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Subjective Hypnotic Efficacy of Trazodone and Zolpidem in DSMIII-R Primary Insomnia

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Trazodone is an antidepressant which is used at low doses as a hypnotic. The hypnotic efficacy of trazodone in non-depressed insomniacs is unknown, especially in comparison to hypnotic medications such as zolpidem. Following a placebo screening week, DSM-IIIR defined primary insomniacs were randomized into a parallel-group, double-blind, 14-day comparison of trazodone 50 mg, zolpidem 10 mg and placebo. Patients completed daily morning questionnaires and weekly office visits. Self-reported sleep latencies were compared by the Cox proportional hazards regression technique; self-reported sleep duration by ANOVA. During treatment Week 1, both drugs produced significantly shorter self-reported sleep latencies and longer self-reported sleep durations than placebo. Self-reported sleep latency was significantly shorter with zolpidem than with trazodone. During Week 2, only the zolpidem group maintained a significantly shorter sleep latency than the placebo group, and self-reported sleep duration did not vary significantly among groups. The incidence of adverse events was low in all groups. Both trazodone and zolpidem improved self-reported sleep latency and duration of non-depressed, primary insomniacs; zolpidem was somewhat more efficacious at the doses studied. © 1998 John Wiley & Sons, Ltd.

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KEY WORDS — insomnia; hypnotic efficacy; trazodone; zolpidem

INTRODUCTION

Insomnia may be defined as the experience of inadequate quality and quantity of sleep together with negative daytime consequences (American Sleep Disorders Association, 1990). Most estimates place the annual national prevalence of insomnia in the range of 30–35% (Mellinger *et al*., 1985). Such values include transient and short-term insomnia, both of which occur for short periods of time (no more than 4 weeks), usually as a consequence of exogenous influences (Gillin and Byerley, 1990). When other etiological factors like medical or psychiatric disorders, medications, environmental factors, or circadian rhythm disturbances have been ruled out and the disturbance persists for more than one month, the diagnosis (DSMIII-R) of primary chronic insomnia applies (Gillin and Byerley, 1990). Present awareness indicates that insomnia is widely under-diagnosed and its medical and socioeconomic significance is underestimated (Gallup Organization, 1995; Walsh *et al*., 1995).

Insomniacs are treated with psychotherapeutic, pharmacological, and behavioral approaches (Lacks and Morin, 1992). Short-acting hypnotics like the benzodiazepines (Roth and Roehrs, 1992), triazolam and temazepam or the imidazopyridine zolpidem (Scharf *et al*., 1994), are generally indicated for pharmacological treatment. Due to the

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real or perceived apprehension about potential for adverse reactions, dependence, and/or withdrawal effects associated with use of hypnotics, particularly the benzodiazepines (Woods *et al.*, 1992), there has been a growing trend to use other drugs with sedative properties to treat insomnia (Walsh and Engelhardt, 1992). Such drugs include sedative antidepressants, especially trazodone, at doses lower than those used in the treatment of depression. Previous studies indicate that trazodone improves the sleep of depressed patients (Nierenberg *et al.*, 1994; Wheatley, 1984); however, few data are available in non-depressed insomniacs. The objective of this study was to compare the hypnotic efficacy of trazodone 50 mg, zolpidem 10 mg, and placebo in patients with primary insomnia.

METHODS

Patients

After Institutional Review Board approval of the protocol, patients were recruited primarily via media advertisements. Male and female adults 21–65 years old were enrolled after providing written informed consent if they met the following 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. Additionally, complaints of significant daytime fatigue or decreased daytime functioning as a result of poor sleep must have been reported.

Screening involved a physical examination, medical history and clinical laboratory assessment. 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 Metropolitan Life Insurance Table, pregnancy or risk of becoming pregnant, and lactation, excluded patients from participation. A recent history of drug addiction, alcoholism or drug abuse, a history of sensitivity to CNS depressants, regular use of any medication that would interfere with the study, use of any investigational drug within 30 days of study entry, and previous use of zolpidem, also precluded participation. Benzodiazepines or over-the-counter sleep medication had to be discontinued for 7–25 days, depending upon duration of action. Finally, a positive urine drug screen for CNS-active drugs, participation in a weight loss program, shift work or any other regularly changing sleep schedule, precluded study participation.

