Sleep, 14(5):399–407

Subjective Versus Objective Evaluation of Hypnotic Efficacy: Experience with Zolpidem

M. H. Kryger, D. Steljes, Z. Pouliot, H. Neufeld and T. Odynski

Section of Respiratory Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

Summary: There is little published literature on the correlation between subjective and objective efficacy of hypnotics. We wanted to determine whether there was a correlation between the patient's subjective evaluation of the efficacy of the hypnotic with the polysomnographic (PSG) findings. We studied 16 patients with chronic insomnia (sleep latency, ≥30 minutes; total sleep time, >240 but <420 minutes) for 11 nights who took placebos on nights 1 and 2, zolpidem (imidazopyridine) on nights 3–9 and placebo on nights 10 and 11. Patients completed a questionnaire each morning following PSG, which evaluated subjective sleep quality, sleep latency and total sleep time. These data were compared to PSG findings to answer specific questions about sleep latency reduction, efficacy of the hypnotic after a week's use, sleep quality after discontinuing the drug, and any correlation between subjective and objective measures. PSG findings indicated a shortened sleep latency, increased total sleep time, decreased total wake time and increased sleep efficiency when patients ingested zolpidem 30 minutes before bedtime. We found that after 7 nights (nights 3–9) the drug was still effective in reducing sleep latency and increasing total sleep time. Upon withdrawal (nights 10 and 11) sleep returned to baseline (nights 1 and 2). Subjectively, the patients confirmed those findings on the questionnaire, as well as a subjective reduction in the number of awakenings and, interestingly, a subjective increase in the time spent awake after sleep. Many of the objective variables we examined correlated highly with the subjective variables. While on zolpidem, subjects believed and were objectively shown to have a decreased sleep latency, increased total sleep time and decreased time awake before persistent sleep, although they tended to overestimate sleep latency and time spent awake before persistent sleep and underestimated total sleep time. Although the correlation between objective and subjective measures was high for the group, in individual patients there was an impressive difference between the two, and the highest coefficient of variation between a subjective and objective measures was 0.453. No correlations were found with subjective measures of refreshing quality of sleep, decrease in number of awakenings, how sleepy patients felt in the morning or their ability to concentrate in the morning. Thus, we believe the PSG remains the keystone in the evaluation of hypnotic efficacy. **Key Words:** Insomnia, hypnotics, polysomnogram, zolpidem

Hypnotic efficacy is usually assessed using objective polysomnographic (PSG) measures. Whether patients actually continue to use a medication depends on their subjective response. We wondered how subjective measures compared with objective measures in the evaluation of hypnotic efficacy. Zolpidem is a recently introduced imidazopyridine sedative–hypnotic. This agent, which is chemically an imidazopyridine, binds selectively only to the type I benzodiazepine recognition site, but not to the other two (type II and type III) benzodiazepine recognition sites to which benzodiazepines also bind (1,2). Because it has a short half-life of elimination (1.5–2.4 hours) (3,4), it theoretically has the features that would result in a short sleep latency with few residual effects the following day. We evaluated this agent with subjective and objective measures to answer the following questions in patients with chronic insomnia: Is sleep latency reduced? Is the agent still efficacious after a week of use? Is there worsening of sleep after discontinuation of the agent? What is the correlation of objective and subjective measures?

Accepted for publication June 1991.
Address correspondence and reprint requests to Dr. M. Kryger, Sleep Laboratory, Room R2008, St. Boniface Research Centre, 351 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada.

METHODS

Screening and patient selection

Patients with insomnia were recruited from a busy family medical practice clinic and by public service announcements on the radio. They were evaluated by standardized detailed history and medical examina-

tion. Those with a history suggestive of sleep apnea (heavy snoring or observed apnea) or restless legs syndrome were excluded from further evaluation. If patients clinically had a sleep latency greater than 30 minutes and a total sleep time of between 4 and 6 hours, following informed consent, they were screened in the sleep laboratory with complete PSG. In addition to the routine neurophysiological variables recorded in sleep studies [electroencephalography (EEG), electrooculography (EOG), electromyography (EMG)], leads were attached to the anterior tibialis to record EMG and the patients were instrumented with Respitrace transducers, an electrocardiograph (EKG), pulse oximeters and CO_2 analyzers in front of the nose and mouth to detect respiratory abnormalities. The recording time was fixed to be 480 minutes from lights out. The data were recorded using a polygraph (Grass Model 78) with a paper speed of 10 mm/second.

