Appendix 1: Review of Various Trials using zolpidem at Higher Doses

Double-Blind, Randomized Placebo-Controlled Clinical Studies:

In a randomized, double-blind, placebo-controlled, parallel group, multicenter sleep laboratory study Scharf et al. (1994b) evaluated the effectiveness of zolpidem IR 10mg and 15mg in chronic insomniacs (n=75, range 21-60 years of age), for 35 nights following 4 nights of polysmnography (PSG) screening. Sleep stage, motor and cognitive effects during the 35-night treatment and 3-night posttreatment period were also investigated. Within the first week of treatment, 10mg of zolpidem had a significant effect on latency to persistent sleep and sleep efficiency. Efficacy was maintained throughout the 35 nights of drug administration. No evidence of residual effect with 10mg of zolpidem was seen. Stage 3-4 sleep was preserved with both the 10 mg and 15 mg zolpidem dosages. No evidence of tolerance at either dose or significant treatment differences between the 10 mg zolpidem group and placebo in latency to persistent sleep or sleep efficiency during the posttreatment period was observed. Similar results were observed with the 15 mg zolpidem dosage. However, significant decreases in REM sleep at weeks 3 and 4 with 15 mg of zolpidem compared with placebo were seen. In addition, worse sleep quality and greater wake time during sleep on the first night post-treatment when compared to placebo was observed. Overall, the incidence rates of treatment-emergent adverse events in the zolpidem groups were similar to those in the placebo group. In this study, 10 mg of zolpidem was found to be safe and effective for chronic insomnia over 35 nights, demonstrating hypnotic efficacy without affecting sleep stages or producing tolerance effects, rebound effects, or detrimental effects on psychomotor performance. The 15-mg zolpidem dosage provided no clinical advantage over the 10-mg zolpidem dosage. (See Table 1)

Lahmeyer et al. (1997) conducted a double-blind, randomized, placebo-controlled, multi-center, parallel group study to compare the subjective hypnotic efficacy of zolpidem IR 10 or 15mg with that of placebo in 178 chronic insomniacs 19 to 60 years of age (mean age 45 years) for 31 nights. The primary efficacy measures taken from the morning questionnaire (performed on days 1, 2, 3, and 7 of each week and a Clinical Global Impressions on day 7 of treatment week 4) were the patients' numerical estimate of subjective sleep latency and subjective total sleep time.

Sleep Latency: Zolpidem IR 10 and 15mg had significantly greater changes from baseline in self-reported subjective sleep latency than the placebo group at all treatment weeks, except for the 4-week value in the 15mg zolpidem IR group, which did not reach statistical significance. The estimates of sleep latency remained essentially constant during the 4 weeks of treatment, and there was no significant difference between the two zolpidem groups at any time.

Total Sleep Time: No difference between the two groups throughout the treatment period was noted. All three groups perceived significant improvements in total sleep time over baseline after 4 weeks of treatment, with increases of 41.5 minutes, 69.7 minutes and 60.3 minutes with placebo, zolpidem 10mg, and zolpidem 15mg, respectively.

Secondary outcome measures (number of awakenings, sleep quality, next-morning sleepiness): Both the subjective ratings of number of awakenings and of sleep quality were significantly improved during the early phase of treatment with zolpidem. No significant differences among the three groups in next-morning sleepiness were seen as assessed by visual analogue scale. All three groups rated their sleep quality as improved over the course of the study, without significant differences between groups. The numerical change for sleep quality at week 4 was + 9.3 points in the placebo group, + 17.5 points in the zolpidem 10mg group, and + 14.8 points in the zolpidem 15mg group.

Clinical Global Impressions of Therapy: Both zolpidem groups rated their improvement significantly better than placebo on every rating, with no significant difference between the two zolpidem groups.

Adverse Event Rates: Incidence of adverse events occurred in 43, 57 and 70% for the placebo, zolpidem IR 10, and zolpidem IR 15mg groups, respectively. The highest overall AE rate was related to the central and peripheral nervous systems. Subjective sleep latency on post-treatment nights was generally equal to or shorter than at baseline, with the exception of a 27-minute increase in the zolpidem 15mg group on the first night following discontinuation ($p < 0.10$). Similarly, there was a trend towards shorter mean subjective total sleep time in the 15mg group on post-treatment nights. Morning sleepiness was significantly greater in the 15mg group than in the placebo group on post-treatment days 1, 2, and 3. Thus, in the 15mg group, a subjective perception of rebound insomnia was possible.

Overall, patients did not detect a difference in hypnotic efficacy between 10 and 15mg of zolpidem. The increased dose of zolpidem beyond the recommended dose of 10mg daily did not result in increased hypnotic efficacy, although a higher incidence of AEs was observed. (See Table 2)

Roth et al. (1995) compared the efficacy and the psychomotor function the morning after treatment of 7.5 and 10mg zolpidem IR with placebo; and assessed the dose-related effects of zolpidem at doses of 5, 7.5, 10, 15 and 20mg in an unbalanced randomized, double-blind, placebo-controlled, single-night study in healthy volunteers (n=462) between the ages of 21 and 60 years old. Only the 7.5 and 10mg zolpidem groups were analyzed statistically in comparison with placebo. Mean latency to persistent sleep decreased with increase in dosage up to the 7.5-10mg range. Thereafter, the trend was toward a slight increase, to a mean of 19 minutes for the 15mg treatment group and 21 minutes for the 20mg group. Sleep efficiency increased with the 10mg dose and decreased slightly with the 15 and 20mg doses. Although this study was not designed to statistically compare the zolpidem 15 and 20mg doses to placebo, it is noteworthy that dosing above 10mg did not result in a corresponding increase in hypnotic efficacy. Forty-seven (10.2%) subjects reported a total of 71 AEs, ranging from dry mouth to headache. The percentage of subjects who experienced an AE with zolpidem $\leq$ 10mg was not significantly different from the placebo group. At the higher dose of 15mg zolpidem, 17.6% of patients experienced an AE ($p=0.069$ vs. placebo) and at 20mg, 31.4% reported AE ($p=0.001$ vs. placebo).