A total of 589 patients met entry criteria and entered the study. Based on daily sleep questionnaires completed for a 1-week, single-blind placebo lead-in period, patients meeting the following two criteria on each of at least 3 nights were allowed to continue: (1) SSL of at least 30 min, and (2) SSD of 4–6 h. Three hundred and six patients were randomized to treatment: 104 to placebo, 102 to zolpidem and 100 to trazodone. Twenty-eight patients discontinued during double-blind treatment (7 placebo, 11 zolpidem, 10 trazodone): 12 for adverse events (2 placebo, 5 each for zolpidem and trazodone), one patient for an abnormal laboratory value (zolpidem), and 15 patients for administrative reasons or protocol violations. Thus, the final study sample included 278 patients (97 placebo, 91 zolpidem, and 90 trazodone); 193 patients (63 per cent) were female, and 253 (84 per cent) were Caucasian.

Study Design and Procedures

The study was a double-blind, randomized, parallel-group, placebo-controlled trial conducted at 10 U.S. sites. The double-blind treatment period was 14 days with weekly office visits. Patients were instructed to maintain a regular work and activity schedule, avoid naps, consume minimal alcohol, and have no caffeine after 15:00 hours. They were also instructed to maintain their normal bedtime and to take one capsule with water each night prior to going to bed. During the treatment period, patients completed a daily evening questionnaire within 1 h of going to bed and a daily morning questionnaire within 30 min of rising. At each weekly office visit, urine was collected for drug screen (analyzed at the investigator's discretion), and patients completed a global impressions questionnaire and the Sheehan Disability Scale. The investigator completed a clinical global impressions questionnaire. At the end of treatment, patients underwent a complete physical examination and clinical laboratory assessment.

Efficacy measures

The primary efficacy measures, taken from the morning questionnaire, were the patient's

numerical estimate of SSL (time required to fall asleep) and SSD.

Secondary measures obtained from the same questionnaire were: ease of falling asleep, number of awakenings, wake time after sleep onset, quality of sleep, morning sleepiness and ability to concentrate in the morning. The patient's global impressions included ratings of severity of illness, therapeutic effect and intensity of side effects. On the Sheehan Disability Scale patients rated the disruption caused by insomnia on their work, social life or family life. Number of awakenings and subjective wake time after sleep onset required numerical responses. Ease of falling asleep and next-morning sleepiness were assessed by 100 mm visual analog scales; all other measures were categorical in nature.

Safety assessments

Spontaneous reports of adverse events, pre-and post-treatment changes in results of physical examination and laboratory tests, and any other clinically significant changes were recorded during each office visit.

Statistical methods

For each continuous efficacy measure, an ANOVA model was used to test for the effects of treatment, center, and treatment-by-center interaction. In the event of significant effects observed with ANOVA, pairwise comparisons were performed using Fisher's least significant difference test. Because of the skewed SSL distribution, the natural logarithm was used in the analyses. Additional analyses using Cox's proportional hazards model and the Wald χ^2 statistic (a type of survival analysis) were performed on SSL values, since some of the values had to be censored (e.g. a report of no sleep), and are the analyses for which p values are reported below. Paired comparisons were made using contrasts. Primary efficacy variable analyses performed on change-from-baseline values produced identical results and are not reported here.

The Cochran-Mantel-Haenzel (CMH) test was used to compare the distributions of categorical data across treatment groups, with the exception of 'quality of sleep' collected on the daily questionnaire. If significant treatment effects were observed in the CMH analyses, the treatment groups were compared pairwise, also using the CMH test. ANOVA was used for 'quality of sleep' as it is a more powerful statistic and the sample size was judged to be adequate to assume normal distribution.

