criteria:   |                   |
| 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 if 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 imidazopyridines. 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 abnoea syndrom. Patients who had received benzodiazepines regularly for more than one month, or for more than 15 days in the month prior to inclusion, were also excluded from the study, as were patients |                   |
| 3. Run-in:   | 3-7               |
| Wash out:  | NR                |
| 4. Class naive patients only   | NR                |
| 5. Controlled group standard of care:  | NR                |
| 6. Funding:  | Sanofi-Synthelabo |
| 7. Relevance:  | Yes               |

**Comment:** Zolpidem was administrated as needed, not every night.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Ancoli-Israel</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1999</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst</b>

---

**Internal validity**

- |                                   |      |
|-----------------------------------|------|
| 1. Randomization adequate?        | NR   |
| 2. Allocation adequate?           | NR   |
| 3. Groups similar at baseline:    | Yes  |
| 4. Eligibility criteria specified | Yes  |
| 5. Outcome assessors masked       | Yes  |
| 6. Care provider masked           | NR   |
| 7. Patients masked                | Yes  |
| 8. Reporting of Attrition         | Yes  |
| Crossover                         | No   |
| Adherence                         | No   |
| Contamination                     | No   |
| 9. Loss to follow-up              |      |
| differential/ high                | No   |
| If Yes, please report:            |      |
| 10. Intention-to-treat analysis:  | No   |
| 11. Postrandomization exclusions: | Yes  |
| 12. Quality rating:               | Fair |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | 1224   |
| Eligible:                             | 551  |
| Enrolled:                             | 549  |
| 2. Exclusion criteria:                |  |
|                                       | 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 $\geq 50$ . 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. |
| 3. Run-in:                            | 7  |
| Wash out:                             | 7-21   |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Wyeth-Ayerst   |
| 7. Relevance:                         | Yes  |

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**Comment:** Elderly



## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Anderson</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

- |   |      |
|---|------|
| 1. Randomization adequate?  | NR   |
| 2. Allocation adequate?   | NR   |
| 3. Groups similar at baseline:  | Yes  |
| 4. Eligibility criteria specified   | Yes  |
| 5. Outcome assessors masked   | No   |
| 6. Care provider masked   | NR   |
| 7. Patients masked  | Yes  |
| 8. Reporting of Attrition   | Yes  |
| Crossover   | No   |
| Adherence   | Yes  |
| Contamination   | No   |
| 9. Loss to follow-up differential/ high   | Yes  |
| If Yes, please report:  |      |
| 17% who withdrew before taking medication or did not comply excluded from analysis. |      |
| 10. Intention-to-treat analysis:  | No   |
| 11. Postrandomization exclusions:   | Yes  |
| 12. Quality rating:   | Fair |

**External validity**

- |   |              |
|---|--------------|
| 1. Number Screened:   | NR           |
| Eligible:   | NR           |
| Enrolled:   | 119          |
| 2. Exclusion criteria:  |              |
| 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. |              |
| 3. Run-in:  | 7            |
| Wash out:   | 7            |
| 4. Class naive patients only  | No           |
| 5. Controlled group standard of care:   | Yes          |
| 6. Funding:   | Not reported |
| 7. Relevance:   | Yes          |

**Comment:**

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Ansoms	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1991	<b>Country:</b> US	<b>Funding:</b> Not reported

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes, but not describe
- 6. Care provider masked: NR
- 7. Patients masked: Yes, but not describe
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: Yes
  - If Yes, please report:  
54 enrolled, 27 zopiclone and 25 lormetazepam evaluable, but numbers randomized not reported.
- 10. Intention-to-treat analysis: No
- 11. Postrandomization exclusions: Yes
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: 54
  - Enrolled: 52
- 2. Exclusion criteria:
  - 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 accompanied 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
- 3. Run-in: 2
  - Wash out: NR
- 4. Class naive patients only: No
- 5. Controlled group standard of care: Yes
- 6. Funding: Not reported
- 7. Relevance: alcoholism

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**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Autret</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | Not randomized        |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | NR                    |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes, but not describe |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | No                    |
| Adherence                               | Yes                   |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Unable to determine   |
| 11. Postrandomization exclusions:       | Unable to determine   |
| 12. Quality rating:                     | Poor                  |

**External validity**

- |                                       |     |
|---------------------------------------|-----|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 121 |
| 2. Exclusion criteria:                | NR  |
| 3. Run-in:                            | 4   |
| Wash out:                             | 3   |
| 4. Class naive patients only          |     |
| 5. Controlled group standard of care: |     |
| 6. Funding:                           |     |
| 7. Relevance:                         |     |

---

**Comment:** Poor quality: No baseline characteristics reported, not reported if randomized, and unable to determine the number analyzed.

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Begg	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1992	<b>Country:</b> NR	<b>Funding:</b> Roche Products (NZ) Ltd.

---

**Internal validity**

- |                                     |      |
|-------------------------------------|------|
| 1. Randomization adequate?          | Yes  |
| 2. Allocation adequate?             | NR   |
| 3. Groups similar at baseline:      | No   |
| 4. Eligibility criteria specified   | Yes  |
| 5. Outcome assessors masked         | Yes  |
| 6. Care provider masked             | NR   |
| 7. Patients masked                  | Yes  |
| 8. Reporting of Attrition           | Yes  |
| Crossover                           | No   |
| Adherence                           | Yes  |
| Contamination                       | No   |
| 9. Loss to follow-up                |      |
| differential/ high                  | Yes  |
| If Yes, please report:              |      |
| 42% withdrew, but not differential. |      |
| 10. Intention-to-treat analysis:    | No   |
| 11. Postrandomization exclusions:   | Yes  |
| 12. Quality rating:                 | Poor |

**External validity**

- |   |                          |
|---|--------------------------|
| 1. Number Screened:   | NR                       |
| Eligible:   | NR                       |
| Enrolled:   | 88                       |
| 2. Exclusion criteria:  |                          |
| 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. |                          |
| 3. Run-in:  | 2                        |
| Wash out:   | 2                        |
| 4. Class naive patients only  | No                       |
| 5. Controlled group standard of care:   |                          |
| 6. Funding:   | Roche Products (NZ) Ltd. |
| 7. Relevance:   |                          |

---

**Comment:** Poor quality: very high withdrawal rate (42%) and no intention-to-treat analysis. No information on baseline characteristics.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Bergener</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>German</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

- |  |                       |
|--|-----------------------|
| 1. Randomization adequate?   | NR                    |
| 2. Allocation adequate?  | NR                    |
| 3. Groups similar at baseline:   | NR                    |
| 4. Eligibility criteria specified  | Yes                   |
| 5. Outcome assessors masked  | Yes, but not describe |
| 6. Care provider masked  | Yes, but not describe |
| 7. Patients masked   | Yes                   |
| 8. Reporting of Attrition  | Yes                   |
| Crossover  | No                    |
| Adherence  | No                    |
| Contamination  | No                    |
| 9. Loss to follow-up differential/ high  | Yes                   |
| If Yes, please report:   |                       |
| 16 of 42 patients (38%) dropped out, but not differential (8 in each group) and information provided on reasons for dropout. |                       |
| 10. Intention-to-treat analysis:   | Unable to determine   |
| 11. Postrandomization exclusions:  | No                    |
| 12. Quality rating:  | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 42  |
| 2. Exclusion criteria:                | Patients with a history of a delirium or a predelittumm 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 |
| 3. Run-in:                            | 4   |
| Wash out:                             | 7   |
| 4. Class naive patients only          | NR  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | elderly inpatients  |

**Comment:**

## Evidence Table 16. Quality Assessment

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**Author:** Bozin-Juracic      **Trial type:** Active      **Quality rating:** Fair  
**Year:** 1995      **Country:** Croatia      **Funding:** May and Becker and Rhone-

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**Internal validity**

- |                                   |                     |
|-----------------------------------|---------------------|
| 1. Randomization adequate?        | NR                  |
| 2. Allocation adequate?           | NR                  |
| 3. Groups similar at baseline:    | Yes                 |
| 4. Eligibility criteria specified | No                  |
| 5. Outcome assessors masked       | Yes                 |
| 6. Care provider masked           | NR                  |
| 7. Patients masked                | Yes                 |
| 8. Reporting of Attrition         | No                  |
| Crossover                         | No                  |
| Adherence                         | No                  |
| Contamination                     | No                  |
| 9. Loss to follow-up              |                     |
| differential/ high                | No                  |
| If Yes, please report:            |                     |
| 10. Intention-to-treat analysis:  | Unable to determine |
| 11. Postrandomization exclusions: | Yes                 |
| 12. Quality rating:               | Fair                |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR                                     |
| Eligible:                             | 32                                     |
| Enrolled:                             | 29                                     |
| 2. Exclusion criteria:                | NR                                     |
| 3. Run-in:                            | 0                                      |
| Wash out:                             | 0                                      |
| 4. Class naive patients only          | NR                                     |
| 5. Controlled group standard of care: | Yes                                    |
| 6. Funding:                           | May and Becker and Rhone-Poulenc Sante |
| 7. Relevance:                         | Shiftworkers                           |

---

**Comment:** Not clear if randomized.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Chaudoir</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	<b>NR (May &amp; Baker provided m</b>

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes, but not describe
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
High (16.7%, 2 zopiclone, 3 placebo)	
10. Intention-to-treat analysis:	No (25/30 analyzed)
11. Postrandomization exclusions:	No
12. Quality rating:	Poor

**External validity**

1. Number Screened:	NR
Eligible:	30
Enrolled:	25
2. Exclusion criteria:	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.
3. Run-in:	NR
Wash out:	NR
4. Class naive patients only	No
5. Controlled group standard of care:	NR
6. Funding:	NR (May & Baker provided medications and placebo)
7. Relevance:	Yes

**Comment:** Crossover design, but the results combined placebo outcomes and treatment outcomes from two groups.

## Evidence Table 16. Quality Assessment

---

**Author:** Chaudoir                      **Trial type:** Placebo                      **Quality rating:** Poor  
**Year:** 1983                              **Country:** UK                              **Funding:** NR (May & Baker provided m

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Not clear             |
| 11. Postrandomization exclusions:       | Unable to determine   |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 38  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | no  |
| Wash out:                             | 7   |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | Yes   |

**Comment:**



## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Dockhorn</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Loxex Pharmaceuticals</b>

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes                   |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | No (136/139 analyzed) |
| 11. Postrandomization exclusions:       | Yes (1 patient)       |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 138  |
| 2. Exclusion criteria:                | 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 |
| 3. Run-in:                            | NR   |
| Wash out:                             | NR   |
| 4. Class naive patients only          | NR   |
| 5. Controlled group standard of care: | NR   |
| 6. Funding:                           | Loxex Pharmaceuticals  |
| 7. Relevance:                         | Acute insomnia   |

**Comment:**

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Dorsey	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sanofi-Synthelabo

---

**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes, but not describe
- 6. Care provider masked: NR
- 7. Patients masked: Yes
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: No  
If Yes, please report:
  
- 10. Intention-to-treat analysis: Yes
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: 242
  - Eligible: 141
  - Enrolled: 141
- 2. Exclusion criteria:
 

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 urinate screening test for medication that could interfere with the assessment of study medication, including benzodiazepines, barbituates, 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.
  