Table 1: PSG (Objective) Study: Treatment of Chronic Insomnia with zolpidem 10 and 15mg

Trial/ Purpose	Inclusion/Exclusion/Endpoints	Treatment	Results	Adverse Events/Withdrawals
Scharf, 1994 R, DB, PC, MC, parallel-group, sleep laboratory study Purpose: To determine the efficacy of IR- zolpidem tartrate (10mg and 15mg) in the long-term treatment of chronic insomnia and evaluate the impact of zolpidem tartrate IR after 35 consecutive nights.	**Inclusion Criteria:** Outpatient chronic insomniacs, aged between 21 and 60 years of age with no significant medical or psychiatric disorders. [Chronic insomnia defined as a history of the following for at least 3 months preceding screening: usual reported sleep duration between 4-6 hours, usual reported sleep latency of at least 30 minutes, and daytime complaints associated with disturbed sleep.] **Exclusion Criteria:** 1) No investigational drug within 30 days of the start of the study. 2) Ingestion of any short-acting central nervous system medication or alcohol throughout the study.	Run-in 11 days: 2 days washout Randomized following 4 nights of PSG screening. The first week was a single-blind placebo period and baseline values were obtained by using the means of data from the last 3 screening nights and the first 2 nights of week 1. Patients were evaluated in the sleep laboratory on the screening nights, the first 2 nights of the first week, the first 2 nights of week 2 through 6, and all 3 nights following treatment. Subjective measures were obtained through evening and morning patient questionnaires and by a modified Global Impressions Scale.	**Baseline:** Mean age 38 (range, 21-60 years); female 64%; Caucasian 73.3%. No differences among treatment groups with respect to sex, race, age, weight, height, and sleep history. No significant difference among treatment groups with respect to any Morning Questionnaire item or the mean performance scores (Digit Symbol Substitution Test (DSST) or Digit Symbol Copying Test (DSCT) at baseline. Table 1. Summary of Objective Primary Efficacy Results **Sleep Induction Endpoint** | **Zolpidem 10mg (n =22)** | **Zolpidem 15mg (n=22)** | **Placebo (n=23)** Mean Sleep Latency, min. Week 6 (p vs. placebo) | 25.8 (0.063) | 28.1 (p<0.05) | 48.0 (NA) *Post-treatment (p vs. placebo) | 47.1 (NS) | 47.7 (NS) | 42.9 (NA) **Sleep Duration** **Mean Sleep Efficiency (%) Week 6 (p vs. placebo) | 87.9 (0.063) | 87.3 (p<0.05) | 80.7 (NA) Post-treatment (p vs. placebo) | 83.1 (NS) | 79.9 (NS) | 81.9 (NA) * Mean values of 3-night period during which patients received placebo. **Sleep efficiency= Total sleep time/time in bed, multiplied by 100; NS=not significant; NA=Not applicable Table 2. Summary of Subjective Efficacy Results **Subjective Sleep Latency** | **Zolpidem 10mg (n =22)** | **Zolpidem 15mg (n=22)** | **Placebo (n=23)** Mean Sleep Latency, min. Week 6 (p vs. placebo) | 38.4 (0.063) | 31.7 (p<0.05) | 56.6 (NA) *Post-treatment (p vs. placebo) | 62.3 (NS) | 78.2 (NS) | 47.5 (NA) **Ease of falling sleep^** Mean Ease of falling sleep Week 6 (p vs. placebo) | 50.7 (0.063) | 35.7**(p<0.05) | 48.4 (NA) Post-treatment (p vs. placebo) | 63.7 (NS) | 64.0 (p<0.05) | 44.4 (NA) **Sleep Quality†** | **Zolpidem 10mg (n =22)** | **Zolpidem 15mg (n=22)** | **Placebo (n=23)** Mean sleep Quality Week 6 (p vs. placebo) | 2.5 (NS) | 2.5 (NS) | 2.6 (NA) *Post-treatment (p vs. placebo) | 2.9 (p<0.05) | 3.1 (p<0.05) | 2.6 (NA) **Subjective Total Sleep (min)** Mean Total sleep (min) Week 6 (p vs. placebo) | 369 | 394 | 356 (NA) Post-treatment (p vs. placebo) | 333 | 341 | 369 (NA) * Mean values of 3-night period during which patients received placebo; ^ 100-mm scale: 0=very easy, 100=not easy; ** significantly different from 10mg, p<.05, †scale: 1=excellent, 2= good, 3= fair, 4= poor; NS=not significant; NA=Not applicable Effect on sleep stages: Stages 1,2, and 3-4 sleep were not significantly affected by either the 10 or 15mg doses of zolpidem treatment compared with placebo at any time during the study period. Percent REM sleep was similar to placebo throughout the study for the 10mg group but was significantly decreased (p<.05) in the 15mg zolpidem group compared with placebo at weeks 3 and 4.	178 screened/75 eligible/75 enrolled/67 completed study Eight patients (10.7%) withdrew after randomization due to adverse events: (n=3, **zolpidem 15mg**; gallstones (n=1) and dizziness, drowsiness, and visual distortion (n=2); (n=4, **zolpidem 10mg**; change in work schedule (n=2), moved (n=1), and noncompliance (n=1); (n=1, **placebo** due to hernia recurred). The study was completed by 67 patients (23 placebo, and 22 each in the IR zolpidem groups). Treatment-emergent AE were reported by 58, 50, and 52% of patients receiving placebo, zolpidem 10mg, and zolpidem 15mg, respectively. Table 2: Number (%) of Patients Reporting Treatment-Emergent Adverse Events* Adverse Events | Placebo n=24 (%) | Zolpidem10mg n=26 (%) | Zolpidem 15mg n=25 (%) Autonomic nervous Dry mouth | 0 | 0 | 2 (8) Central and peripheral nervous Headache | 7 (29) | 2 (8) | 4 (16) Drowsiness | 2 (8) | 3 (12) | 5 (20) Dizziness | 0 | 3 (12) | 4 (16) Lethargy | 1 (4) | 2 (8) | 1 (4) Drugged | 0 | 2 (8) | 1 (4) Confusion | 0 | 0 | 2 (8) Gastrointestinal Nausea | 1 (4) | 1 (4) | 3 (12) Dyspepsia | 0 | 2 (8) | 2 (8) Musculoskeletal Arthralgia | 2 (8) | 1 (4) | 0 Psychiatric Amnesia | 0 | 1 (4) | 2 (8) Respiratory Rhinitis | 2 (8) | 0 | 0 *Includes all treatment-emergent adverse events with an incidence of ≥ 5% in at least one treatment group.
Quality Rating: Fair **Study Conclusions**				

•Efficacy

- Mean latency to persistent sleep for the two zolpidem groups was 20 to 35 minutes shorter than for the placebo group during the 5 weeks of active treatment.
- Mean percent sleep efficiency for the 10mg zolpidem group was typically 6%-8% higher than for the placebo group, representing an increase of 25 to 40 minutes. Statistical significance was achieved with the 10mg zolpidem compared to placebo at weeks 2-5, but not at week 6. Statistical significance was reached with zolpidem 15mg compared to placebo for weeks 2-6.