Throughout all analyses (except for safety analyses where $p < 0{\cdot}10$ was used), significance was noted if $p < 0{\cdot}05$. All pairwise comparisons were two-sided. To avoid effects of markedly different sample sizes at various study sites, five sites (each with 13–21 patients) were combined to form two for the purpose of analyses. The remaining five sites each accounted for 26–49 patients.

RESULTS

Patient samples

The three treatment groups did not differ significantly in sleep history, gender, age, race, and height, but patients in both the zolpidem and trazodone group weighed significantly less (71·9 kg and 72·2 kg, respectively versus 76·5 kg) than those in the placebo group (P versus Z: $F = 5{\cdot}67$, $df = 1{,}201$, $p < 0{\cdot}018$; P versus T: $F = 5{\cdot}76$, $df = 1{,}199$, $p < 0{\cdot}017$). This difference was not considered to be clinically significant.

Hypnotic efficacy

At baseline, none of the efficacy variables differed among the three treatment groups (Table 1). The results obtained for the two primary efficacy variables, SSL and SSD, are presented in Figures 1 and 2, respectively. There was a significant condition effect for SSL for both treatment weeks ($\chi^2 = 21{\cdot}14$, $df = 2$, $p < 0{\cdot}001$ for week 1 and $\chi^2 = 8{\cdot}08$, $df = 2$, $p < 0{\cdot}018$ for week 2). During

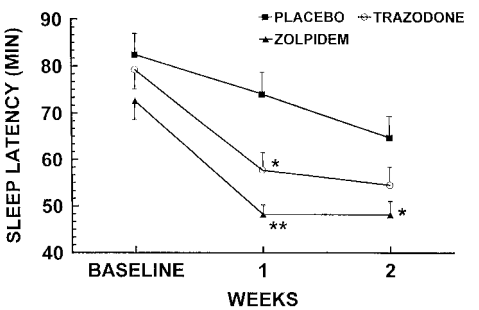

Figure 1. Mean (and standard error bars) self-reported sleep latency for each week for the three treatment groups. Kaplan-Meier estimates are used because of censored data. Significant differences refer to paired comparisons $^{**}p < 0{\cdot}001$; $^{*}p < 0{\cdot}01$ compared to placebo

Table 1. Mean ± SE baseline data for each treatment group

Variable	Placebo ($n = 103$)	Zolpidem ($n = 100$)	Trazodone ($n = 98$)	p-Value
SSL (mins)*	82.4 ± 5.0	72.6 ± 3.8	79.2 ± 4.3	0.3051†
SSD (mins)	319.6 ± 4.3	323.0 ± 4.3	317.2 ± 5.4	0.536
Number of Awakenings	2.1 ± 0.1	2.2 ± 0.2	2.1 ± 0.1	0.960
Wake Time After Sleep Onset (mins)	69.6 ± 4.6	63.3 ± 4.3	66.1 ± 5.0	0.622
Ease of Falling Asleep‡	58.7 ± 1.6	58.1 ± 1.4	61.0 ± 1.8	0.150
Morning Sleepiness§	44.7 ± 1.7	44.4 ± 1.7	44.2 ± 2.0	0.780
Sleep Quality‖	2.94 ± 0.5	2.98 ± 0.04	2.91 ± 0.06	0.806
Ability to Concentrate‖	2.65 ± 0.5	2.50 ± 0.06	2.53 ± 0.06	0.265

*Kaplan Meyer estimate; †p-Value is for proportional hazards model.
‡0 = Very easy; 100 = Not at all easy.
§1 = Very sleepy; 100 = Not at all sleepy.
‖1 = Excellent; 2 = Good; 3 = Fair; 4 = Poor.