- 3. Run-in: 6-14
  - Wash out: NR
- 4. Class naive patients only: NR
- 5. Controlled group standard of care: NR
- 6. Funding: Sanofi-Synthelabo
  
- 7. Relevance: Women

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**Comment:**

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Drake (1)	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst Research

---

**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: NR
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes, but not describe
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover 0
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high No
  - If Yes, please report:
- 10. Intention-to-treat analysis: Unable to determine
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: NR
  - Enrolled: 47
- 2. Exclusion criteria:
  - 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.
- 3. Run-in: NR
  - Wash out: 5-12
- 4. Class naive patients only No
- 5. Controlled group standard of care: Yes
- 6. Funding: Wyeth-Ayerst Research
- 7. Relevance: Yes

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**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Drake (2)</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Wyeth-Ayerst Research</b>

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**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | NR                    |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes                   |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | No                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | Unable to determine   |
| 11. Postrandomization exclusions: | No                    |
| 12. Quality rating:               | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 36  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | NR  |
| Wash out:                             | 5-12  |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Wyeth-Ayerst Research   |
| 7. Relevance:                         | Yes   |

**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Elie	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990b	<b>Country:</b> Canada	<b>Funding:</b> Not reported

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**Internal validity**

- |                                   |                     |
|-----------------------------------|---------------------|
| 1. Randomization adequate?        | NR                  |
| 2. Allocation adequate?           | NR                  |
| 3. Groups similar at baseline:    | NR                  |
| 4. Eligibility criteria specified | Yes                 |
| 5. Outcome assessors masked       | Yes                 |
| 6. Care provider masked           | NR                  |
| 7. Patients masked                | Yes                 |
| 8. Reporting of Attrition         | No                  |
| Crossover                         | No                  |
| Adherence                         | No                  |
| Contamination                     | No                  |
| 9. Loss to follow-up              |                     |
| differential/ high                | NR                  |
| If Yes, please report:            |                     |
| 10. Intention-to-treat analysis:  | Unable to determine |
| 11. Postrandomization exclusions: | Unable to determine |
| 12. Quality rating:               | Fair                |

**External validity**

- |  |              |
|--|--------------|
| 1. Number Screened:  | NR           |
| Eligible:  | NR           |
| Enrolled:  | 36           |
| 2. Exclusion criteria:   |              |
| 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. |              |
| 3. Run-in:   | 7            |
| Wash out:  | 3            |
| 4. Class naive patients only   | No           |
| 5. Controlled group standard of care:  | Yes          |
| 6. Funding:  | Not reported |
| 7. Relevance:  | Yes          |

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Elie</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990b</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>
<b>Internal validity</b>			<b>External validity</b>		
1. Randomization adequate?	NR	1. Number Screened:	NR		
2. Allocation adequate?	NR	Eligible:	NR		
3. Groups similar at baseline:	NR	Enrolled:	44		
4. Eligibility criteria specified	Yes	2. Exclusion criteria:			
5. Outcome assessors masked	Yes, but not describe				Psychotic and neurotic patients, history of blood dyscrasia, neurological disorders, drug hypersensitivity, chronic alcoholism, drug abuse and coffee or tea abuse.
6. Care provider masked	NR				Patients with severe medical conditions, those treated with CNS drugs and those receiving treatments which could modify drug kinetics were not accepted.
7. Patients masked	Yes				
8. Reporting of Attrition	No				
Crossover	No				
Adherence	No				
Contamination	No				
9. Loss to follow-up differential/ high	NR				
If Yes, please report:					
		3. Run-in:	7		
		Wash out:	4		
		4. Class naive patients only	No		
		5. Controlled group standard of care:	Yes		
		6. Funding:	Not reported		
10. Intention-to-treat analysis:	Yes				
11. Postrandomization exclusions:	Unable to determine				
12. Quality rating:	Fair	7. Relevance:	elderly residents of		

**Comment:** Elderly patients living in nursing homes.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Elie</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990b</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>
<b>Internal validity</b>			<b>External validity</b>		
1. Randomization adequate?	NR	1. Number Screened:	NR		
2. Allocation adequate?	NR	Eligible:	NR		
3. Groups similar at baseline:	NR	Enrolled:	615		
4. Eligibility criteria specified	Yes	2. Exclusion criteria:	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.		
5. Outcome assessors masked	Yes				
6. Care provider masked	NR				
7. Patients masked	Yes				
8. Reporting of Attrition	Yes				
Crossover	No				
Adherence	Yes				
Contamination	No				
9. Loss to follow-up differential/ high	No				
If Yes, please report:					
		3. Run-in:	Yes		
		Wash out:	Yes		
		4. Class naive patients only	No		
		5. Controlled group standard of care:	Yes		
		6. Funding:	Wyeth-Ayerst		
10. Intention-to-treat analysis:	No				
11. Postrandomization exclusions:	Yes				
12. Quality rating:	Fair	7. Relevance:	Yes		

**Comment:** Analyzed 574/615 patients randomized. 39 patients excluded from efficacy analysis because of inadequate source documentation. Baseline demographic characteristics given only on 574 patients analyzed, and no statistical analysis of baseline characteristics.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Erman (FDA #190-0</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>NR</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Sepracor</b>

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**Internal validity**

- |                                   |                        |
|-----------------------------------|------------------------|
| 1. Randomization adequate?        | NR                     |
| 2. Allocation adequate?           | NR                     |
| 3. Groups similar at baseline:    | NR                     |
| 4. Eligibility criteria specified | Yes                    |
| 5. Outcome assessors masked       | Yes (but concern re.   |
| 6. Care provider masked           | NR                     |
| 7. Patients masked                | Yes (but concern re.   |
| 8. Reporting of Attrition         | No                     |
| Crossover                         | No                     |
| Adherence                         | No                     |
| Contamination                     | No                     |
| 9. Loss to follow-up              |                        |
| differential/ high                | NR                     |
| If Yes, please report:            |                        |
| 10. Intention-to-treat analysis:  | Pts who rec'd at least |
| 11. Postrandomization exclusions: | Unable to determine    |
| 12. Quality rating:               | Fair                   |

**External validity**

- |                                       |          |
|---------------------------------------|----------|
| 1. Number Screened:                   |          |
| Eligible:                             |          |
| Enrolled:                             |          |
| 2. Exclusion criteria:                | NR       |
| 3. Run-in:                            |          |
| Wash out:                             |          |
| 4. Class naive patients only          | NR       |
| 5. Controlled group standard of care: | NR       |
| 6. Funding:                           | Sepracor |
| 7. Relevance:                         | Yes      |

**Comment:**



## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Fleming</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

1. Randomization adequate?	Yes
2. Allocation adequate?	NR
3. Groups similar at baseline:	NR
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No (48/52 analyzed)
11. Postrandomization exclusions:	Yes
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	NR
Enrolled:	52
2. Exclusion criteria:	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, analgesis, 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.
3. Run-in:	3
Wash out:	4
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

**Comment:** Enrolled population characteristics were not reported. Analyzed population characteristics: mean age=45.5 years; 23 (48%) female.

Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Fleming</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

Internal validity		External validity	
1. Randomization adequate?	NR	1. Number Screened:	222
2. Allocation adequate?	NR	Eligible:	144
3. Groups similar at baseline:	Yes	Enrolled:	144
4. Eligibility criteria specified	Yes	2. Exclusion criteria:	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.
5. Outcome assessors masked	Yes, but not describe	3. Run-in:	1
6. Care provider masked	NR	Wash out:	NR
7. Patients masked	Yes	4. Class naive patients only	No
8. Reporting of Attrition	Yes	5. Controlled group standard of care:	Yes
Crossover	Yes	6. Funding:	Not reported
Adherence	No	7. Relevance:	Yes
Contamination	Yes		
9. Loss to follow-up differential/ high	Yes		
If Yes, please report:			
7 (10%) zolpidem vs 1 (3%) flurazepam discontinued			
10. Intention-to-treat analysis:	No		
11. Postrandomization exclusions:	Yes		
12. Quality rating:	Fair		

**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Fontaine</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

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**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | Yes                   |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes                   |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | No                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | Yes                   |
| 11. Postrandomization exclusions: | No                    |
| 12. Quality rating:               | Fair                  |

**External validity**

- |  |                      |
|--|----------------------|
| 1. Number Screened:  | NR                   |
| Eligible:  | NR                   |
| Enrolled:  | 75                   |
| 2. Exclusion criteria:   |                      |
| 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). |                      |
| 3. Run-in:   | 7                    |
| Wash out:  | 21                   |
| 4. Class naive patients only   | No                   |
| 5. Controlled group standard of care:  | Yes                  |
| 6. Funding:  | Rhone-Poulenc Pharma |
| 7. Relevance:  | Yes                  |

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**Comment:** Subgroup: generalized anxiety disorder

## Evidence Table 16. Quality Assessment

<b>Author:</b> Fry	<b>Trial type:</b> H2H	<b>Quality rating:</b> Fair
<b>Year:</b> 2000	<b>Country:</b> US	<b>Funding:</b> Wyeth-Ayerst

**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | NR                    |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes, but not describe |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | No                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | No                    |
| 11. Postrandomization exclusions: | Yes                   |
| 12. Quality rating:               | Fair                  |