•Safety:

- No development of tolerance was noted for zolpidem IR 10mg or 15mg by both objective and subjective measurements throughout the 5 weeks of treatment.
- No next-day residual effects were noted with objective and subjective testing of patients on zolpidem IR 10mg throughout the study period.
- There was a lack of objectively measured rebound insomnia following abrupt discontinuation of IR zolpidem 10mg, relative to placebo, on any of the first 3 nights post-treatment. A significantly greater wake time during sleep during first post treatment night in the 15mg zolpidem group compared with placebo group (53.8 minutes vs. 25.3 minutes, respectively, p<.05) was observed. Also, in the 15mg zolpidem group, mean sleep quality of the first posttreatment night was significantly worse than that observed with placebo (3.4 vs. 2.8, respectively, p,.05), but there were no differences in the change from baseline between the two active treatment groups. No significant differences were seen during the subsequent 2 nights posttreatment.
- Treatment-emergent adverse events were reported by 58% of the patients receiving placebo, 50% of the patients receiving zolpidem 10mg, and 52% of the patients receiving zolpidem 15mg. Two patients in the 15mg zolpidem group were withdrawn from the study because of adverse events: 1 patient experienced drowsiness, dizziness, and nausea; and 1 patient experienced visual disturbance and oversedation.

Table 2: Subjective Study: Treatment of Chronic Insomnia with zolpidem 10mg and 15mg

Trial/ Purpose	Inclusion/Exclusion/Endpoints	Treatment	Results	Adverse Events/Withdrawals
Lahmeyer, 1997 R, DB, PC, MC, parallel-group subjective study Purpose: To compare the subjective hypnotic efficacy of IR zolpidem 10mg or 15 mg compared to placebo in chronic insomnia outpatients for 31 consecutive nights.	**Inclusion Criteria:** History of a minimum of 3 months of disturbed sleep characterized by typical sleep duration of 4-6 hours, a typical sleep latency of at least 30 minutes, and associated daytime complaints. **Exclusion Criteria:** 1) Any investigational drug within 30 days of the start of the study; 2) had used alcohol or a short acting CNS medication within 1 year; 3) had a positive urine drug screen (for benzodiazepines, barbiturates, opiates and amphetamines) performed at screening; 4) history of exaggerated responses to benzodiazepines or other CNS depressants; 5) had been an illicit drug addict within the previous year; 6) had subjective symptoms of sleep apnea; 7) had nocturnal myoclonus or seizures. Patients who were shift workers and women who were breastfeeding were also excluded. 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. Primary efficacy measures were self-reported sleep latency and self-reported total sleep time. Secondary measures were: ease of falling asleep, # of awakenings, time spent awake after falling asleep before final	Run-in 3 days; wash out: 4 days Zolpidem IR 10mg, 15mg or placebo in a ratio of 4:4:5, respectively. First 3 days of the first week and the last 4 days of the final week were single-blind treatment. Patients completed a morning questionnaire on days 1, 2, 3, and 7 of each week and a Clinical Global Impression on day 7 of treatment week 4.	**Baseline:** Mean age 44.9 (range, 19-60); 56% female; 92% Caucasian; 6% black At randomization, the treatment groups did not differ significantly in terms of sleep history, gender, age, race, height and bodyweight. Table 1. **Summary of Subjective Primary Efficacy Results** **Efficacy Outcomes** / **Zolpidem 10mg n =45** (p vs. placebo) / **Zolpidem 15mg (n=46)** (p vs. placebo) / **Placebo (n=54)** (p vs. Placebo) Change in Subjective Sleep Latency (SSL) from baseline (min)† 4 weeks average: -30 / -33.5 / -9 At week 4: -31 (<0.05) / -31 (NS) / -1 (NA) Post-treatment: -10 (NS) / -11 (NS) / -25 (NA) Subjective Total Sleep Time (min) 4 weeks average: 379 / 381 / 346 At week 4: 390 (NS) / 385 (NS) / 360 (NA) Post-treatment: 354 (NS) / 332 (NS) / 359 (NA) Mean Subjective Number of awakenings 4 weeks average: 1.3 / 1.3 / 1.85 At week 4: 1.4 (NS) / 1.2 (NS) / 1.7 (NA) Post-treatment: 1.7 (NS) / 1.9 (NS) / 1.9 (NA) Mean Sleep quality scores* 4 weeks average: 2.4 / 2.4 / 2.8 At week 4 (p vs. placebo): 2.4 (NS) / 2.4 (NS) / 2.6 (NA) Post-treatment: 2.8 (NS) / 2.9 ** / 2.8 (NA) † SSL Data read off of graph. *Scale: 1=excellent; 2=good; 3=fair; 4=poor; ** p < 0.10 vs. placebo	178 screened/ 145 eligible/145 enrolled/118 completed all 6 weeks of double-blind phase. 27 patients withdrew after randomization (10 placebo, 8 zolpidem 10mg, (1 of whom was withdrawn before receiving double-blind treatment because of noncompliance with study medication) and 9 from zolpidem 15mg (3 of whom were withdrawn before receiving double-blind treatment, 2 because of lack of efficacy and 1 because of an adverse event) During the double-blind treatment, 10 patients were withdrawn from the placebo group, 5 because of lack of efficacy and 5 for various study-related reasons. In all, 7 patients were withdrawn from the zolpidem 10mg group and 6 from the zolpidem 15mg group because of: adverse events (4 patients), lack of efficacy (3), an adverse event (3), and study-related reasons (3). Table 2: Number of Patients Reporting Adverse Events Adverse Events / Placebo (n=53) / Zolpidem 10mg (n=44) / Zolpidem 15mg (n=43) Automatic Nervous: 1 / 2 / 0 Body as a whole: 5 / 3 / 7 Central and peripheral nervous: 15 / 19 / 15 Gastrointestinal: 6 / 6 / 7 Heart rate and rhythm disorders: 0 / 0 / 1 Musculoskeletal: 5 / 3 / 4 Psychiatric: 3 / 3 / 3 Reproductive: 1 / 0 / 0 Resistance: 0 / 1 / 1 Skin and appendages: 0 / 1 / 0 Special senses: 0 / 1 / 2 Urinary: 1 / 2 / 2 Vision: 1 / 2 / 2 Miscellaneous: 1 / 0 / 0 Overall*: 23 / 25 / 30 * Each patient is counted only once in the total

	morning waking, quality of sleep, morning sleepiness and ability to concentrate in the morning.			Treatment-emergent AE were reported in 23 (43%), 25 (57%), and 30 (70%) patients receiving placebo, IR zolpidem 10mg and IR zolpidem 15mg, respectively, (p=0.080). Events that occurred with greater frequency in either of the zolpidem groups than in the placebo group were drowsiness (6% with placebo, 11% with zolpidem 10mg, 12% with zolpidem 15mg), lethargy (0%, 7%, 2%, respectively), and dizziness (4%, 5%, 7%, respectively), pharyngitis (2%, 2%, 9%, respectively) and rhinitis (2%, 0%, 7%, respectively). Discontinuation: 4 patients in the zolpidem 10mg group, 3 in zolpidem 15mg, and none in the placebo group discontinued treatment because of adverse events. The adverse events leading to discontinuation included dry mouth, mental confusion, headache, and lightheadedness, anxiety, panic attack and mild, uncontrolled crying.