treatment Week 1, zolpidem ($\chi^2 = 21{\cdot}08$, $df = 1$, $p < 0{\cdot}001$) and trazodone ($\chi^2 = 6{\cdot}63$, $df = 1$, $p < 0{\cdot}01$) significantly reduced SSL, relative to placebo, by 35 and 22 per cent, respectively. SSL in the zolpidem group (48·2 ± 2·7 min) was also significantly shorter than that in the trazodone group (57·7 ± 4·0 min; $\chi^2 = 4{\cdot}34$, $df = 1$, $p < 0{\cdot}037$). During Week 2, SSL was still significantly shorter for patients treated with zolpidem (48·1 ± 3·1 min) than for patients treated with placebo (64·7 ± 4·6 minutes; $\chi^2 = 7{\cdot}93$, $df = 1$, $p < 0{\cdot}005$), but did not differ significantly from that recorded by patients treated with trazodone (54·5 ± 4·1 min; $\chi^2 = 1{\cdot}12$, $df = 1$, ns). The trazodone group did not differ significantly from the placebo group at Week 2 ($\chi^2 = 3{\cdot}04$, $df = 1$, ns).

Means and standard errors for SSD are plotted in Figure 2. There was a significant treatment effect for SSD during week 1 ($F = 9{\cdot}54$, $df = 2{,}279$, $p < 0{\cdot}001$). Patients treated with zolpidem (Z) or trazodone (T) reported significantly longer SSD (378·8 ± 5·3 and 366·4 ± 6·4 min, respectively) than patients treated with placebo (P) (344·6 + 5·3 min) during Week 1 (Z versus P; $F = 18{\cdot}63$, $df = 1{,}200$, $p < 0{\cdot}001$; T versus P; $F = 7{\cdot}24$, $df = 1{,}199$, $p < 0{\cdot}008$). The main effect of treatment analysis for Week 2 showed a trend toward significance ($F = 2{\cdot}84$, $df = 2{,}263$, $p < 0{\cdot}060$). Paired comparisons showed only the zolpidem versus placebo comparison to be significantly different at Week 2 ($F = 4{\cdot}83$, $df = 1{,}200$, $p < 0{\cdot}02$). It should be noted that there was progressive improvement in the placebo group with an SSD increase of 25 min by the end of Week 1 and a further lengthening to 37 min greater than baseline by Week 2. This is in contrast to an increase from baseline during treatment Week 1 of 55·7 and 49·2 min for zolpidem and trazodone, respectively, which remained essentially unchanged during the second week of treatment.

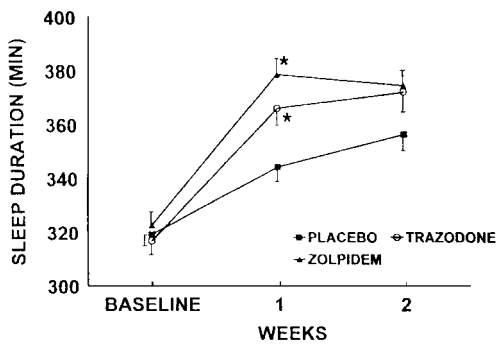

Figure 2. Mean (and standard error bars) self-reported sleep duration for each week for the three treatment groups. Significant differences refer to paired comparisons *$p < 0{\cdot}01$ or better, compared to PBO

Secondary outcome measures from the daily questionnaire are summarized in Table 2. All four parameters showed essentially parallel results. There were no group differences during the baseline week. The two active groups generally differed significantly from the placebo group during the first treatment week, with no difference between zolpidem and trazodone, and there were no significant treatment effects during Week 2 (primarily due to improvement in the placebo group). Patients reported significantly greater Ease of Falling Asleep (0 = very easy; 100 = not at all easy) during Week 1 for zolpidem ($F = 10{\cdot}45$, $df = 1{,}201$, $p < 0{\cdot}001$) and for trazodone ($F = 3{\cdot}95$, $df = 1{,}199$, $p < 0{\cdot}048$) as compared to placebo. Only the

Table 2. Secondary hypnotic efficacy variables (mean ± SE) from morning questionnaire