**External validity**

- |   |              |
|---|--------------|
| 1. Number Screened:   | NR           |
| Eligible:   | 830          |
| Enrolled:   | 595          |
| 2. Exclusion criteria:  |              |
| 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. |              |
| 3. Run-in:  | 7            |
| Wash out:   | no           |
| 4. Class naive patients only  | NR           |
| 5. Controlled group standard of care:   | Yes          |
| 6. Funding:   | Wyeth-Ayerst |
| 7. Relevance:   | Yes          |

**Comment:** Patients with mild non-psychotic psychiatric disorders. Baseline characteristics reported only for 586/595 randomized (98%) Data on primary outcome (sleep latency) reported graphically only.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Goldenberg</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>UK, France</b>	<b>Funding:</b>	<b>NR</b>

**Internal validity**

- |   |                        |
|---|------------------------|
| 1. Randomization adequate?                    | NR                     |
| 2. Allocation adequate?                       | NR                     |
| 3. Groups similar at baseline:                | Yes (for analyzed pop) |
| 4. Eligibility criteria specified             | Yes                    |
| 5. Outcome assessors masked                   | Yes, but not describe  |
| 6. Care provider masked                       | NR                     |
| 7. Patients masked                            | Yes                    |
| 8. Reporting of Attrition                     | Yes                    |
| Crossover                                     | No                     |
| Adherence                                     | No                     |
| Contamination                                 | No                     |
| 9. Loss to follow-up differential/ high       | Yes                    |
| If Yes, please report:                        |                        |
| High: 36.8% dropped out; groups not specified |                        |
| 10. Intention-to-treat analysis:              | No                     |
| 11. Postrandomization exclusions:             | Unable to determine    |
| 12. Quality rating:                           | Poor                   |

**External validity**

- |   |     |
|---|-----|
| 1. Number Screened:   | NR  |
| Eligible:   | NR  |
| Enrolled:   | 524 |
| 2. Exclusion criteria:  |     |
| 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 of pregnancy. Nursing mothers, and those performing skilled tasks, shiftwork 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. |     |
| 3. Run-in:  | NR  |
| Wash out:   | NR  |
| 4. Class naive patients only  | NR  |
| 5. Controlled group standard of care:   | NR  |
| 6. Funding:   | NR  |
| 7. Relevance:   | Yes |

**Comment:** Only analyzed population characteristics were reported: Mean age=42.9 years; 36.4% male; Ethnicity NR.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Hajak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1998, 1995, 1994</b>	<b>Country:</b>	<b>Germany</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

1. Randomization adequate?	Yes
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postrandomization exclusions:	No
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	NR
Enrolled:	1507
2. Exclusion criteria:	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
3. Run-in:	7
Wash out:	3
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

---

**Comment:** Patients were observed for a further period of 14 days without medication for rebound.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Hayoun</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1989</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported (corresponding</b>

**Internal validity**

- |  |                       |
|--|-----------------------|
| 1. Randomization adequate?   | NR                    |
| 2. Allocation adequate?  | NR                    |
| 3. Groups similar at baseline:   | Yes                   |
| 4. Eligibility criteria specified  | Yes                   |
| 5. Outcome assessors masked  | Yes, but not describe |
| 6. Care provider masked  | NR                    |
| 7. Patients masked   | Yes                   |
| 8. Reporting of Attrition  | Yes                   |
| Crossover  | No                    |
| Adherence  | No                    |
| Contamination  | Yes                   |
| 9. Loss to follow-up differential/ high  | Yes                   |
| If Yes, please report:   |                       |
| 2 of 68 (3%) triazolam vs 5 of 66 (8%) zopiclone patients discontinued and not included in analysis. |                       |
| 10. Intention-to-treat analysis:   | No                    |
| 11. Postrandomization exclusions:  | Yes                   |
| 12. Quality rating:  | Fair                  |

**External validity**

- |  |   |
|--|---|
| 1. Number Screened:  | NR  |
| Eligible:  | NR  |
| Enrolled:  | 136   |
| 2. Exclusion criteria:   |   |
| 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. |   |
| 3. Run-in:   | NR  |
| Wash out:  | NR  |
| 4. Class naive patients only   | No  |
| 5. Controlled group standard of care:  | Yes   |
| 6. Funding:  | Not reported (corresponding author from Upjohn) |
| 7. Relevance:  | Yes   |

**Comment:** Sleep aid, drug abuse???

More patients on zopiclone had insomnia as a major complaint compared with those on triazolam (70%) vs 55%, respectively; p=0.04). More patients described themselves as tranquil compared with patients on zopiclone.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Hedner</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2000</b>	<b>Country:</b>	<b>Europe</b>	<b>Funding:</b>	

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes for analyzed pop  |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes                   |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | No                    |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | NR                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | No (422/437 analyzed) |
| 11. Postrandomization exclusions:       | NR                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 437   |
| 2. Exclusion criteria:                | Patients with a raw score of > 50 on the Zung Anxiety or Depression scales were not enrolled. |
| 3. Run-in:                            | 7   |
| Wash out:                             | 7   |
| 4. Class naive patients only          |   |
| 5. Controlled group standard of care: |   |
| 6. Funding:                           |   |
| 7. Relevance:                         | Older adults  |

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**Comment:** Only analyzed population characteristics were reported: Mean age=72.5 years; 32.3% male; 99% white, 1% black.



### Evidence Table 16. Quality Assessment

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<b>Author:</b> Herrmann	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 1993	<b>Country:</b> France	<b>Funding:</b> NR

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: NR
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes, but not describe
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high Yes
  - If Yes, please report:  
16% not analyzed
- 10. Intention-to-treat analysis: No (21/25 analyzed)
- 11. Postrandomization exclusions: Yes (1/25)
- 12. Quality rating: Poor

**External validity**

- 1. Number Screened: NR
  - Eligible: 25
  - Enrolled: 21
- 2. Exclusion criteria:
  - 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.
- 3. Run-in: 7
  - Wash out: 7
- 4. Class naive patients only NR
- 5. Controlled group standard of care: NR
- 6. Funding: NR
- 7. Relevance: Yes

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**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Hindmarch</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1995</b>	<b>Country:</b>	<b>UK</b>	<b>Funding:</b>	

---

**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | global QOL score hig  |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes, but not describe |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | Yes                   |
| If Yes, please report:            |                       |
| High- 36.8%; groups not specified |                       |
| 10. Intention-to-treat analysis:  | No                    |
| 11. Postrandomization exclusions: | Unable to determine   |
| 12. Quality rating:               | Fair                  |

**External validity**

- |  |     |
|--|-----|
| 1. Number Screened:  | NR  |
| Eligible:  | NR  |
| Enrolled:  | 458 |
| 2. Exclusion criteria:   |     |
| 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. |     |
| 3. Run-in:   | NR  |
| Wash out:  | NR  |
| 4. Class naive patients only   |     |
| 5. Controlled group standard of care:  |     |
| 6. Funding:  |     |
| 7. Relevance:  |     |

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**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b> Klimm	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1987	<b>Country:</b> France	<b>Funding:</b> Not reported

**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | Yes                   |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes                   |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | Yes                   |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | No                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | No                    |
| 11. Postrandomization exclusions: | No                    |
| 12. Quality rating:               | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 74  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | 7   |
| Wash out:                             | 7   |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | elderly patients  |

**Comment:** no psychotropic or centrally active drugs were allowed, but medication for concomitant disease were continued, including antihypertensives, non-steroidal anti-inflammatory drugs, hypoglycemic agents, uricosuric agents, anti-anginal agents, and hypolipidaemic agents.

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Krystal	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2003	<b>Country:</b> US	<b>Funding:</b> Sepracor

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: weight and BMI > in e
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high No
  - If Yes, please report:
- 10. Intention-to-treat analysis: Yes
- 11. Postrandomization exclusions: 3 patients discontinue
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: 1194
  - Eligible: 791
  - Enrolled: 788
- 2. Exclusion criteria: NR
- 3. Run-in: NR
  - Wash out: 5-7
- 4. Class naive patients only NR
- 5. Controlled group standard of care: NR
- 6. Funding: Sepracor
- 7. Relevance: Yes

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**Comment:**

## Evidence Table 16. Quality Assessment

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**Author:** Lahmeyer                      **Trial type:** Placebo                      **Quality rating:** Fair  
**Year:** 1997                              **Country:** US                              **Funding:** ?orex Pharmaceuticals

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**Internal validity**

- |  |      |
|--|------|
| 1. Randomization adequate?               | NR   |
| 2. Allocation adequate?                  | NR   |
| 3. Groups similar at baseline:           | Yes  |
| 4. Eligibility criteria specified        | Yes  |
| 5. Outcome assessors masked              | Yes  |
| 6. Care provider masked                  | NR   |
| 7. Patients masked                       | Yes  |
| 8. Reporting of Attrition                | Yes  |
| Crossover                                | No   |
| Adherence                                | Yes  |
| Contamination                            | No   |
| 9. Loss to follow-up                     |      |
| differential/ high                       | Yes  |
| If Yes, please report:                   |      |
| High- 19% discontinued; not differential |      |
| 10. Intention-to-treat analysis:         | No   |
| 11. Postrandomization exclusions:        | No   |
| 12. Quality rating:                      | Fair |

**External validity**

- |   |     |
|---|-----|
| 1. Number Screened:   | 178 |
| Eligible:   | 33  |
| Enrolled:   | 145 |
| 2. Exclusion criteria:  |     |
| 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 shortacting 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 nights 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 yar; (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. |     |
| 3. Run-in:  | 3   |
| Wash out:   | 4   |
| 4. Class naive patients only  | NR  |
| 5. Controlled group standard of care:   | Yes |
| 6. Funding: ?orex Pharmaceuticals   |     |
| 7. Relevance:   | Yes |

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Lemoine</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1995</b>	<b>Country:</b>	<b>France</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	Yes
4. Eligibility criteria specified	
5. Outcome assessors masked	Yes
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postrandomization exclusions:	No
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	NR
Enrolled:	394
2. Exclusion criteria:	History of depression or other psychiatric disorder, a current depressive episode (total score on the QD2A questionnaire $\geq 7$ ) 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.
3. Run-in:	0
Wash out:	0
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

**Comment:** Study of withdrawal effects- separate studies of zopiclone and zolpidem; efficacy not assessed. Comparisons were treatment vs withdrawal within drug groups.