On arising every morning, the patients were administered two performance tests: The Digit Symbol Substitution Test and the Symbol Copying Test. Every morning of the study, whether in the sleep lab or at home, the patients also filled in a questionnaire regarding their sleep quality.

After the first adaptation night the patients slept an additional two to three nights in the laboratory. Patients with sleep apnea (apnea/hypopnea index > 5) or periodic movements in sleep (more than five episodes per hour) were excluded from the formal study. To proceed to the formal study patients had to demonstrate, on at least two of the screening nights, a sleep latency of more than 30 minutes and a total sleep time of > 240 minutes but < 420 minutes. Once insomnia was confirmed, subjects began the formal protocol. If insomnia was not confirmed subjects were excluded from further study.

Formal protocol

The formal protocol generally began on the night following the last screening night and consisted of four consecutive nights of PSG in the sleep laboratory, followed by three nights during which the patients were at home, followed by an additional four nights in the sleep laboratory.

Medications

The patients received and were observed to ingest 10 mg zolpidem or placebo 30 minutes before lights out every night they were in the sleep laboratory, including the screening nights. Eighteen subjects who entered the formal study were not told whether they were taking placebo or medication; 16 were on the formal protocol, which consisted of two nights of placebo followed by seven nights of drug, followed by two nights of placebo. PSG was done on nights 1, 2, 3 and 4 (two days placebo followed by two days of drug) and again on nights 8, 9, 10 and 11 (two days of drug followed by two days of placebo). Two subjects received placebo during the entire study and were introduced primarily to blind the experimenters as to which subjects were in the formal protocol and which were not. These two subjects were excluded from further analysis.

In addition to the sleep studies, all of the patients had a urine drug screen done prior to each night's study to exclude chemical ingestion that might confound the results. These urine tests screened for benzodiazepines, opiates, antihistamines and illicit drugs including cocaine and marijuana. Sleep staging was done using standard criteria and the definitions used are described in the appendix. The code of which patients were on drug or placebo was broken after all the PSG data had been analyzed.

Statistical analysis

Two-way analysis of variance was used. For most of the analyses, the independent variables were night number and treatment (drug or placebo) and the dependent variables were the end points measured on PSG. Post-hoc multiple comparisons were done using the Newman/Keul's range test. The data were analyzed using NCSS version 5.0. Linear regression was used to correlate subjective and objective measures.

RESULTS

The demographic characteristics of the 16 patients are presented in Table 1. All had the complaint of insomnia that had been present for 16.2 ± 12.2 (SD) years.

Subjective measurements

Table 2 shows the questions used to determine subjective sleep quality and the results. There was a significant ($p < 0.001$) reduction in subjective sleep latency (questions 1 and 6), with an increase in subjective total sleep time ($p < 0.001$) (question 4) and an improvement in sleep quality ($p < 0.005$) (questions 5 and 7). There was a subjective reduction in the number of awakenings (question 2), although there was an increase in the subjective time spent awake after falling asleep (question 3).

There was no effect on the subjective evaluation of

TABLE 1. *Subject demographics*

Patient number	Sex	Age (years)	Weight (kg)	Height (cm)	Insomnia (years)	BMI[a]
1	M	55	93.6	188	50	26.5
2	F	59	54.5	157.5	31	22.0
3	F	58	68.2	162.6	30	26.0
4	F	56	52.3	152.4	20	21.5
5	M	39	65.9	186.4	7	19.0
6	F	52	52.7	160	7	20.6
7	F	38	47.3	156.2	17	19.4
8	F	43	56.8	158.7	9	22.5
9	F	56	65.9	157.5	10	26.6
10	M	59	88.6	179	20	27.7
11	F	31	65.9	167	16	23.6
12	F	27	86.4	170	7	29.9
13	M	33	76.4	172.7	9	25.6
14	F	33	56.8	172.7	10	19.0
15	F	49	70.5	162.6	8	26.7
16	F	36	61	162	15	23.2
Mean		45.3	66.4	166.6	16.2	23.8
SD		11.4	13.8	10.7	12.2	3.32
17	F	29	61.4	152.4	2.3	
18	M	30	96.4	198	1.5	

[a] Body mass index (kg/m^2).

sleepiness or the ability to concentrate (questions 8 and 9) the following morning.

Objective measurements

As shown in Table 3, zolpidem had a highly significant effect on increasing total sleep time ($p < 0.001$), reducing total wake time ($p < 0.001$) and increasing sleep efficiency ($p < 0.001$).