Treatment week	Assigned treatment			*F*	*p*
	Placebo	Zolpidem	Trazodone		
Ease of Falling Asleep (0 = very easy; 100 = not at all easy)					
Baseline	58·7 (1·7)	58·0 (1·4)	61·0 (1·8)	1·91	ns
Week 1	50·3 (1·9)	40·9 (1·7)*	44·2 (2·2)*	5·33	0·005
Week 2	46·5 (2·1)	44·3 (1·8)	44·0 (2·3)	0·52	ns
Number of awakenings (mean per night)					
Baseline	2·1 (0·1)	2·2 (0·1)	2·1 (0·1)	0·04	ns
Week 1	1·7 (0·1)	1·3 (0·1)*	1·4 (0·1)*	3·26	0·04
Week 2	1·8 (0·1)	1·5 (0·2)	1·4 (0·1)	2·58	ns
Subjective wake time after sleep onset (minutes)					
Baseline	69·6 (4·6)	63·3 (4·3)	66·6 (5·0)	0·48	ns
Week 1	54·5 (3·7)	37·0 (3·3)*	42·0 (3·7)*	6·37	0·002
Week 2	49·8 (4·0)	39·5 (3·6)	42·1 (4·3)	1·59	ns
Sleep quality (1 = excellent; 2 = good; 3 = fair; 4 = poor)					
Baseline	2·92 (0·04)	2·97 (0·04)	2·91 (0·05)	0·22	ns
Week 1	2·64 (0·05)	2·39 (0·05)*	2·40 (0·06)*	5·83	0·003
Week 2	2·56 (0·06)	2·45 (0·05)	2·43 (0·07)	1·15	ns

*Significantly different from placebo on paired comparison ($p < 0·05$).

zolpidem group reported a lower Number of Awakenings ($F = 6·032$, $df = 1,201$, $p < 0·015$) than the placebo group during Week 1. Wake Time After Sleep Onset was significantly lower at Week 1 relative to placebo for both zolpidem ($F = 12·14$, $df = 1,200$, $p < 0·001$) and trazodone ($F = 5·62$, $df = 1,199$, $p < 0·018$). Ratings of sleep quality (1 = excellent; 2 = good; 3 = fair; 4 = poor) at Week 1 for zolpidem ($F = 9·02$, $df = 1,201$, $p < 0·003$) and trazodone ($F = 8·31$, $df = 1,199$, $p < 0·004$) were significantly better than for placebo.

Weekly patient Global Impression ratings are summarized in Table 3. For all four items of the scale, the baseline ratings do not differ among the groups, but the groups differ significantly with respect to patient distribution during both treatment weeks. With the exceptions of 'sleep status' and 'sleep time increase' in the zolpidem group during treatment Week 2, the distributions of both active treatment groups were significantly different from those in the placebo group. The distributions of the zolpidem and trazodone groups did not differ from each other for any item at either time point.

The proportion of patients rating their sleep status as 'excellent' or 'good' during the first week of treatment was 56 per cent for zolpidem ($\chi^2 = 19·12$, $df = 1$, $p < 0·001$) and 47 per cent for trazodone ($\chi^2 = 18·49$, $df = 1$, $p < 0·001$), compared to 32 per cent for placebo. During Week 2, the distributions slightly shifted in that 37 per cent of placebo patients rated their sleep either 'excellent' or 'good' , whereas the corresponding values for zolpidem and trazodone were 54 and 52 per cent, respectively (Z versus P: $\chi^2 = 6·83$, $df = 1$, ns; T versus P: $\chi^2 = 8·40$, $df = 1$, $p < 0·038$). Similarly, a significantly larger proportion of patients rated their sleep improved either 'a lot' or 'somewhat' after treatment with zolpidem (78 and 66 per cent for Week 1 and 2, respectively; $\chi^2 = 25·11$, $df = 1$, $p < 0·001$ and $\chi^2 = 9·80$, $df = 1$, $p < 0·044$) or with trazodone (74 and 69 per cent for Week 1 and 2, respectively; $\chi^2 = 18·49$, $df = 1$, $p < 0·001$ and $\chi^2 = 11·18$, $df = 1$, $p < 0·025$) when compared to placebo (47 and 56 per cent). The number of patients that rated their time to fall asleep decreased either 'a lot' or 'somewhat' was significantly larger for both zolpidem ($\chi^2 = 16·72$, $df = 1$, $p < 0·002$ and $\chi^2 = 11·12$, $df = 1$, $p < 0·025$) and trazodone ($\chi^2 = 10·34$, $df = 1$, $p < 0·035$ and $\chi^2 = 18·59$, $df = 1$, $p < 0·001$) than for placebo during both treatment weeks. Lastly, the number of patients that perceived their sleep time increased either 'a lot' or 'somewhat' was greater than placebo during both weeks for trazodone ($\chi^2 = 13·66$, $df = 1$, $p < 0·008$ and $\chi^2 = 13·04$, $df = 1$, $p < 0·011$), but only during Week 1 for