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Leppik	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1997	<b>Country:</b> US	<b>Funding:</b> Lornex Pharmaceuticals

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes, but not describe
- 6. Care provider masked: NR
- 7. Patients masked: Yes
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: No
  - If Yes, please report:
- 10. Intention-to-treat analysis: Yes
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: 457
  - Enrolled: 335
- 2. Exclusion criteria:
  - 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 or myoclonus were excluded. Shift workers and other individuals with changing sleep schedules were also excluded.
- 3. Run-in: 7
  - Wash out: 4
- 4. Class naive patients only: No
- 5. Controlled group standard of care: Yes
- 6. Funding: Lornex Pharmaceuticals
- 7. Relevance: Elderly

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**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Li Pi Shan</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

1. Randomization adequate?	Yes
2. Allocation adequate?	NR
3. Groups similar at baseline:	NR
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes
6. Care provider masked	Yes
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	No
11. Postrandomization exclusions:	No
12. Quality rating:	Fair

**External validity**

1. Number Screened:	44
Eligible:	27
Enrolled:	18
2. Exclusion criteria:	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.
3. Run-in:	0
Wash out:	0
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Inpatients with stro

**Comment:** Although there was no formal washout period between weeks 1 and 2, the questionnaire was not administered on any of the first 3 days to allow for a washout of the medication taken during week 1. Any additional medications the patients were receiving were maintained constant throughout the trial. Those whose medications changed over the course of the study were excluded.



## Evidence Table 16. Quality Assessment

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<b>Author:</b> Liu	<b>Trial type:</b> Active	<b>Quality rating:</b> Poor
<b>Year:</b> 1997	<b>Country:</b> Taiwan	<b>Funding:</b>

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**Internal validity**

- |  |                       |
|--|-----------------------|
| 1. Randomization adequate?                                     | NR                    |
| 2. Allocation adequate?  | NR                    |
| 3. Groups similar at baseline:                                 | NR                    |
| 4. Eligibility criteria specified                              | Yes                   |
| 5. Outcome assessors masked                                    | Yes, but not describe |
| 6. Care provider masked  | NR                    |
| 7. Patients masked   | Yes, but not describe |
| 8. Reporting of Attrition                                      | Yes                   |
| Crossover  | No                    |
| Adherence  | Yes                   |
| Contamination  | No                    |
| 9. Loss to follow-up differential/ high                        | Yes                   |
| If Yes, please report:   |                       |
| 8 patients did not finish the trial due to lack of compliance. |                       |
| 10. Intention-to-treat analysis:                               | Unable to determine   |
| 11. Postrandomization exclusions:                              | Unable to determine   |
| 12. Quality rating:  | Poor                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 15  |
| 2. Exclusion criteria:                | Patients with psychoses or mood disorders, history of severe physical illness, alcohol abuse or drug abuse. |
| 3. Run-in:                            | 0   |
| Wash out:                             | 7   |
| 4. Class naive patients only          |   |
| 5. Controlled group standard of care: |   |
| 6. Funding:                           |   |
| 7. Relevance:                         |   |

---

**Comment:** Poor quality- baseline characteristics not reported, no information on randomization and allocation concealment methods. Unable to determine if an intention-to-treat analysis was used, and high loss to followup. (8 patients did not complete the trial; unclear if 8 of 15 or 8 of 23).

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Mamelak</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Not reported</b>

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**Internal validity**

- |                                   |                     |
|-----------------------------------|---------------------|
| 1. Randomization adequate?        | NR                  |
| 2. Allocation adequate?           | NR                  |
| 3. Groups similar at baseline:    | NR                  |
| 4. Eligibility criteria specified | Yes                 |
| 5. Outcome assessors masked       | Yes                 |
| 6. Care provider masked           | NR                  |
| 7. Patients masked                | Yes                 |
| 8. Reporting of Attrition         | No                  |
| Crossover                         | No                  |
| Adherence                         | No                  |
| Contamination                     | No                  |
| 9. Loss to follow-up              |                     |
| differential/ high                | No                  |
| If Yes, please report:            |                     |
| 10. Intention-to-treat analysis:  | Unable to determine |
| 11. Postrandomization exclusions: | Unable to determine |
| 12. Quality rating:               | Fair                |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 30   |
| 2. Exclusion criteria:                |  |
|                                       | 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. |
| 3. Run-in:                            | 2  |
| Wash out:                             | 3  |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Not reported   |
| 7. Relevance:                         | assessments perfo  |

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**Comment:** Ethanol-drug interaction study.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Monchesky</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1986</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>NR</b>

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | Yes                   |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes (for 91/99 analyz |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | Unable to determine   |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | No (91/99 analyzed)   |
| 11. Postrandomization exclusions:       | 1/99                  |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 99  |
| 2. Exclusion criteria:                | 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 |
| 3. Run-in:                            | 7   |
| Wash out:                             | 7   |
| 4. Class naive patients only          | NR  |
| 5. Controlled group standard of care: | NR  |
| 6. Funding:                           | NR  |
| 7. Relevance:                         | Yes   |

**Comment:** Zopiclone 7.5mg for run-in and wash-out periods.  
Only analyzed population characteristics were reported: Mean age=46.8; 28.6% male; Ethnicity NR.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Monti</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Uruguay</b>	<b>Funding:</b>	<b>Not reported</b>

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**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | Yes                   |
| Adherence                               | Yes                   |
| Contamination                           | Yes                   |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Yes                   |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 24  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | 3   |
| Wash out:                             | 3   |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | Yes   |

**Comment:**

## Evidence Table 16. Quality Assessment

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**Author:** Monti                      **Trial type:** Active                      **Quality rating:** Fair  
**Year:** 1994                      **Country:** Uruguay                      **Funding:** Not reported

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | No                    |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Yes                   |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 12  |
| 2. Exclusion criteria:                |   |
|                                       | 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. |
| 3. Run-in:                            | 2   |
| Wash out:                             | 3   |
| 4. Class naive patients only          | Yes   |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | NR  |
| 7. Relevance:                         | Yes   |

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**Comment:**

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Monti_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 2000	<b>Country:</b> Uruguay	<b>Funding:</b> NR

---

**Internal validity**

- 1. Randomization adequate? No (sequential order)
- 2. Allocation adequate? No (randomized in se
- 3. Groups similar at baseline: Lower weight in zolpid
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition No
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high NR
  - If Yes, please report:
- 10. Intention-to-treat analysis: Unable to determine
- 11. Postrandomization exclusions: Unable to determine
- 12. Quality rating: Poor

**External validity**

- 1. Number Screened: NR
  - Eligible: NR
  - Enrolled: 12
- 2. Exclusion criteria:
  - 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 swere pregnant women, breast-feeding mothers, subjects deemed insufficiently compliant, or those with cliniclally significant diviations 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
- 3. Run-in: 3
  - Wash out: 3
- 4. Class naive patients only No
- 5. Controlled group standard of care: NR
- 6. Funding: NR
- 7. Relevance: Women

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**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Nair</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Canada</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

---

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | 0                     |
| Adherence                               | Yes                   |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | No                    |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 60   |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | 1  |
| Wash out:                             | NR   |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Rhone-Poulenc Pharma   |
| 7. Relevance:                         |  |

**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Ngen</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1990</b>	<b>Country:</b>	<b>Malaysia</b>	<b>Funding:</b>	<b>Rhone-Poulenc Pharma</b>

---

**Internal validity**

1. Randomization adequate? Yes
2. Allocation adequate? Yes
3. Groups similar at baseline:
4. Eligibility criteria specified
5. Outcome assessors masked Yes
6. Care provider masked NR
7. Patients masked Yes
8. Reporting of Attrition
  - Crossover 0
  - Adherence
  - Contamination
9. Loss to follow-up differential/ high Yes
  - If Yes, please report:
  - 27% discontinued, but not differential (7 placebo, 5 zopiclone, 4 temazepan)
10. Intention-to-treat analysis: No
11. Postrandomization exclusions: No
12. Quality rating: Fair

**External validity**

1. Number Screened: NR
  - Eligible: NR
  - Enrolled: 60
2. Exclusion criteria:
  - (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
3. Run-in: 7
  - Wash out: NR
4. Class naive patients only No
5. Controlled group standard of care: Yes
6. Funding: Rhone-Poulenc Pharma
7. Relevance: Yes

**Comment:**



### Evidence Table 16. Quality Assessment

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<b>Author:</b> Pagot	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1993	<b>Country:</b> France	<b>Funding:</b> Not reported

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes, but not describe
- 6. Care provider masked: NR
- 7. Patients masked: Yes
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: Yes
  - If Yes, please report:
  - 32% zolpidem and 38% triazolam dropped out
- 10. Intention-to-treat analysis: No
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: NR
  - Enrolled: 95
- 2. Exclusion criteria:
  - 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.
- 3. Run-in: 4
  - Wash out: 30
- 4. Class naive patients only: No
- 5. Controlled group standard of care: Yes
- 6. Funding: Not reported
- 7. Relevance: patients with anxiet

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**Comment:**

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Perlis	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

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**Internal validity**

- 1. Randomization adequate? Yes
- 2. Allocation adequate? Yes
- 3. Groups similar at baseline: More women in place
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence Yes
  - Contamination Yes
- 9. Loss to follow-up differential/ high No  
If Yes, please report:
  
- 10. Intention-to-treat analysis: No
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: 322  
Eligible: 277  
Enrolled: 199
- 2. Exclusion criteria:  
Exclusion criteria included presene 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; postiive urine screen for medication that could interfere with the assessment of study medication; history of drug addiciton, alcoholism, or drug abuse; and histroy 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.
  
- 3. Run-in: 6-14  
Wash out: NR
- 4. Class naive patients only
- 5. Controlled group standard of care:
- 6. Funding: Lorex Pharmaceuticals
  
- 7. Relevance:

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**Comment:** Patients were instructed to "take the medication when you think you need it, at bedtime, for a total of between 3 and 5 capsules per week". They were also told to take only 1 pill per night and not to use the study medication to treat early awakenings.