Quality Rating: Fair
Study Conclusions

- **Efficacy**
  - Both the 10mg and 15mg groups had significantly greater changes from baseline in subjective sleep latency than the placebo group at all treatment weeks. Mean change in sleep latency from reported baseline in minutes at week 4 were -16 for placebo, -31 zolpidem 10mg ($p<0.05$) and -31 for zolpidem 15 mg. There were no differences between the two IR zolpidem groups at any time.
  - No statistically significant improvement in sleep quality or number of awakenings was observed.
- **Safety:**
  - No tolerance or next-day residual effects were seen.
    Adverse events that occurred more often in either of the IR zolpidem groups than in the placebo groups were drowsiness, lethargy and dizziness.

Table 3: Objective and Subjective Study: Treatment of Transient Insomnia with zolpidem 5, 7.5, 10, 15 and 20mg

Trial/ Purpose	Inclusion/Exclusion/ Endpoints	Treatment	Results	Adverse Events/Withdrawals
Roth, 1995 Unbalanced R, DB, PC, two-center, single-night Purpose: Efficacy of 7.5mg and 10mg zolpidem compared with placebo in transient insomnia	**Inclusion Criteria:** Healthy volunteers with normal sleep habits (sleep latency ≤ 30 minutes and sleep duration ≥ 6 hours) Aged 21 and 60 **Exclusion Criteria:** Previously slept in sleep laboratory; histories of drug addiction or alcoholism within the past year; significant mental or psychiatric disorders; seizures, serious head injury or a history of sleep apnea. Shift workers and others whose sleep schedules were expected to change by at least 6 hours within 7 days of the study; history of exaggerated response or hypersensitivity to benzodiazepines.	Zolpidem 5mg , 7.5,10,15, 20	**Baseline:** Mean age 44.9 (range, 19-60); 56% female; 92% Caucasian; 6% African-American Table 1. **Summary of Sleep Parameters Efficacy Results** **PSG= Polysomnography; * †=data unavailable for 1 patient; * compared to placebo;¶ overall treatment comparison; Sleep efficiency= total time asleep/time in bed** Treatment with zolpidem had no effect on stage 1, stage 2, and stages 3-4 sleep. Both the 7.5mg and 10mg groups had significantly less rapid eye movement (REM) sleep than placebo; 21% with placebo, 18% ($p<0.001$) with 7.5mg and 19% ($p<0.001$) with 10mg. When zolpidem dose was increased, similar reductions in REM were observed, but there was no alteration in any other stage of the sleep architecture. Table 2: Next-day performance and alertness	462 screened/ 462 eligible/462 enrolled/ 24 patients were ecxluded because of positive alcohol/drug tests (n=11), consumption of caffeinated beverages (n=10) and daytime napping (n=3) 47 patients (10.2%) spontaneously reported a total of 71 AE, ranging from dry mouth to headache. The percentage of subjects who experienced AE with zolpidem doses at or below the recommended therapeutic dose of 10mg was not significantly different form the percentage in the placebo group (7.8% with placebo, 3.8% at 5mg, 4.9% at 7.5mg and 6.7% at 10mg). At the higher dose of 15mg zolpidem, 17.6% of patients experienced AE ($p=0.069$ vs. placebo) and at 20mg 31.5% reported AE ($p<0.001$ vs. placebo).

Efficacy Outcomes	Zolpidem 5mg (n=52)	Zolpidem 7.5mg (n=102)	Zolpidem 10mg (n =103)	Zolpidem 15mg (n=51)	Zolpidem 20mg (n-51)	Placebo (n=102)	p-value¶
Mean Sleep Latency (min)							
PSG	23.8 ±30	17.0 ±1.4 p < 0.001)*	17.4 ±1.6† (p<0.001)*	18.7± 2.5	20.6 ± 3.6	27.1 ±2.6	0.003
Patient Assessment	29.2± 2.0†	18.9 ±1.2 (p=0.009)†	18.2 ±1.5 (p<0.001)†	18.1 ±2.7†	13.6 ±1.4	28.8 ±3.0	<0.001
Sleep efficiency via PSG	89.1 ±1.0	91.7 ± 0.7 (p< 0.001)*	91.8± 0.7 (p< 0.001)*	91.0 ±1.0	91.1± 1.2	87.8 ± 0.9	<0.001
Sleep maintenance via PSG	5.8± 0.6	5.0 ±0.3 (p=0.004)*	5.3± 0.4 (p=0.014)*	5.4± 0.7	4.7± 0.6	6.7 ±0.4	0.024
Wake time during sleep (minutes)	26.5 ±3.1	21.2± 2.4 (p=0.004)*	21.4 ±2.4 (p=0.005)*	21.3 ±3.1	21.0 ±3.5	31.4 ±3.1	0.027

Efficacy Outcomes	Zolpidem 5mg (n=52)	Zolpidem 7.5mg (n=102)	Zolpidem 10mg (n =103)	Zolpidem 15mg (n=51)	Zolpidem 20mg (n-51)	Placebo (n=102)
Digit Symbol Substitution Test	53.9 ± 2.5	54.3 ±1.3	55.8 ±1.7	55.6 ±1.9	52.1 ±1.7	53.9 ±1.6
Symbol Copying Test	117.2 ± 4.1	119.1 ± 2.5	119.7 ± 3.2	121.0 ±4.2	115.7± 3.8	121.±1 2.7
Ability to concentrate*	1.8 ± 0.1	1.8 ± 0.1	1.0 ± 0.1	1.9 ± 0.1	2.0 ± 0.1	1.9 ± 0.1
Morning sleepiness**	69.0 ± 2.3	64.0 ± 2.5	62.2 ± 2.5	69.9 ± 3.7	63.0 ± 3.3	69.0 ± 2.3
Daytime sleepiness†	39.2%	31.0%	31.7%	27.5%	47.1%	39.2%
Drugged feeling¶	85.6 ±1.9	85.2 ± 2.0	83.1 ± 1.8	80.1 ± 3.3	77.6 ± 3.7	85.6 ±1.9

*1=excellent, 2=very good, 3=fair, 4=poor; **Not at all sleepy, 100=very sleepy; Percent responding yes; ¶0=very drugged, 100=not at all drugged.

Quality Rating: Fair

Study Conclusions

- **Efficacy**
- Zolpidem 7.5mg and 10mg was significantly more effective than placebo in all sleep induction and maintenance parameters. Although the study was not designed to statistically compare zolpidem 15mg and 20mg to placebo, it was observed that increasing the dose above 10mg did not result in a corresponding increase in hypnotic efficacy.
- No significant between-group differences in next-day performance and alertness.
- **Safety:**
  - No subjects reported clinically important adverse events at any zolpidem dosage. The percentage of patients experiencing side effects at doses of 10mg or less was comparable to the placebo group. A statistically significant increase in the incidence of adverse events was seen with zolpidem 15 and 20mg compared to placebo.