Table 3. Patient global impression of effect of therapy: number of patients (per cent) responding

Treatment week	Assigned treatment			χ^2	p
	Placebo ($n = 101$)	Zolpidem ($n = 98$)	Trazodone ($n = 93$)		
Sleep status (excellent and good)					
Baseline	10 (9·9)	10 (10·2)	14 (15·0)	9·37	ns
Week 1	32 (31·7)	56 (56·2)*	44 (47·3)*	27·48	0·001
Week 2	35 (36·5)	49 (53·8)	47 (52·2)*	16·77	0·01
Sleep improvement (a lot and somewhat)					
Baseline	18 (17·8)	15 (15·3)	23 (24·8)	13·61	ns
Week 1	47 (46·5)	76 (77·5)*	69 (74·2)*	30·40	0·001
Week 2	44 (45·8)	60 (66·0)*	62 (68·8)*	15·60	0·048
Time to fall asleep (shortened a lot and shortened somewhat)					
Baseline	17 (17)	13 (13·3)	16 (17·2)	6·32	ns
Week 1	38 (37·6)	64 (65·3)*	52 (55·0)*	21·58	0·006
Week 2	40 (41·6)	56 (61·5)*	50 (55·5)*	27·67	0·001
Sleep time (increased a lot and increased somewhat)					
Baseline	19 (18·8)	13 (13·3)	17 (18·3)	4·66	ns
Week 1	46 (45·5)	70 (71·4)*	61 (65·6)*	20·85	0·008
Week 2	42 (43·8)	56 (61·5)	61 (67·8)*	15·54	0·049

*Paired comparison is significantly different from placebo ($p < 0·05$). See text for χ^2 values.

zolpidem ($\chi^2 = 15·87$, $df = 1$, $p < 0·003$ and $\chi^2 = 7·69$, $df = 1$, ns).

Investigators were asked to rate severity of illness (7 point scale), at baseline and at each patient office visit. In the combined categories reflecting 'mild to no illness', baseline distributions for placebo, zolpidem and trazodone were 8, 11 and 11 per cent, respectively. The corresponding values at Week 1 were 32, 54 and 46 per cent, a significant difference among groups in patient distribution ($\chi^2 = 26·80$, $df = 2$, $p < 0·003$). Zolpidem ($\chi^2 = 20·05$, $df = 1$, $p < 0·001$) and trazodone ($\chi^2 = 21·207$, $df = 1$, $p < 0·001$) group distributions favored the 'less ill' end of the scale at Week 1. At treatment Week 2, there were no significant differences among groups.

Impact on ability to function

The daily morning ratings of sleepiness did not differ among groups at any time point during the study. At the weekly office visits, patients were asked to rate the disruption caused by the symptoms of their sleep problem on their work, social life and family life by using the ten-point Sheehan Disability Scale (0 = not at all, 10 = extremely). No significant differences were observed among the groups with respect to the patient distribution in these categories at baseline or at any time of treatment. This was expected as the study was not powered for this outcome measure. At baseline, approximately 88 per cent of the patients felt that their sleep disturbances disrupted their work, social life, or family life to some extent. This percentage fell to between 70 and 75 at treatment week 2, regardless of group.