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Ponciano	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Portugal	<b>Funding:</b> Not reported

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: NR
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high No
  - If Yes, please report:
- 10. Intention-to-treat analysis: Yes
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: NR
  - Enrolled: 26
- 2. Exclusion criteria:
  - 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.
- 3. Run-in: 7
  - Wash out: 7
- 4. Class naive patients only No
- 5. Controlled group standard of care: Yes
- 6. Funding: Not reported
- 7. Relevance: Yes

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**Comment:** Results were reported in figures only. Therefore, the data reported in the evidence table were estimated from the figures.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Quadens</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1983</b>	<b>Country:</b>	<b>Belgium</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | NR                    |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes                   |
| 8. Reporting of Attrition         | No                    |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | NR                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | Unable to determine   |
| 11. Postrandomization exclusions: | Unable to determine   |
| 12. Quality rating:               | Poor                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 12   |
| 2. Exclusion criteria:                | (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. |
| 3. Run-in:                            | 6  |
| Wash out:                             | 35   |
| 4. Class naive patients only          | NR   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Not reported   |
| 7. Relevance:                         | postmenopausal w   |

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**Comment:** Poor quality- insufficient information to assess quality.

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Roger	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1993	<b>Country:</b> France	<b>Funding:</b> Not reported

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**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | Yes, but not describe |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | Yes                   |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Unable to determine   |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 221  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | 3  |
| Wash out:                             | 7  |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Not reported   |
| 7. Relevance:                         | Elderly inpatients   |

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**Comment:** Inpatients at geriatric wards.

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Rosenberg</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1994</b>	<b>Country:</b>	<b>Denmark</b>	<b>Funding:</b>	<b>Synthelabo Scandinavia A/S</b>

**Internal validity**

- |  |      |
|--|------|
| 1. Randomization adequate?   | Yes  |
| 2. Allocation adequate?  | Yes  |
| 3. Groups similar at baseline:   | NR   |
| 4. Eligibility criteria specified  | Yes  |
| 5. Outcome assessors masked  | Yes  |
| 6. Care provider masked  | Yes  |
| 7. Patients masked   | Yes  |
| 8. Reporting of Attrition  | Yes  |
| Crossover  | No   |
| Adherence  | No   |
| Contamination  | No   |
| 9. Loss to follow-up differential/ high  | Yes  |
| If Yes, please report:   |      |
| 19% excluded due to lack of data or protocol violations (16 zolpidem, 23 triazolam, number randomized not reported by group) |      |
| 10. Intention-to-treat analysis:   | No   |
| 11. Postrandomization exclusions:  | Yes  |
| 12. Quality rating:  | Poor |

**External validity**

- |  |                            |
|--|----------------------------|
| 1. Number Screened:  | NR                         |
| Eligible:  | NR                         |
| Enrolled:  | 178                        |
| 2. Exclusion criteria:   |                            |
| 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 |                            |
| 3. Run-in:   | NR                         |
| Wash out:  | NR                         |
| 4. Class naive patients only   | No                         |
| 5. Controlled group standard of care:  | Yes                        |
| 6. Funding:  | Synthelabo Scandinavia A/S |
| 7. Relevance:  | Yes                        |

**Comment:** Enrolled patients characteristics were not reported. Analyzed patients characteristics were reported instead: mean age=51 years, range 19-79 years; 31% male.

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Scharf	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2005	<b>Country:</b> US	<b>Funding:</b>

---

**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes
- 6. Care provider masked: NR
- 7. Patients masked: Yes
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: No
  - If Yes, please report:
- 10. Intention-to-treat analysis: Yes
- 11. Postrandomization exclusions: Unable to determine
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: 353
  - Eligible: NR
  - Enrolled: 231
- 2. Exclusion criteria:
  - 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 excluded.
- 3. Run-in: 3-14
  - Wash out: NR
- 4. Class naive patients only: No
- 5. Controlled group standard of care: NR
- 6. Funding:
- 7. Relevance: Older adults

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**Comment:**

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Scharf_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 1994	<b>Country:</b> US	<b>Funding:</b> NR

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**Internal validity**

- |                                   |                     |
|-----------------------------------|---------------------|
| 1. Randomization adequate?        | NR                  |
| 2. Allocation adequate?           | NR                  |
| 3. Groups similar at baseline:    | Yes                 |
| 4. Eligibility criteria specified | Yes                 |
| 5. Outcome assessors masked       | Yes                 |
| 6. Care provider masked           | NR                  |
| 7. Patients masked                | Yes                 |
| 8. Reporting of Attrition         | Yes                 |
| Crossover                         | No                  |
| Adherence                         | No                  |
| Contamination                     | Yes                 |
| 9. Loss to follow-up              |                     |
| differential/ high                | No                  |
| If Yes, please report:            |                     |
| 10. Intention-to-treat analysis:  | Unable to determine |
| 11. Postrandomization exclusions: | No                  |
| 12. Quality rating:               | Fair                |

**External validity**

- |                                       |     |
|---------------------------------------|-----|
| 1. Number Screened:                   | 178 |
| Eligible:                             | 75  |
| Enrolled:                             | 75  |
| 2. Exclusion criteria:                |     |
| 3. Run-in:                            | 11  |
| Wash out:                             | 2   |
| 4. Class naive patients only          | NR  |
| 5. Controlled group standard of care: | NR  |
| 6. Funding:                           | NR  |
| 7. Relevance:                         | Yes |

**Comment:**



## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Schwartz</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

- |   |          |
|---|----------|
| 1. Randomization adequate?              | NR       |
| 2. Allocation adequate?                 | No- open |
| 3. Groups similar at baseline:          | NR       |
| 4. Eligibility criteria specified       | No       |
| 5. Outcome assessors masked             | No       |
| 6. Care provider masked                 | No       |
| 7. Patients masked                      | No       |
| 8. Reporting of Attrition               | Yes      |
| Crossover                               | No       |
| Adherence                               | No       |
| Contamination                           | No       |
| 9. Loss to follow-up differential/ high | No       |
| If Yes, please report:                  |          |
| 10. Intention-to-treat analysis:        | Yes      |
| 11. Postrandomization exclusions:       | No       |
| 12. Quality rating:                     | Poor     |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 16  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | NR  |
| Wash out:                             | NR  |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | psychiatric inpatient   |

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**Comment:** Psychiatric inpatients

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Silvestri</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1996</b>	<b>Country:</b>	<b>Italy</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?  | NR                    |
| 2. Allocation adequate?   | NR                    |
| 3. Groups similar at baseline:                                      | Yes                   |
| 4. Eligibility criteria specified                                   | Yes                   |
| 5. Outcome assessors masked   | Yes, but not describe |
| 6. Care provider masked   | NR                    |
| 7. Patients masked  | Yes, but not describe |
| 8. Reporting of Attrition   | Yes                   |
| Crossover   | No                    |
| Adherence   | No                    |
| Contamination   | No                    |
| 9. Loss to follow-up differential/ high                             | Yes                   |
| If Yes, please report:  |                       |
| 2/12 triazolam (10%) patients vs 0/10 zolpidem patients lost to f/u |                       |
| 10. Intention-to-treat analysis:                                    | No                    |
| 11. Postrandomization exclusions:                                   | Yes                   |
| 12. Quality rating:   | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 22  |
| 2. Exclusion criteria:                | 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 (myoclones, kinaesthesia 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. |
| 3. Run-in:                            | 3   |
| Wash out:                             | No  |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | Yes   |

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b> Singh	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1990	<b>Country:</b> Canada	<b>Funding:</b> Rhone-Poulenc Pharma Inc.

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	NR
4. Eligibility criteria specified	No
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up	
differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Yes
11. Postrandomization exclusions: Yes (1 patient)	
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	61
Enrolled:	60
2. Exclusion criteria:	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.
3. Run-in:	4
Wash out:	NR
4. Class naive patients only	NR
5. Controlled group standard of care:	Yes
6. Funding:	Rhone-Poulenc Pharma Inc.
7. Relevance:	Yes

**Comment:** Two patients were taking a benzodiazepine hypnotic medication at time of recruitment and they both fulfilled the inclusion criteria after a 4-day minimum washout period.  
The study did not report patient number for each treatment groups, and the analyzed results were the mean from parts of the patients as well. (?!)

## Evidence Table 16. Quality Assessment

<b>Author:</b> Steens	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1993	<b>Country:</b> Canada	<b>Funding:</b> Lorex Pharmaceuticals

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | NR                    |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | NR                    |
| 7. Patients masked                      | Yes                   |
| 8. Reporting of Attrition               | No                    |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Yes                   |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 24   |
| 2. Exclusion criteria:                | 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, known 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. |
| 3. Run-in:                            | 0  |
| Wash out:                             | 0  |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Lorex Pharmaceuticals  |
| 7. Relevance:                         | Patients with COP  |

**Comment:** One of 24 patients designated an outlier and excluded from group analysis, but results reported separately.

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Stip	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1999	<b>Country:</b> Canada	<b>Funding:</b> Not reported

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**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | NR                    |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes                   |
| 8. Reporting of Attrition         | Yes                   |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | Yes                   |
| If Yes, please report:            |                       |
| 17% excluded from analysis        |                       |
| 10. Intention-to-treat analysis:  | No                    |
| 11. Postrandomization exclusions: | Yes                   |
| 12. Quality rating:               | Fair                  |

**External validity**

- |                                       |              |
|---------------------------------------|--------------|
| 1. Number Screened:                   | NR           |
| Eligible:                             | NR           |
| Enrolled:                             | 60           |
| 2. Exclusion criteria:                | NR           |
| 3. Run-in:                            | 7            |
| Wash out:                             | 7            |
| 4. Class naive patients only          | NR           |
| 5. Controlled group standard of care: | Yes          |
| 6. Funding:                           | Not reported |
| 7. Relevance:                         | Yes          |

---

**Comment:** Participants who had been taking hypnotic drugs with a long half-life received lorazepam for one week, prior to a week placebo. Patients who had been taking benzodiazepines with a short or intermediate half-life were put only on placebo for one week. Enrolled population characteristic were not reported. Analyzed population characteristics: mean age=42.6 years; 21 (42%) female

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Tamminen</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>1987</b>	<b>Country:</b>	<b>Finland</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	NR
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
28% not included in the analysis (10 zopiclone, 16 nitrazepam excluded)	
10. Intention-to-treat analysis:	No
11. Postrandomization exclusions:	Yes
12. Quality rating:	Poor

**External validity**

1. Number Screened:	NR
Eligible:	130
Enrolled:	94
2. Exclusion criteria:	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.
3. Run-in:	7
Wash out:	NR
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

**Comment:** Poor quality: no baseline demographic characteristics, high and differential loss to followup and no intention to treat analysis