Single-blind Studies:

Schlich et al. (1991) conducted a 6-month, single-blind flexible-doing study, general practitioner, observational study in 107 middle-aged and elderly insomnia outpatients (mean age 63 years old) in France. A total of 87 patients completed the study. The initial dose was zolpidem IR 20mg/day. By day 20, 18 (17.5%) patients were using 10 mg/day, and 3 patients were using doses > 20 mg/day. At the end of the 6-month active treatment period, 32 (36%) patients were receiving zolpidem 10mg dose. In the first placebo treatment period, 7 patients experienced ten AEs (agitation, anxiety, palpitation, postural hypotension, and renal pain). During the active treatment phase (day 8-180), 24 patients had 42 AEs which had a possible, probably, or certain relationship to zolpidem (or where no relationship was stated). The most frequently reported events included malaise (5 events), vertigo, (5 events), and anterograde amnesia (5 events). All patients who experienced vertigo (5 patients) and confusion (2 patients) were aged 70 years or more. Rebound insomnia or tolerance was not observed. Five adverse events led to study withdrawal. All the sleep parameters monitored (sleep latency, duration of nocturnal sleep, number of awakenings and frequency and duration of diurnal napping) showed improvement during active treatment, whether assessed by the investigators or subjectively by the patients. The adverse events were minor and infrequent, and in many patients the AEs resolved after a dose reduction, which suggests, "that a starting dose of 10mg/day zolpidem may be appropriate in this group of patients."

Scharf et al, (1994a) evaluated zolpidem 15mg per day in 233 insomnia patients (mean age 52 years; range 18-62 years) during a 12 week period in a multicenter, single-blind, observational study. All the patients had a history of insomnia of at least 3 months in duration. The patients received placebo for 4-7 nights followed by zolpidem 15mg for 12 weeks. If an adverse events occurred, the investigator could reduce the nightly dose to zolpidem 10mg. Patients unable to tolerate 10mg doses were withdrawn from the study. Seventy-eight patients discontinued zolpidem treatment prematurely, the majority (n=56) during the first 4 weeks of the study, 4 of which did not return after the start of zolpidem therapy. Thirty-three patients (14%) had their dose of zolpidem decreased to 10mg/day at some point in the study due to either lack of efficacy, adverse event, intermittent illness, lost to follow-up, noncompliance or other reasons. There were no dose reductions after week 8. A total of 155 (67%) patients completed all 12 weeks of treatment. During the 12-week treatment period with zolpidem 15mg, most of the adverse events were within the mild-to-moderate range of severity; 17% of all adverse events were of marked severity, with no single event having and incidence greater than 2%. Of the 229 patients in the zolpidem 15mg group, 188 patients (82%) reported adverse events during zolpidem treatment and 26 patients (11%) reported adverse events during the placebo follow-up; 19 (8%) withdrew from the study because of adverse events during active treatment. The most frequently occurring adverse events included: headache (28%), drowsiness (26%), fatigue (17%), upper respiratory infection (17%), and dizziness (14%). During the placebo follow-up phase, headaches were the most frequent adverse event (5%). Sixteen patients (15 taking 15mg) experienced amnestic episodes while receiving zolpidem, seven of which had a single episode of inability to remember events that occurred between drug administration and sleep onset, or occurred during the night. The other nine reported more than one episode of memory disturbance that occurred during the night after taking zolpidem (n=6) or during the day (n=3). The Clinical Global Impression Scale (CGI) assessment of side effects showed a slight, but significant, increase in severity in investigator ratings of side effects from baseline to weeks 2, 4, and 8 at end point. No evidence of tolerance or rebound insomnia was reported. The authors concluded that patients whose dose was reduced to 10mg reported fewer side effects without the loss of hypnotic efficacy.

Table 4: Number (%) of patients with treatment-emergent adverse events

Adverse events	Zolpidem 10mg n=33 no. (%)	Zolpidem 15mg n=229 no. (%)
Autonomic Nervous		
Dry Mouth	2 (6.1)	14 (6.1)
Central and Peripheral Nervous		
Ataxia	2 (6.1)	7 (3.1)
Confusion	2 (6.1)	14 (6.1)
Dizziness	2 (3.1)	32 (14.0)
Drowsiness	5 (15.2)	60 (26.2)
Fatigue	6 (18.2)	38 (16.6)
Headache	7 (21.2)	65 (28.4)
Lethargy	1 (3.0	14 (6.1)
Light-headedness	1 (3.0)	24 (10.5)
Gastrointestinal		
Abdominal pain	0 (0)	13 (5.7)
Dyspepsia	1 (3.0)	20 (8.7)
Nausea	1 (3.0)	28 (12.2)
Musculoskeletal		
Arthralgia	2 (3.1)	7 (3.1)
Psychiatric		
Amnesia	1(3.0)	15 (6.6)
Nervousness	3 (9.1)	11 (4.8)
Respiratory/Infections		
Herpes Simplex	2(6.1)	6 (2.6)
Pharyngitis	2(6.1)	6 (2.6)
URI	4(12.1)	38 (16.6)

*Treatment-emergent adverse events (mild, moderate, marked) reported by at least 5% of patients. Patients are counted only once (at the most severe column) at each dose level. URI= Upper respiratory infection.

Verster et al. (2002) performed a two-part study. Part I of the study was a single-blind, two period crossover design to determine the effects of a single dose of ethanol (0.03% < blood alcohol content (BAC) < 0.05%) or ethanol-placebo on the driving ability, memory, and psychomotor performance. Part 2 was a double-blind, five-period crossover study designed to measure the effects of a middle-of-the-night administration of zaleplon 10 or 20 mg, zolpidem 10 or 20 mg, or placebo on the driving ability 4 hours after administration and the memory and psychomotor performance 6 hours after administration. Subjects operated an instrumented automobile in a naturalistic environment of a 100-km highway circuit at a constant speed (58 mph) while maintaining a steady lateral position between the right lane boundaries. The amount of weaving of the car measured by the standard deviation of the lateral position (SDLP, cm) is an index of driving safety and was the primary performance parameter of the driving test for this study. Thirty healthy volunteers (15 men and 15 women; mean age 24 years old) participated in the study. The duration of the driving test was approximately 75 minutes. All the subjects possessed a valid driver's license and driving experience of more than 5000 km a year during each of the preceding 3 years. Subjective assessments performed in the study included: Digit Symbol Substitution Test (DSST); Critical Tracking Test (CTT); Divided Attention Test (DAT); Word Learning Test which included relative word recall (RWR); delayed free word recall (DWR); immediate free word recall (IWR), recognition in reaction time (RRT), and delayed free word recall (DWR). See Tables 5 and 6 for results:

Subjective assessments: In Part I, subjective driving quality and mental effort during driving did not differ significantly between ethanol and placebo. In part 2, overall treatment effects were significant for subjective driving quality ($p<0.001$) and mental effort during driving ($p<0.001$). Further analysis revealed that subjective driving quality was significantly worse after zolpidem 20mg. Relative to placebo, subjective driving quality also worsened after zolpidem 10mg, but not significantly. Subjective driving quality after both doses of zaleplon matched placebo. Mental effort during driving was significantly increased after zolpidem 20mg. In contrast, mental effort after zolpidem 10mg and both doses of zaleplon did not differ significantly from placebo.