Side effects/safety

Twelve randomized patients (two placebo, five zolpidem and five trazodone) withdrew from the study because of adverse events, which consisted of excessive sleepiness, dizziness, drowsiness, headache, vomiting and mild elevation of blood pressure. Treatment-emergent adverse events were reported by 68 (65·4 per cent) of placebo patients, 78 (76·5 per cent) of zolpidem patients and 75 (75 per cent) of trazodone patients. The adverse events with the highest incidence rates were headache (placebo 19 per cent, zolpidem 24 per cent, trazodone 30 per cent) and somnolence (placebo 8 per cent, zolpidem 16 per cent, trazodone 23 per cent).

For the side effects of therapy, investigators rated the three groups equally at baseline. The two active treatment groups had significantly more side effects than the placebo group during both treatment weeks, but there was no difference between active drugs. The percentage of patients with side effects

at treatment Week 2 were 89, 71 and 69 per cent for the placebo, zolpidem ($\chi^2 = 9{\cdot}46$, $df = 3$, $p < 0{\cdot}024$) and trazodone ($\chi^2 = 11{\cdot}94$, $df = 3$, $p < 0{\cdot}003$) groups, respectively.

DISCUSSION

Based on subjective outcome measures, the present study showed zolpidem 10 mg and trazodone 50 mg to be effective hypnotics for the short-term treatment of patients with primary insomnia. After one week of treatment, both zolpidem and trazodone produced significantly shorter SSL than placebo, with zolpidem producing significantly shorter SSL than trazodone. By treatment Week 2, only the zolpidem group had a significantly shorter SSL than the placebo group and the zolpidem and trazodone groups did not differ from each other. Both drugs were also rated efficacious in significantly prolonging SSD compared to placebo during Week 1, but not during treatment Week 2. The loss of statistical significance appears to be primarily due to improvement in the placebo group as a function of time.

Some caution regarding over-generalization of these results is warranted as only a single dose of each drug was studied. The 10 mg zolpidem dose is the recommended dose for the patient sample investigated, and the results are in agreement with previous studies reporting subjective and objective hypnotic efficacy (Scharf *et al*., 1994; Dockhorn and Dockhorn, 1996; Fleming *et al*., 1995; Kryger *et al*., 1991; Walsh *et al*., 1990). On the other hand, the objective hypnotic efficacy of 50 mg trazodone, although fairly commonly used for insomnia in clinical practice, remains to be established. In one small study of self-reported poor sleepers (Montgomery *et al*., 1984), low dose trazodone did not improve objective total sleep time or sleep latency. Evaluation of multiple doses of trazodone would be helpful in more clearly determining the potential role of trazodone in the treatment of primary insomnia, not only with respect to efficacy, but also the rate of side effects for other doses. Polysomnographic measures would be particularly appropriate as they are more sensititve than subjective estimates in differentiating two active drugs or multiple doses of active drug.

For the secondary efficacy variables, groups treated with zolpidem or trazodone perceived their sleep as significantly better than the placebo group only at treatment Week 1, with the two active groups not differing. After 2 weeks, the active treatment groups did not differ from placebo. Once again, this change was primarily due to improvement in the placebo group rather than a perceived loss of efficacy. Other studies (Scharf *et al*., 1994; Fleming *et al*., 1995; Kryger *et al*., 1991) with both subjective and objective measures of sleep, have shown an absence of tolerance development with zolpidem.

Contrary to the variables assessed by the daily questionnaire, patient's and physician's Global Impression ratings indicated that the beneficial impact of both zolpidem and trazodone was maintained over the 2-week treatment period. A reasonable explanation for this difference is that overall impressions would include judgements of sleep quality as well as quantity. Once again, there were minimal differences between the two active treatment groups.

The patient sample in the present study consisted of chronic primary insomniacs based on randomization criteria that were particularly stringent. In association with daytime complaints, patients were required to report a sleep latency of greater than 30 min together with a total sleep time of 4–6 hours on 3 out of 7 nights of single-blind placebo treatment to be included in the study. The severity of this requirement is confirmed by the fact that 283 patients out of 589 did not meet these criteria and is reflected in a baseline SSL of approximately 70 min and a SSD of approximately 5 h. In demographic aspects, the patient sample appears to be representative of patients with chronic insomnia consisting of two-thirds females, with a mean age of 42 years.