Latency measures

With zolpidem there was a highly significant reduction in the latency to stage 1 ($p < 0.001$), latency to stage 2 ($p < 0.01$), latency to persistent sleep ($p < 0.001$), wake before persistent sleep ($p < 0.001$) and latency to nonwake ($p < 0.001$). Latency to rapid eye movement (REM) (without wake) was increased, while latency to stages 3 and 4 (without wake) was not affected by the medication.

Maintenance measures

Zolpidem did not have a significant effect on awakenings (Table 4), entries to wake, wake during sleep, wake after sleep and entries to stage 1. Examination of sleep efficiencies for each 1-hour period of the night (Table 4) showed that there was a significant increase in sleep efficiency the first ($p < 0.001$), second ($p < 0.05$), third ($p < 0.05$) and fourth ($p < 0.05$) hours with zolpidem. In hours 5–8 there was no difference between drug and placebo.

Sleep stages

When sleep stage distribution was expressed in minutes, there was an overall significant increase in the absolute amount of stage 2 and slow-wave sleep. The amount of time spent in the other stages including movement time was not affected by medication. When sleep stage was expressed as percentage, percent stage 1 was reduced by treatment. None of the other sleep stages expressed as percent were changed by treatment.

Effect of drug withdrawal

To examine the effect of drug withdrawal, we compared the first postdrug night to the other nights using Newman/Keul's range tests. Differences between the first postdrug night and the other two placebo pretreatment nights are indicated in Table 3.

Total sleep time, time (minutes) spent in stages 3/4 and percent of the night spent in stages 3/4 were decreased on night 10, the first postdrug night.

Latency to stage 1, latency to persistent sleep, time spent awake before persistent sleep and latency to nonwake were all increased slightly on the first postdrug night but returned to baseline on the second night.

Correlation between objective and subjective measures

Table 4 is a correlation grid examining the relationship of subjective and objective measures. For clarity of presentation, only correlations in which $p < 0.001$ have been included. There is correlation between several of the subjective measures and objective measures. Of interest, there were no significant correlations found with subjective measures of refreshing quality of sleep, how sleepy patients felt in the morning, ability to concentrate, or number of awakenings.

Subjective versus objective variables had significant correlation. On zolpidem, subjects did have decreased sleep latency, which they were able to predict, although they still overestimated sleep latency. Similarly, with total sleep time and time spent awake before persistent sleep patients could correlate improvement on drugs even though they in general underestimated total sleep time and overestimated time spent awake before persistent sleep. The highest coefficient of variation (r^2) between subjective and objective measures was only 0.453.

DISCUSSION

We found that 10 mg zolpidem was a highly effective hypnotic with its major effect being a reduction in sleep latency. The only effect on sleep stage was an absolute

TABLE 2. *Subjective evaluation*[a]

			PSG night								Treatment	
			1	2	3	4	8	9	10	11	P	D
How long after bedtime (lights-out) did you fall asleep?	Number (minutes)	Mean	116.56[b]	70.94[b]	**36.56**	**43.44**	**64.38**	**40.94**	170.00[b]	84.06	110.39	**46.33**[c]
		SE	32.33	11.58	6.84	10.52	18.31	11.68	31.11	21.35	13.35	6.27
How many times did you wake up during the night?	Number	Mean	2.75	2.88	**2.19**	**2.00**	**3.19**	**2.44**	3.50	2.75	2.97	**2.45**
		SE	0.50	0.57	0.34	0.37	0.50	0.41	1.13	0.60	0.36	0.21
How much time did you spend awake after falling asleep?	Number (minutes)	Mean	73.31	84.38	**89.44**	**91.56**	**105.50**	**82.81**	87.81	57.00	75.63	**92.33**[c]
		SE	17.90	16.14	25.25	23.13	21.39	17.01	14.31	15.52	7.94	10.74
How long did you sleep last night?	Number	Mean	285.44[b]	298.25[b]	**357.75**	**346.88**	**311.38**	**355.00**	218.50[b]	312.69	278.72	**342.75**[c]
		SE	33.49	25.56	27.73	29.01	32.30	19.45	36.11	31.36	16.20	13.64
How would you describe your sleep last night?	Categories[d]	Mean	3.00	2.63	**2.25**	**2.44**	**3.06**	**2.56**	3.50	2.81	2.98	**2.58**[c]
		SE	0.20	0.18	0.23	0.22	0.17	0.18	0.18	0.21	0.10	0.11
How easy was it for you to fall asleep last night?	VAS[e]	Mean	67.09	58.19	**31.19**	**34.53**	**45.78**	**39.81**	85.25	63.56	68.52	**37.83**[c]
		SE	6.12	4.29	5.60	6.28	7.34	7.05	4.60	6.93	3.01	3.30
How would you evaluate the refreshing quality of your sleep last night?	Categories[d]	Mean	2.94[b]	2.81[b]	**2.56**	**2.75**	**2.88**	**2.63**	3.50[b]	2.94	3.05	**2.70**[c]
		SE	0.23	0.16	0.22	0.19	0.18	0.20	0.18	0.21	0.10	0.10
Do you feel sleepy this morning?	VAS[f]	Mean	51.31	47.56	**47.69**	**50.59**	**51.06**	**61.69**	44.78	5.16	49.70	**52.76**
		SE	6.55	3.86	7.09	6.60	7.04	7.28	6.66	6.21	2.94	3.48
How would you describe your ability to concentrate this morning?	Categories[d]	Mean	2.56	2.44	**2.69**	**2.38**	**2.75**	**2.44**	2.75	2.56	2.58	**2.56**
		SE	0.16	0.13	0.20	0.20	0.21	0.20	0.21	0.20	0.09	0.10