Psychomotor performance: In part I, ethanol significantly impaired DSST performance and DAT. In part 2, the overall treatment effects for all psychomotor variables were significant. The performance after zolpidem 20mg was significantly worse than that with placebo for all psychomotor variables. With other treatments, there were no significant differences from placebo on any of the psychomotor assessments. Again, a significant dose-response relation was found for both doses of zolpidem but not for zaleplon.

Memory performance: In part I, IWR and RWR were significantly smaller with ethanol compared to placebo. In part 2, there were significant overall treatment effects for DWR, RWR, and RRT. Pairwise comparisons showed no significant differences between placebo and zaleplon 10 or 20mg or zolpidem 10mg. However, the analyses showed that DWR, RWR, and RRT were significantly worse with zolpidem 20mg than with placebo ($p<0.001$). A significant dose-response relationship between zolpidem 10 and 20mg was found for DWR, RWR, and RRT.

Driving performance: In part I, the standard deviation of lateral position (SDLP, cm) with ethanol (BAC < 0.05%) was significantly greater than that with placebo, with a difference between means of 1 cm. In part 2, there were significant overall treatment effects for SDLP and standard deviation of speed (SDS, km/h). No significant difference with zaleplon 10 or 20mg for either SDLP or SDS. In contrast, mean SDLPs with zolpidem 10mg and zolpidem 20mg were significantly greater than with placebo, $p<0.001$). Also, SDS with zolpidem 20mg was significantly greater than with placebo. A significant dose-response relationship for both SDLP and SDS was seen between zolpidem 10 and 20mg was seen but not with zaleplon 10 and 20mg.

Adverse events: The incidence of any adverse event tended to be greater after zolpidem 10mg and particularly after zolpidem 20mg and ethanol than with either dose of zaleplon or placebo (part 1 and 2). Adverse events reported after both doses of zaleplon matched the placebo condition. In part I, the driving test data of one female were omitted from statistical analyses due to a severe cold that interfered with test performance. The driving instructor discontinued the driving test of one male subject due to extreme sleepiness after 90 km were completed. In part 2, three female subjects that took zolpidem 20mg were unable to complete the driving. For safety reasons, the driving instructor stopped their driving tests after approximately 40 km.

Conclusion: Driving four hours after zaleplon 10 and 20mg did not significantly differ from placebo, whereas zolpidem 10 and 20 mg significantly impaired the driving performance in a dose-dependent manner. However, although zolpidem 10mg significantly increased SDLP, the magnitude of the difference from placebo was small. Further, SD speed was unaffected after zolpidem 10mg. In contrast, zolpidem 20mg significantly impaired the driving performance, expressed by the elevated SDLP and SD speed. After zolpidem 20mg, the loss of the ability to keep the car within the right traffic lane was accompanied by increased speed variability, indicating severe driving impairment. Moreover, the decision to terminate a driving test before its scheduled completion occurred only after treatment with twice the recommended dose of zolpidem. The objective findings in the driving test were confirmed by subjective assessments. Laboratory test results also showed significant impairment after zolpidem 20mg on all psychomotor and memory tests.

Table 5. Part 2: Summary of Mean Performance Parameters

Variable	Placebo Mean ± SD	Zaleplon 10mg Mean ± SD	Zaleplon 20mg Mean ± SD	Zolpidem 10mg Mean ± SD	Zolpidem 20mg Mean ± SD
Driving Performance					
SDLP (cm)	17.5 ±4.2	17.2 ±4.1	18.1 ±4.6	21.3± 6.7	28.1± 11.9
SDS (km/h)	2.25 ± 0.65	2.40 ±0.65	2.43 ±0.71	2.43 ±0.60	3.08 ±1.30
Psychomotor Performance					
DSST (# correct)	139 ± 21	139 ± 18	138 ± 18	135 ± 21	129 ± 25
CTT (RMS)	5.36 ± 5.59	4.27 ± 4.01	4.43 ± 3.45	5.12 ± 4.51	8.00 ±3.7
DAT (RMS)	6.62 ± 5.11	6.15 ± 4.20	5.91 ± 4.11	6.23 ± 4.65	9.52 ±7.02
DAT (RT, ms)	499 ± 73	491 ± 57	496 ± 62	502 ± 67	571 ± 158
Memory Performance					
IWR (#)	14.7 ± 0.9	14.6 ±0.0	14.6 ± 0.0	14.6 ± 1.1	14.2 ± 1.4
DWR (#)	14.2 ±1.2	13.8 ±1.8	13.4 ±1.7	13.7± 2.1	12.5 ± 3.2
RWR (%)	96.2 ±7.0	94.7 ±11.0	91.4 ± 9.0	93.0 ±10.8	86.9 ±17.4
RS (#)	28.9 ±1.1	28.9 ±1.3	28.9 ± 1.2	28.6 ±1.6	28.5 ± 1.6
RRT (ms)	589 ± 87	599 ±83	600 ± 77	616 ± 81	672 ± 128

SDLP= standard deviation of lateral position; SDS=standard deviation of speed; DSST=Digit Symbol Substitution Test; CTT (RMS)= Critical Tracking Test, (root mean square of the racking error); DAT (RMS)=Divided Attention Test (root mean square of the tracking error); DAT (RT, ms)= Divided Attention Test (mean reaction time); IWR= immediate free word recall; DWR=delayed free word recall; RWR= Relative word recall (DWR/IWF x 100%); RS=recognition score (number of correct responses out of 30 presented words); RRT=recognition reaction time.

Table 6: Treatment-emergent events reported by > 5% of the subjects (n=30) in at least one treatment condition.