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Terzano	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 1992	<b>Country:</b> Italy	<b>Funding:</b> Partially supported by Italian

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**Internal validity**

- |                                   |                       |
|-----------------------------------|-----------------------|
| 1. Randomization adequate?        | NR                    |
| 2. Allocation adequate?           | NR                    |
| 3. Groups similar at baseline:    | NR                    |
| 4. Eligibility criteria specified | Yes                   |
| 5. Outcome assessors masked       | Yes, but not describe |
| 6. Care provider masked           | NR                    |
| 7. Patients masked                | Yes, but not describe |
| 8. Reporting of Attrition         | No                    |
| Crossover                         | No                    |
| Adherence                         | No                    |
| Contamination                     | No                    |
| 9. Loss to follow-up              |                       |
| differential/ high                | NR                    |
| If Yes, please report:            |                       |
| 10. Intention-to-treat analysis:  | NR                    |
| 11. Postrandomization exclusions: | NR                    |
| 12. Quality rating:               | Poor                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | NR  |
| Eligible:                             | NR  |
| Enrolled:                             | 12  |
| 2. Exclusion criteria:                | patients had nocturnal myoclonus or sleep apnea syndrome                      |
| 3. Run-in:                            | 14  |
| Wash out:                             | NR  |
| 4. Class naive patients only          | NR  |
| 5. Controlled group standard of care: | NR  |
| 6. Funding:                           | Partially supported by Italian Ministry of University and Scientific Research |
| 7. Relevance:                         | Yes   |

**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Tsutsui</b>	<b>Trial type:</b>	<b>H2H</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2001</b>	<b>Country:</b>	<b>Japan</b>	<b>Funding:</b>	<b>Not reported</b>

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	NR
4. Eligibility criteria specified	Yes
5. Outcome assessors masked	Yes
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	Yes
Contamination	No
9. Loss to follow-up differential/ high	Yes
If Yes, please report:	
13.9% zolpidem vs 18.1% zopiclone withdrew (p=NS)	
10. Intention-to-treat analysis:	No
11. Postrandomization exclusions:	Yes
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	NR
Enrolled:	479
2. Exclusion criteria:	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, breastfeeding, participation in other clinical trials within the past 6 months, and inappropriateness for the study according to the investigator's judgment.
3. Run-in:	no
Wash out:	7
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

**Comment:** Baseline demographic data reported only on patients included in efficacy analysis (428/479; 89%). Additional rebound information: Overall, sleep onset latency, frequency of nocturnal awakenings, sleep duration, daytime mood and daytime physical condition remained significantly improved in both groups relative to baseline (p<0.01, data not reported).



### Evidence Table 16. Quality Assessment

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<b>Author:</b> van der Kleijn	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1989	<b>Country:</b> Nijmegen	<b>Funding:</b> Rhone-Poulenc Pharma

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: NR
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes, but not describe
- 6. Care provider masked NR
- 7. Patients masked Yes
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high No
  - If Yes, please report:
- 10. Intention-to-treat analysis: No
- 11. Postrandomization exclusions: Unable to determine
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: NR
  - Eligible: 60
  - Enrolled: 55
- 2. Exclusion criteria:
  - 1. Patients taking a non-benzodiazapine hypnotic prior to the studym 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 benzodiazapine tranquilizers 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
- 3. Run-in: 2
  - Wash out: 7
- 4. Class naive patients only No
- 5. Controlled group standard of care: Yes
- 6. Funding: Rhone-Poulenc Pharma
- 7. Relevance: Yes

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**Comment:**

## Evidence Table 16. Quality Assessment

<b>Author:</b> Venter	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1986	<b>Country:</b> South Africa	<b>Funding:</b> Not reported

**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?              | NR                    |
| 2. Allocation adequate?                 | NR                    |
| 3. Groups similar at baseline:          | Yes                   |
| 4. Eligibility criteria specified       | Yes                   |
| 5. Outcome assessors masked             | Yes, but not describe |
| 6. Care provider masked                 | Yes, but not describe |
| 7. Patients masked                      | Yes, but not describe |
| 8. Reporting of Attrition               | No                    |
| Crossover                               | No                    |
| Adherence                               | No                    |
| Contamination                           | No                    |
| 9. Loss to follow-up differential/ high | No                    |
| If Yes, please report:                  |                       |
| 10. Intention-to-treat analysis:        | Yes                   |
| 11. Postrandomization exclusions:       | No                    |
| 12. Quality rating:                     | Fair                  |

**External validity**

- |                                       |   |
|---------------------------------------|---|
| 1. Number Screened:                   | 58  |
| Eligible:                             | 41  |
| Enrolled:                             | 41  |
| 2. Exclusion criteria:                | 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. |
| 3. Run-in:                            | 7   |
| Wash out:                             | 0   |
| 4. Class naive patients only          | No  |
| 5. Controlled group standard of care: | Yes   |
| 6. Funding:                           | Not reported  |
| 7. Relevance:                         | elderly residents of  |

**Comment:** 22 patients were already receiving another hypnotic drug; the investigators decided a washout period in these patients would be undesirable. It was therefore decided that this group of patients should discontinue their previous hypnotic therapy and immediately start the trial medicine, without a washout phase. Day 7 of the treatment was recorded as the first day of baseline assessment for this study. Zopiclone-2(10%) and Triazolam-7(33.3%) patients increased the dosage twice after day 8.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Voshaar</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>2004</b>	<b>Country:</b>	<b>Netherlands</b>	<b>Funding:</b>	<b>Sanfi-Synthelabo</b>

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**Internal validity**

- |   |                       |
|---|-----------------------|
| 1. Randomization adequate?                            | NR                    |
| 2. Allocation adequate?                               | NR                    |
| 3. Groups similar at baseline:                        | Yes                   |
| 4. Eligibility criteria specified                     | Yes                   |
| 5. Outcome assessors masked                           | Yes, but not describe |
| 6. Care provider masked                               | NR                    |
| 7. Patients masked                                    | Yes                   |
| 8. Reporting of Attrition                             | Yes                   |
| Crossover   | 0                     |
| Adherence   | No                    |
| Contamination   | No                    |
| 9. Loss to follow-up differential/ high               | Yes                   |
| If Yes, please report:                                |                       |
| More zolpidem patients dropped out (24 vs 12, p<0.05) |                       |
| 10. Intention-to-treat analysis:                      | No                    |
| 11. Postrandomization exclusions:                     | Yes                   |
| 12. Quality rating:                                   | Fair                  |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | NR   |
| Enrolled:                             | 221  |
| 2. Exclusion criteria:                | 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 |
| 3. Run-in:                            | NR   |
| Wash out:                             | 4  |
| 4. Class naive patients only          | No   |
| 5. Controlled group standard of care: | Yes  |
| 6. Funding:                           | Sanfi-Synthelabo   |
| 7. Relevance:                         | Yes  |

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**Comment:** Enrolled population characteristics were not reported. Only analyzed population characteristics were reported:

### Evidence Table 16. Quality Assessment

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<b>Author:</b> Walsh	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Poor
<b>Year:</b> 2000a	<b>Country:</b> US	<b>Funding:</b>

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**Internal validity**

- 1. Randomization adequate? Not clear (allocation s
- 2. Allocation adequate? Not clear (allocation s
- 3. Groups similar at baseline: NR
- 4. Eligibility criteria specified Yes
- 5. Outcome assessors masked Yes, but not describe
- 6. Care provider masked NR
- 7. Patients masked Yes, but not describe
- 8. Reporting of Attrition Yes
  - Crossover No
  - Adherence No
  - Contamination No
- 9. Loss to follow-up differential/ high  
If Yes, please report: No- unclear if different
- 10. Intention-to-treat analysis: No (48/54 analyzed)
- 11. Postrandomization exclusions: Yes
- 12. Quality rating: Poor

**External validity**

- 1. Number Screened: 311
  - Eligible: 54
  - Enrolled: 48
- 2. Exclusion criteria:
 

Significant medical and psychiatric illnesses were ruled out by clinical interview, physical and neurological examinations, ECG, and clinical laboratory tests (haematology, chemistry and urine analysis). Specifically, 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
- 3. Run-in: 5-12
  - Wash out: 5-12
- 4. Class naive patients only
- 5. Controlled group standard of care:
- 6. Funding:
- 7. Relevance: Older adults

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**Comment:**

### Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Walsh</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000a</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	

Internal validity		External validity	
1. Randomization adequate?	NR	1. Number Screened:	NR
2. Allocation adequate?	NR	Eligible:	589
3. Groups similar at baseline:	Yes	Enrolled:	306
4. Eligibility criteria specified	Yes	2. Exclusion criteria:	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.
5. Outcome assessors masked	Yes, but not describe		
6. Care provider masked	NR		
7. Patients masked	Yes		
8. Reporting of Attrition	Yes		
Crossover	No		
Adherence	No		
Contamination	No		
9. Loss to follow-up differential/ high	No	3. Run-in:	7
If Yes, please report:		Wash out:	NR
		4. Class naive patients only	No
		5. Controlled group standard of care:	Yes
		6. Funding:	Lorex Pharmaceuticals
10. Intention-to-treat analysis:	No		
11. Postrandomization exclusions:	Yes		
12. Quality rating:	Fair	7. Relevance:	Yes

**Comment:** Enrolled population characteristics were not reported. Instead, analyzed population characteristics were reported: 63% female; 84% Caucasian.

### Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Walsh</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000a</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	

Internal validity		External validity	
1. Randomization adequate?	Yes	1. Number Screened:	673
2. Allocation adequate?	NR	Eligible:	456
3. Groups similar at baseline:	Yes	Enrolled:	132
4. Eligibility criteria specified	Yes	2. Exclusion criteria:	
5. Outcome assessors masked	Yes, but not describe	Individuals with significant medical or psychiatric illness, as determined by history and physical examination, clinical laboratory tests, the Zung Anxiety and Depressopm scales (scores >40) were excluded, as were those using CNS active medication. Individuals with prior exposure to zaleplone, or sensitivity to benzodiazepines or other psychotropic drugs, were excluded.	
6. Care provider masked	NR		
7. Patients masked	Yes		
8. Reporting of Attrition	Yes		
Crossover	No		
Adherence	No		
Contamination	No		
9. Loss to follow-up differential/ high	No		
If Yes, please report:			
		3. Run-in:	3
		Wash out:	2
		4. Class naive patients only	No
		5. Controlled group standard of care:	Yes
		6. Funding:	Wyeth Ayerst
10. Intention-to-treat analysis:	Yes		
11. Postrandomization exclusions:	No		
12. Quality rating:	Good	7. Relevance:	Yes

**Comment:** day 1-3 placebo; day 4-17 treatment; day 18-19 placebo

## Evidence Table 16. Quality Assessment

<b>Author:</b>	<b>Walsh</b>	<b>Trial type:</b>	<b>Placebo</b>	<b>Quality rating:</b>	<b>Poor</b>
<b>Year:</b>	<b>2000a</b>	<b>Country:</b>	<b>US</b>	<b>Funding:</b>	
<b>Internal validity</b>			<b>External validity</b>		
1. Randomization adequate?	NR	1. Number Screened:	73	Eligible:	39
2. Allocation adequate?	NR			Enrolled:	30
3. Groups similar at baseline:	NR	2. Exclusion criteria:	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, previous exposure to zaleplon, benzodiazepine sensitivity, use of another investigational drug, psychotropic medication, tryptophan, or melatoanthistamine in the past week, or use of medications that would interfere with the absorption or metabolism of the study drugs.		
4. Eligibility criteria specified	Yes	3. Run-in:	NR	4. Class naive patients only	Yes
5. Outcome assessors masked	Yes, but not describe	Wash out:	NR	5. Controlled group standard of care:	Yes
6. Care provider masked	NR			6. Funding:	Wyeth-Ayerst Research
7. Patients masked	Yes, but not describe				
8. Reporting of Attrition	Yes				
Crossover	0				
Adherence	Yes				
Contamination	No				
9. Loss to follow-up differential/ high	Yes	4. Class naive patients only	Yes		
If Yes, please report:		5. Controlled group standard of care:	Yes		
8 of 30 (27%) randomized were excluded from analysis; groups not specified.		6. Funding:	Wyeth-Ayerst Research		
10. Intention-to-treat analysis:	No	7. Relevance:	No- very stringent e		
11. Postrandomization exclusions:	Yes				
12. Quality rating:	Poor				

**Comment:** The population characteristics of enrolled subjects were not reported. Only the characteristics for analyzed subjects were reported. 22 subjects were analyzed, 11 men; mean age, 42 y; range, 22-49.

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Walsh_	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2000b, 2002	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

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**Internal validity**

- |  |                       |
|--|-----------------------|
| 1. Randomization adequate?               | Yes                   |
| 2. Allocation adequate?                  | NR                    |
| 3. Groups similar at baseline:           | Yes                   |
| 4. Eligibility criteria specified        | Yes                   |
| 5. Outcome assessors masked              | Yes, but not describe |
| 6. Care provider masked                  | NR                    |
| 7. Patients masked                       | Yes                   |
| 8. Reporting of Attrition                | Yes                   |
| Crossover                                | No                    |
| Adherence                                | Yes                   |
| Contamination                            | Yes                   |
| 9. Loss to follow-up differential/ high  | Yes                   |
| If Yes, please report:                   |                       |
| 18% withdrew:12.3% placebo, 30% zolpidem |                       |
| 10. Intention-to-treat analysis:         | No                    |
| 11. Postrandomization exclusions:        | Yes                   |
| 12. Quality rating:                      | Fair                  |

**External validity**

- |                                       |                       |
|---------------------------------------|-----------------------|
| 1. Number Screened:                   | 365                   |
| Eligible:                             | 163                   |
| Enrolled:                             | 163                   |
| 2. Exclusion criteria:                | NR                    |
| 3. Run-in:                            | 7                     |
| Wash out:                             | 7                     |
| 4. Class naive patients only          | NR                    |
| 5. Controlled group standard of care: | Yes                   |
| 6. Funding:                           | Lorex Pharmaceuticals |
| 7. Relevance:                         | Yes                   |

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**Comment:** Patients were instructed to "take the medication when you thini you need it, at bed time, between three and five nights per week".



### Evidence Table 16. Quality Assessment

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<b>Author:</b> Ware	<b>Trial type:</b> Active	<b>Quality rating:</b> Fair
<b>Year:</b> 1997	<b>Country:</b> US	<b>Funding:</b> Lorex Pharmaceuticals

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**Internal validity**

- 1. Randomization adequate? NR
- 2. Allocation adequate? NR
- 3. Groups similar at baseline: Yes
- 4. Eligibility criteria specified: Yes
- 5. Outcome assessors masked: Yes, but not describe
- 6. Care provider masked: NR
- 7. Patients masked: Yes, but not describe
- 8. Reporting of Attrition: Yes
  - Crossover: No
  - Adherence: No
  - Contamination: No
- 9. Loss to follow-up differential/ high: No
  - If Yes, please report:
- 10. Intention-to-treat analysis: No
- 11. Postrandomization exclusions: No
- 12. Quality rating: Fair

**External validity**

- 1. Number Screened: 358
  - Eligible: NR
  - Enrolled: 110
- 2. Exclusion criteria:
  - 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.
- 3. Run-in: 2
  - Wash out: 3
- 4. Class naive patients only: Yes
- 5. Controlled group standard of care: Yes
- 6. Funding: Lorex Pharmaceuticals
- 7. Relevance: Yes

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**Comment:** No baseline demographic data provided, but states groups did not differ significantly in gender, age, race, height, and weight.

## Evidence Table 16. Quality Assessment

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<b>Author:</b>	<b>Wheatley</b>	<b>Trial type:</b>	<b>Active</b>	<b>Quality rating:</b>	<b>Fair</b>
<b>Year:</b>	<b>1985</b>	<b>Country:</b>	<b>NR</b>	<b>Funding:</b>	<b>Not reported</b>

---

**Internal validity**

1. Randomization adequate?	NR
2. Allocation adequate?	NR
3. Groups similar at baseline:	No
4. Eligibility criteria specified	No
5. Outcome assessors masked	Yes, but not describe
6. Care provider masked	NR
7. Patients masked	Yes
8. Reporting of Attrition	Yes
Crossover	No
Adherence	No
Contamination	No
9. Loss to follow-up differential/ high	No
If Yes, please report:	
10. Intention-to-treat analysis:	Unable to determine
11. Postrandomization exclusions:	Unable to determine
12. Quality rating:	Fair

**External validity**

1. Number Screened:	NR
Eligible:	NR
Enrolled:	36
2. Exclusion criteria:	NR
3. Run-in:	3
Wash out:	NR
4. Class naive patients only	No
5. Controlled group standard of care:	Yes
6. Funding:	Not reported
7. Relevance:	Yes

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**Comment:** zopiclone first group had a higher proportion of patients previously responding well to hypnotics and more heavy smokers.

## Evidence Table 16. Quality Assessment

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<b>Author:</b> Zammit	<b>Trial type:</b> Placebo	<b>Quality rating:</b> Fair
<b>Year:</b> 2004	<b>Country:</b> US	<b>Funding:</b> Sepracor

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**Internal validity**

- |                                   |                        |
|-----------------------------------|------------------------|
| 1. Randomization adequate?        | NR                     |
| 2. Allocation adequate?           | NR                     |
| 3. Groups similar at baseline:    | Differences in gener a |
| 4. Eligibility criteria specified | Yes                    |
| 5. Outcome assessors masked       | Yes                    |
| 6. Care provider masked           | NR                     |
| 7. Patients masked                | Yes                    |
| 8. Reporting of Attrition         | Yes                    |
| Crossover                         | No                     |
| Adherence                         | No                     |
| Contamination                     | No                     |
| 9. Loss to follow-up              |                        |
| differential/ high                | No                     |
| If Yes, please report:            |                        |
| 10. Intention-to-treat analysis:  | No (303/308 at night   |
| 11. Postrandomization exclusions: | No                     |
| 12. Quality rating:               | Fair                   |

**External validity**

- |                                       |  |
|---------------------------------------|--|
| 1. Number Screened:                   | NR   |
| Eligible:                             | 669  |
| Enrolled:                             | 308  |
| 2. Exclusion criteria:                |  |
|                                       | 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. |
| 3. Run-in:                            | 2  |
| Wash out:                             | 5-7  |
| 4. Class naive patients only          | NR   |
| 5. Controlled group standard of care: | NR   |
| 6. Funding:                           | Sepracor   |
| 7. Relevance:                         | Yes  |

**Comment:**

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Results</b>	<b>Funding</b>	
Allain, 1991 France; Delahaye, France	<u>Neuropsychiatric adverse events, no. of AEs (%) / no. of drop-outs</u> 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 Angitation/ 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	<u>Gastrointestinal adverse events, no. of AEs (%) / no. of drop-outs</u> 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  <u>Somatic adverse events, no. of AEs (%) / no. of drop-outs</u> 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 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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 17: Observational Studies**

Author Year Country	Results	Funding
Ancoli-Israel, 2005 US and Europe	<u>Frequency of common Treatment-emergent adverse events (TEAEs) during open-label run-out phase, number(%):</u> Headache- 155(27%) Infection- 73(13%) Backache- 58(10%) Bronchitis/pharyngitis- 65(11%) Rhinitis- 53(9%) Dizziness- 43(7%) <u>The TEAEs most frequently associated with discontinuation, number(%):</u> 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	<u>Use temazepam or zolpidem, discontinuation due to adverse events: zolpidem(n=89) vs. temazepam(n=401), (%)</u> adverse drug reaction- 2.2% vs. 4.2%  <u>Discontinuation due to adverse events: [use temazepam and then switch to zolpidem] vs. [use zolpidem and then switch to temazepam], (%)</u> adverse drug reaction or others- 10.6% vs. 7.5%  <u>Discontinuation due to adverse events after filtering out "change in dose" as a reason for discontinuation.</u> Among discontinuation except "change in dose": adverse drug reation- 4.3% vs.10.1%	Not reported

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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), anxietydepressive 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/irr itability, illness intrusiveness, depressive symptoms