The incidence rates of treatment-emergent adverse events in the three treatment groups were similar and in accordance with this patient population and the use of hypnotics. Both drugs were well tolerated at the doses studied.

In conclusion, it appears that both zolpidem 10 mg and trazodone 50 mg improve the sleep of non-depressed primary insomniacs. Because of the significantly shorter SSL with zolpidem compared to trazodone and placebo (Week 1), and the persistence of a difference between zolpidem and placebo for 2 weeks, zolpidem may have some advantages over trazodone for the management of primary insomnia at the doses investigated.

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REFERENCES

American Sleep Disorders Association (1990). *International Classiification of Sleep Disorders: Diagnostic and Coding Manual*. Diagnostic Classification Steering Committee, Thorpy M. J., Chairman. Rochester, M. N., American Sleep Disorders Association, pp. 28–35.

Dockhorn, D. and Dockhorn, R. (1996). Zolpidem in the treatment of short-term insomnia: a randomized, double-blind, placebo-controlled clinical trial. *Clinical Neuropharmacology*, **19**(4), 333–340.

Fleming, J., Moldofsky, H., Walsh, J. K., Scharf, M., Nino-Murcia, G. and Radonjic, D. (1995). Comparison of the residual effects of short-term zolpidem, flurazepam and placebo in patients with chronic insomnia. *Clinical Drug Investigation*, **9**, 300–313.

Gallup Organization (1995). *Sleep in America, 1995*. Gallup. Princeton, New Jersey.

Gillin, J. C. and Byerley, W. F. (1990). The diagnosis and management of insomnia. *New England Journal of Medicine* **322**, 239–248.

Kryger, M. H., Steljes, D., Pouliott, Z., Neufeld, H. and Odynski, T. (1991). Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. *Sleep*, **14**, 399–407.

Lacks, P. and Morin, C. M. (1992). Recent advances in the assessment and treatment of insomnia. *Journal of Consulting and Clinical Psychology*, **60**, 586–594.

Mellinger, G. E., Balter, M. B. and Uhlenhuth, E. H. (1985). Insomnia and its treatment. *Archives of General Psychiatry*, **42**, 225–232.

Montgomery, I., Oswald, K., Adam, M. and Adam, K. (1984). Trazodone enhances sleep in subjective quality but not in objective duration. *British Journal of Clinical Pharmacology*, **16**, 139–144.

Nierenberg, A. A., Adler, L. A., Peselow, E., Zornberg, G. and Rosenthal, M. (1994). Trazodone for antidepressant-associated insomnia. *American Journal of Psychiatry*, **151**, 1069–1072.

Roth, R. and Roehrs, T. (1992). Issues in the use of benzodiazepine therapy. *Journal of Clinical Psychiatry*, **53** (Suppl.), 14–18.

Scharf, M. B., Roth, T., Vogel, G. W. and Walsh, J. K. (1994). A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *Journal of Clinical Psychiatry*, **55**(5), 192–199.

Walsh, J. and Engelhardt, C. L. (1992). Trends in the pharmacologic treatment of insomnia. *Journal of Clinical Psychiatry*, **53** (Suppl.), 10–18.

Walsh, J. K., Engelhardt, C. L. and Hartman, P. G. (1995). The direct economic cost of insomnia. In *Hypnotics and Anxiolytics. Bailliere's Clinical Psychiatry*, D. J. Nutt and W. Mendelson (Eds), Bailliere Tindall: London, pp. 369–381.

Walsh, J. K., Schweitzer, P. K., Sugerman, J. L. and Muehlbach, M. J. (1990). Transient insomnia associated with a 3-hour phase advance of sleep time and treatment with zolpidem. *Journal of Clinical Psychopharmacology*, **10**(3), 183–189.

Wheatley, D. (1984). Trazodone: alternative dose regiments and sleep. *Pharmatherapeutica*, **3**(9), 607–612.

Woods, J. J., Katz, J. and Winger, C. (1992). Benzodiazepines: use, abuse and consequences. *Pharmacological Review*, **44**, 151–347.