	Part I		Part II				
Adverse Events	Ethanol n=30 no. (%)	Placebo -ethanol n=30 no. (%)	Placebo n=30 no. (%)	Zaleplon 10mg n=30 no. (%)	Zaleplon 20mg n=30 No. (%)	Zolpidem 10mg n=30 no. (%)	Zolpidem 15mg n=30 no. (%)
Any adverse events (1 or more)	25 (83)	15 (50)	14 (47)	10 (33)	15 (50)	21 (70)	25 (83)
Autonomic Nervous							
Dry Mouth	3 (10)	0	0	0	0	1 (3)	1 (3)
Central and Peripheral Nervous							
Amnesia	0	0	0	0	0	0	5 (17)
Ataxia	0	0	1 (3)	0	2 (7)	7 (23)	15 (50)
Diplopia	0	0	0	0	1 (3)	1 (3)	6 (20)
Dizziness	3 (10)	1 (3)	0	0	0	2 (7)	6 (20)
Headache	5 (17)	2 (7)	7 (23)	6 (20)	5 (17)	3 (10)	4 (13)
Incoordination	1 (3)	0	0	0	0	0	4 (13)
Somnolence	14 (47)	8 (27)	7 (23)	5 (17)	8 (27)	11 (37)	21 (70)
Gastrointestinal							
Nausea	1 (3)	1 (3)	1 (3)	0	1 (3)	1 (3)	8 (2.7)
Vomiting	0	0	0	0	0	0	5 (17)
Psychiatric							
Amnesia	0	0	0	0	0	0	5 (17)
Abnormal thinking	14 (47)	8 (27)	4 (13)	3 (10)	6 (20)	10 (33)	13 (43)

Merlotti L et al. (1989) conducted a dose-ranging study of zolpidem (2.5, 5.0, 7.5, 10, 20 mg) or placebo on various sleep measures in 12 healthy males with normal sleep patterns. Subjects spent 7 weeks, 3 consecutive nights per week, in the laboratory and had a 4-night washout between treatments. Treatments were organized in a Latin square design and administered in a double-blind fashion.
See Table 7 for results:
Sleep Induction: The 5 mg and larger doses of zolpidem significantly decreased latency to persistent sleep (minutes from the beginning of the recording to the start for the first 10 consecutive minutes of sleep) and wake before sleep (minutes of wake before persistent sleep). There were no significant differences in latency to persistent sleep between the 2.5mg dose and the three middle doses or the three middle doses and the 20mg dose.
Sleep Maintenance: Sleep maintenance measures were not affected by zolpidem. The three sleep maintenance measures were wake during sleep (minutes of wake after onset of persistent sleep prior to final awakening), wake after sleep (minutes of wake in final awakening-wake entry immediately before the end of the recording) and the number of awakenings (the number of times wake onset of persistent sleep that there is a wake entry of at least 1 minute in duration).
Total Sleep Time: The 7.5mg and higher doses of zolpidem significantly increased total sleep time compared to placebo. Total sleep time showed no significant dose differences.
Sleep Stage: The only significant sleep stage effect was a decrease in percent of rapid eye movement sleep with the zolpidem 20mg dose. Zolpidem was hypnotically active at doses as low as 5.0 and 7.5mg and sleep stage effects occurred only at the 20mg doses.
Adverse Effects: No consistent discontinuation effects were found. Conclusion: Zolpidem was hypnotically active at doses as low as 5.0 and 7.5mg.

Table 7: Dose effects of zolpidem on Various Sleep Parameters

Variables	Zolpidem 0mg Mean (SD)	Zolpidem 2.5mg Mean (SD)	Zolpidem 5 mg Mean (SD)	Zolpidem 7.5mg Mean (SD)	Zolpidem 10 mg Mean (SD)	Zolpidem 20mg Mean (SD)
Sleep Induction						
Wake before sleep (min) p vs. placebo*	21.6 (20.0)	13.6 (6.9) NS	9.0 (7.2) p<0.02	9.9 (6.6) p<0.03	9.7 (6.6) p<0.05	6.4 (5.3) p <0.02
Latency to persistent sleep (min) P vs. placebo	23.7 (21.2)	14.5 (7.7) NS	11.5 (10.2) p <0.03	11.1 (8.2) p < 0.02	11.8 (9.2) p <0.05	7.7 (6.3) p<0.02
Sleep Maintenance						
Wake during sleep (min)	10.8 (8.9)	14.1 (22.2)	12.0 (16.4)	8.8 (1.0)	7.8 (7.1)	9.6 (10.3)
Wake after sleep (min)	0.8 (1.6)	1.0 (3.6)	1.3 (4.2)	1.0 (2.3)	0.8 (2.7)	0.7 (1.4)
Number of awakenings	2.5 (2.2)	2.9 (3.2)	2.3 (1.5)	1.5 (1.3)	2.2 (2.2)	1.8 (2.1)
Overall hypnotic effect						
Total sleep time p vs. placebo	447.2 (20.5)	451.7 (20.3) NS	457.8 (16.7) NS	460.7 (11.3) p<0.02	462.1 (11.6) P <0.05	463.8 (8.9) 0<0.03
Sleep staging						
1 (%)	8.8 (3.9)	9.0 (4.4)	8.4 (3.4)	8.6 (4.1)	8.8 (4.2)	7.1 (3.8)
2 (%)	56.7 (6.4)	55.8 (4.1)	56.8 (4.2)	56.0 (5.0)	56.5 (4.4)	59.2 (6.4)
3/4 (%)	14.3 (6.0)	14.3 (5.0)	14.7 (4.3)	15.2 (5.1)	16.1 (5.4)	16.2 (6.8)
REM (%) p vs. placebo	20.5 (3.7)	21.0 (3.9) NS	20.4 (4.4) NS	20.5 (4.2) NS	18.6 (4.1) NS	17.7 (3.1) p<0.05
Latency to REM	105 (40.9)	103.4 (31.5)	111.1 (37.1)	122.1 (50.3)	119.2 (41.4)	137.4 (42.9)