**Evidence Table 17: Observational Studies**

Author Year Country	Results	Funding
Buckley, 2004 UK	<u>Fatal toxicity index: total no. of deaths</u> zolpidem vs. zopiclone= 3 vs. 23 <u>Fatal toxicity index: no. of prescriptions (thousands)</u> zolpidem vs. zopiclone= 1300 vs. 10763 <u>Fatal toxicity index: deaths/million prescriptions (95%CI)</u> zolpidem vs. zopiclone= 2.3(0.5-6.7) vs. 2.1 (1.4-3.2)	None
Devins, 1995 Canada	<u>Adverse events: [zopiclone] vs. [lorazepam] vs. [triazolan] vs. [nitrazepam or flurazepam] vs. [temazepam], no.(%)</u> 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 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
Diav-Citrin, 1999 Canada	Indications for drug use: depression (n=10), insomnia (n=3), anxietydepressive 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 17: Observational Studies**

<b>Author Year Country</b>	<b>Results</b>	<b>Funding</b>
Diav-Citrin, 1999 Canada	<u>Pregnancy outcome, zopiclone vs. control:</u> Preganancy 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 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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 17: Observational Studies**

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

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

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

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>Results</b>	<b>Funding</b>
Hajak, 1998 Germany	<p>Tolerance: moderate-1.4%, poor- 0.6%</p> <p><u>Adverse events:</u>  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</p>	Synthelabo Arzeimittel GmbH, Germany

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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 17: Observational Studies**

Author Year Country	Results	Funding
Jaffe, 2003 UK	<u>Drug use pattern: zolpidem vs. zopiclone (n=297)</u> % 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	<u>7(7.3%) of all patients withdrew because of adverse events:</u> 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 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
Morishita, 2000 Japan	Mean age 74.4 years (range 70-86 years). Psychiatric diagnoses: depression (n=23), hypomania (n=1), hypochondriacal neurosis (n=2), paraphrenie (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 bisit by the investigator.	January 1st to May 31st, 1994	Reported by the patient at the followup visit.

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>Results</b>	<b>Funding</b>
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	<u>Adverse events reported: All patients (n=1219)/ Patients &lt;65 (n=720)/ Patients &gt;=65 (n=495)</u> 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 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

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

**Evidence Table 17: Observational Studies**

Author Year Country	Results	Nitrazepam	Funding
Reith, 2003	<p><u>Zopiclone involved in poisoning deaths no. of patients</u> &lt;60 vs &gt;=60 years: 8 vs. 4</p> <p><u>Zopiclone</u> No. of death: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)</p> <p><u>Lorazepam</u> No. of death: 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)</p> <p><u>Lormetazepam</u> No. of death: 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)</p> <p><u>Midazolam</u> No. of death: 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)</p>	<p>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)</p> <p><u>Temazepam</u> 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)</p> <p><u>Triazolam</u> 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</p>	Not reported

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
Scharf, 1994	Not reported.	Before-after.	Patient reports Physician assessments	13 weeks	Treatmentemergent adverse events.



**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>Results</b>	<b>Funding</b>
Scharf, 1994	<p data-bbox="386 326 1188 386"><u>Adverse events: zolpidem 10mg (n=33) vs. zolpidem 15mg (n=229), no.(%)</u></p> <p data-bbox="386 391 726 418">Dry mouth: 2(6.1) vs. 14(6.1)</p> <p data-bbox="386 423 722 451">Fatigue: 6(18.2) vs. 38(16.6)</p> <p data-bbox="386 456 663 483">Ataxia: 2(6.1) vs. 7(3.1)</p> <p data-bbox="386 488 709 516">Confusion: 2(6.1) vs. 5(2.2)</p> <p data-bbox="386 521 730 548">Dizziness: 2(3.1) vs. 32(14.0)</p> <p data-bbox="386 553 768 581">Drowsiness: 5(15.2) vs. 60(26.2)</p> <p data-bbox="386 586 684 613">Drugged: 0(0) vs. 12(5.2)</p> <p data-bbox="386 618 751 646">Headache: 7(21.2) vs. 65(28.4)</p> <p data-bbox="386 651 705 678">Lethargy: 1(3.0) vs. 14(6.1)</p> <p data-bbox="386 683 827 711">Light-headedness: 1(3.0) vs. 24(10.5)</p> <p data-bbox="386 716 764 743">Abdominal pain: 0(0) vs. 13(5.7)</p> <p data-bbox="386 748 726 776">Dyspepsia: 1(3.0) vs. 20(8.7)</p> <p data-bbox="386 781 709 808">Nausea: 1(3.0) vs. 28(12.2)</p> <p data-bbox="386 813 705 841">Arthralgia: 2(3.1) vs. 7(3.1)</p> <p data-bbox="386 846 705 873">Amnesia: 1(3.0) vs. 15(6.6)</p> <p data-bbox="386 878 758 906">Nervousness: 3(9.1) vs. 11(4.8)</p> <p data-bbox="386 911 747 938">Herpes simplex: 2(6.1) vs. 0(0)</p> <p data-bbox="386 943 722 971">Pharyngitis: 2(6.1) vs. 6(2.6)</p> <p data-bbox="386 976 680 1003">URI: 4(12.1) vs. 38(16.6)</p>	

**Evidence Table 17: Observational Studies**

<b>Author Year Country</b>	<b>N</b>	<b>Drugs (mean dose); duration of treatment</b>	<b>Duration of treatment</b>	<b>Eligibility Criteria</b>
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 $\geq 65$ 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 17: Observational Studies**

<b>Author Year Country</b>	<b>Other population characteristics</b>	<b>Design</b>	<b>Data sources</b>	<b>Time period of assessment</b>	<b>Adverse events assessment</b>
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 17: Observational Studies**

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

**Evidence Table 18. Case Reports**

<b>Drug</b>	<b>Study</b>	<b>Number of cases</b>	<b>Group</b>	<b>Case Characteristics</b>	<b>Effects during treatment</b>	<b>Effects during treatment reduction or discontinuation</b>
Zolpidem	(Vartzopoulos, Bozikas, Phocas, Karavatos, & Kaprinis, 2000)	4	dependence	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.
Zolpidem	(I. A. Liappas et al., 2003)	3	dependence	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	(I.A. Liappas et al., 2003)	8	dependence	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 discomfortable, irritability, abd agitation 1 with epileptic seizure 1 with instability, duzzubess and a craving for other psychotropic substances 1 not reported

Zolpidem	(Bottlender, Schutz, Moller, & Soyka)	1	dependence	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	(Aragona, 2000)	1	dependence	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	(Sakkas, Psarros, Masdrakis, Liappas, & Christodoulou)	1	dependence	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	(Ravishankar & Carnwath)	2	dependence	depression	the patient increased the dose up to 200mg per day	tachycardia, confusion, anxiety, panic attacks and fear of ogoing outside
Zolpidem	(Sattar, Ramaswamy, Bhatia, & Petty, 2003)	1	somnambulism	bipolar disorder history of drug abuse history of alcohol dependence mania taking valproic at the same time	somnambulism difficulty in concentration	insomnia

Zolpidem	(Harazin & Berigan, 1999)	1	somnambulism	depression	somnambulism	somnambulism stopped
Zolpidem	(Clark, 1999)	1	Hepatic problem	liver transplantation	decline in mentality hepatic encephalopathy abdominal pain awoke in a stupor and was disoriented to place and time	not reported
Zolpidem	(Karsenti, Blanc, Bacq, & Melman, 1999)	1	Hepatic problem	cholecystectomy	abdominal pain hepatotoxicity	not reported
Zolpidem	(Tsai, Huang, & Wu, 2003)	1	hallucination	not reported	visual illusions, confusion and hallucination especially reusing after rapid withdrawals.	insomnia
Zolpidem	(Elko, Burgess, & Robertson, 1998)	5	hallucination	concurrent use of serotonin-reuptake inhibition depression	hallucination	not reported
Zolpidem	(Ginsberg, 2003), (Huang, Chang, Hung, & Lin, 2003)	1	hallucination	concurrent use of other drugs for hormone replacement, osteoporosis and insomnia	headache spotty memory hallucination visual perception distortion	not reported
Zolpidem	(Toner, Tsambiras, Catalano, Catalano, & Cooper, 2000)	3	CNS side effect	motor vehicle accident or psychiatric history	nightmare hallucination visual illusion difficulty in concentration	nightmares, hallucination and visual illusion ceased
Zolpidem	(Tripodianakis, Potagas, Papageorgiou, Lazaridou, & Matikas, 2003)	1	CNS side effect	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	(Markowitz & Brewerton, 1996)	2	CNS side effect	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	(Ortega, Iruela, Ibanez-Rojo, & Baca)	1	others- drug interaction	long term benzodiazepine user no psychiatric history	nervousness, irritability, fainting, asthenia, muscular cramps, excessive heat and sweating, occasional febrile episodes, weight loss, and a surprising sweet taste in the mouth	all symptoms disappeared
Zolpidem	(Morgenthaler & Silber, 2002)	5	others	no history of eating disorders concurrent use of other drugs	amnesic sleep-related eating disorder restless legs syndrome	no nocturnal eating
Zolpidem	(Logan & Couper, 2001)	29	CNS side effect	no common characteristics	driving impairment because of slow movements and reactions visual distortions	not reported
Zolpidem	(Canaday, 1996)	2	CNS side effect	not reported	amnesia	not reported
Zolpidem	(Brodeur & Stirling, 2001)	1	CNS side effect	Extensive medical history	delirium psychosis restless amnesia	not reported
Zopiclone	(Alderman, Gebauer, Gilbert, & Condon, 2001)	1	others- drug interaction	depression concurrent use of antidepressants	morning drowsiness increased plasma concentrations	zopiclone plasma concentrations back to normal after nefazodone discontinuation



Zopiclone	(Aranko, Henriksson, Hublin, & Seppalainen, 1991)	1	dependence	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	(Bramness, Arnestad, Karinen, & Hilberg, 2001)	1	dependence	smoker respiratory problems anxiety	difficulty in breathing death caused by 337.5mg overdose	not reported
Zopiclone	(Ancoli-Israel et al., 2005)	4	dependence	no common characteristics	dependence	severe anxiety with tachycardia, tremor, sweating, rebound insomnia, flushes, palpitations, and derealisation.
Zopiclone	(Sullivan, McBride, & Clee, 1995)	3	others	history of drug abuse alcohol abuse	no evidence of dependence	not reported
Zaleplon	(Stillwell, 2003)	1	CNS side effect	drug abuse concurrent use of other drugs	CNS depression including slow movements and reactions, poor coordination, lack of balance, and poor attention	not reported

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