* post-hoc analysis; NS= Not significant

Sharf MB et al. (1991) conducted a single-blind, multi-center study to evaluate the effects of zolpidem in elderly "noncomplaining" subjects. The effects of zolpidem 5, 10, and 20mg were compared with those of placebo on sleep latency, sleep efficiency, psychomotor performance, memory, and daytime alertness. Eighty healthy volunteers between the ages of 60 and 80 years of age (mean 67.8 years) with no complaints of sleep difficulty were evaluated. Subjects were randomized to one of two crossover treatment groups. Crossover group I received placebo, zolpidem 5mg, and zolpidem 15mg. Crossover group II received placebo, zolpidem 10mg, and zolpidem 20mg. Each treatment period consisted of 3 consecutive study nights. The same dose of zolpidem or placebo was administered on nights 1 and 2. Four to 10 days separated each period.
See Tables 8-10 for results.
Sleep Induction: Zolpidem caused a statistically significant decrease in sleep latency at all doses studied (p<.05). Sleep latency decreased from 38 minutes with placebo to 21 minutes with zolpidem 5mg and to 15 minutes with zolpidem 15mg in Crossover I group. In the Crossover II group, the latency was 49 minutes with placebo, 23 minutes with zolpidem 10mg, and 21 minutes with zolpidem 20mg.
Sleep Efficiency: Zolpidem had no effect on the number of polysomnography (PSG) determined awakenings but did significantly increase sleep efficiency (p<.05). Sleep efficiency increased in Crossover I from 77% with placebo to 84% with zolpidem 5mg and 89% with zolpidem 15mg. In Crossover II, sleep efficiency increased from 80% with placebo to 85% with zolpidem 10mg, and 87% with zolpidem 20mg.
Sleep Staging: Zolpidem had no effect on the percentage of stages 3 and 4 sleep at any doses. Stage 2 sleep was significantly increased with zolpidem 20mg. Stage REM sleep was significantly decreased with zolpidem 10mg and 20mg (p<.05) but not with 5 mg or 15mg.
Adverse Effects: PSG analyses of night 3 indicated that upon withdrawal of zolpidem after 2 nights of 15 mg treatment, subjects experienced a significant reduction (p<.05) in sleep efficiency. No other dose produced a significant reduction in sleep efficiency. There were no significant differences among treatment in PSG sleep latency on placebo night 3. There was a significant increase (p<.05) in PSG determined number of awakenings with zolpidem 10 and 20mg, but not with 5 and 15 mg. Discontinuing zolpidem treatment (night 3) resulted in increased subjective complaints of sleep difficulty in subjects who had received doses of 10mg or more, but that these complaints were not supported by the objective data. Side effects were dose dependent. The total number of subjects that experienced adverse events were: 7 (20.6%), 2 (11.8%), 4 (25.0%), 6 (35.3%), 9 (52.9%) in the placebo, zolpidem 5, 10, 15, 20mg groups, respectively. Drowsiness was reported more frequently at doses of 10mg and higher than with placebo.
Conclusion: Zolpidem showed hypnotic activity at doses as low as 5mg in the elderly. The incidence of AEs was dose dependent.

Table 8: Polysomnographically Determined Sleep Parameters on Sleep Parameters during Treatment Nights 1 and 2

Variable	Placebo Mean (SD)	Zolpidem 5mg Mean (SD)	Zolpidem 10mg Mean (SD)	Zolpidem 15mg Mean (SD)	Zolpidem 20mg Mean (SD)	p value*
Latency to persistent sleep (min)						
Crossover I	38 (19)	21** (14)		15** (14)		<.001
Crossover II	49 (54)		23** (11)		21** (16)	.002
Wake time during sleep (min)						
Crossover I	72 (39)	46** (33)		34** (16)		.001
Crossover II	50 (33)		39 (25)		37 (23)	.265
Sleep efficiencies (%)						
Crossover I	77 (9)	84** (7)		89** (5)		<.001
Crossover II	80 (11)		85** (8)		87** (5)	.008
Number of awakenings						
Crossover I	10 (4)	8 (3)		8 (3)		.065
Crossover II	7 (2)		6 (2)		7 (3)	.428

Crossover I=Placebo, zolpidem 5mg, zolpidem 15mg, Crossover II=Placebo, zolpidem 10mg, zolpidem 20mg. **significantly different from placebo (p<.05); *Overall treatment comparison.

Table 9: Subjectively Dose Response Effects of Zolpidem on Sleep Parameters during Treatment Nights 1 and 2

Variable	Placebo Mean (SD)	Zolpidem 5mg Mean (SD)	Zolpidem 10mg Mean (SD)	Zolpidem 15mg Mean (SD)	Zolpidem 20 mg Mean (SD)	P value *
Subjective Latency to persistent sleep (min)						
Crossover I	30 (15)	17** (11)		12** (8)		<.001
Crossover II	55 (61)		15** (8)		12** (9)	<.001
Subjective total sleep time (min)						
Crossover I	361 (83)	424** (36)		439** (35)		.002
Crossover II	404 (58)		439** (27)		457** (18)	.001
Subjective number of awakenings						
Crossover I	3.6 (2.0)	1.9** (1.2)		1.4** (1.3)		<.001
Crossover II	2.7 (1.3)		1.5** (0.9)		1.0** (0.9)	<.001
Ease to fall asleep†						
Crossover I	50 (21)	2** (15)		17** (11)		<.001
Crossover II	42 (27)		20** (13)		11** (13)	<.001
Quality of sleep¶						
Crossover I	2.3 (0.6)	1.6** (0.4)		1.4** (0.4)		<.001
Crossover II	2.3 (0.6)		1.7** (0.8)		1.5** (0.4)	<.001
Refreshing quality						
Crossover I	2.3 (0.4)	1.7** (0.5)		1.5** (0.4)		<.001
Crossover II	2.3 (0.7)		1.9** (0.6)		1.0** (0.6)	.040

Crossover I=Placebo, zolpidem 5mg, zolpidem 15mg, Crossover II=Placebo, zolpidem 10mg, zolpidem 20mg. **significantly different from placebo (p<.05); *Overall treatment comparison. † 0=very easy, 100=not at all easy. ¶ 1=excellent, 2 =very good, 3=fair, 4=poor

Table 10: Number and Percentage of Patients Affected by Treatment-Emergent Adverse Events during 2 Nights of either Zolpidem or Placebo Treatment

Adverse events	Placebo n=34 no. (%)	Zolpidem 5mg n=17 no. (%)	Zolpidem 10mg n=16 no. (%)	Zolpidem 15mg n=33 no. (%)	Zolpidem 20 mg n=229 no. (%)
Central Nervous System					
Confusion	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)
Drowsiness	3 (8.8)	1 (5.9)	2 (12.5)	4 (23.5)	6 (35.3)
Headache	4 (11.8)	1 (5.9)	0 (0)	1 (5.9)	2 (11.8)
Light-headedness	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.9)
Vertigo	0 (0)	0 (0)	0 (0)	1 (5.9)	1 (5.9)
OVERALL	7 (20.6)	2 (11.8)	3 (18.8)	6 (35.3)	8 (47.1)
Gastrointestinal					
Nausea	0 (0)	1 (5.9)	0 (0)	0 (0)	2 (11.8)
Vomiting	0 (0)	0 (0)	0 (0)	1 (5.9)	1 (5.9)
OVERALL	0 (0)	1 (5.9)	0 (0)	1 (5.9)	2 (11.8)
Musculoskeletal					
Myalgia	0 (0)	0 (0)	1 (6.3)	0 (0)	1 (5.9)
OVERALL	0 (0)	0 (0)	1 (6.3)	0 (0)	1 (5.9)
Total number of subjects experiencing adverse events	7 (20.6)	2 (11.8)	4 (25.0)	6 (35.3)	9 (52.9)

*Events occurred during treatment that were not present at screening, or if present, worsened during treatment. Events occurring within 24 hours after the administration of double-blind treatments are included. Results from Nights 1 and 2 are combined.

Conclusion: These studies suggest that dosing zolpidem greater than 10mg per day does not provide any additional hypnotic efficacy, but rather results in a higher incidence of undesirable adverse effects.

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