[a] PSG = sleep study; P = placebo; D = drug; SE = standard error. Bold entries indicate treatment with drug.
[b] Night 1, 2 or both are significantly different from night 10 using Newman/Keul's range test.
[c] Drug night is significantly different from placebo night using Newman/Keul's range test.
[d] Categories: 1 = excellent; 2 = good; 3 = fair; 4 = poor.
[e] VAS (visual analog scale): 0 = very easy; 100 = not at all easy.
[f] VAS (visual analog scale): 0 = very sleepy; 100 = not at all sleepy.

increase in the amount of stage 2 and stages 3/4. There was no effect on the distribution of sleep stages when expressed as percent. Effectiveness of the medication was maintained over the 1-week administration period. Generally, withdrawal of the medication after a week's use resulted in a return to the previous sleep. There were no significant changes in sleep maintenance parameters or sleep efficiency. The mean increase in latency to persistent sleep was only 10 minutes on the first posttreatment night and there was no difference on the second posttreatment night.

Noteworthy was the finding that the effect of the medication was primarily in the first 4 hours of the night. This is consistent with the pharmacokinetics of zolpidem, which has a mean plasma half-life of 2.4 ± 0.2 hours. In spite of the short half-life we did not find that zolpidem resulted in an increase over placebo in early morning awakenings, as indicated by a lack of differences in the sleep efficiency from hours 5–8 of the night.

Our results are consistent with results in both normals and insomniacs treated with zolpidem. Normals had increased total sleep time, decreased sleep latency, increased REM latency and fewer awakenings compared to insomniacs treated with zolpidem (5,6). On withdrawal of treatment, normals had no differences in total sleep time, decreased sleep latency, REM latency, number of awakenings or amount of slow-wave sleep compared to a placebo group (6). Similar findings occurred in the Monti study of insomniacs comparing pre- to posttreatment with the exception that the absolute number of minutes of slow-wave sleep was less on withdrawal, although this was not statistically significant (5). Normals and insomniacs on treatment

TABLE 3. *Objective evaluation of sleep*[a]

		PSG night								Treatment	
		1	2	3	4	8	9	10	11	P	D
Overall measures											
Total sleep time	Mean	357.56	395.51[b]	**411.06**	**412.34**	**399.19**	**413.13**	352.81[b]	377.97	371.06	**408.93**[c]
	SE	23.09	12.15	15.50	12.53	14.65	11.37	20.68	21.39	9.89	6.68
Total wake time	Mean	121.91	83.94	**62.69**	**67.69**	**80.91**	**66.78**	127.00	101.31	108.54	**69.52**[c]
	SE	23.18	12.32	13.82	12.49	14.68	11.32	20.71	21.41	9.93	6.47
Sleep efficiency	Mean	74.60	82.52	**86.96**	**85.89**	**83.16**	**86.09**	73.53	78.86	77.38	**85.52**[c]
	SE	4.83	2.56	2.87	2.61	3.05	2.36	4.31	4.46	2.07	1.35
Symbol copying test	Mean	243.88	248.13	**247.31**	**239.38**	**244.25**	**242.44**	245.25	252.13	247.34	**243.34**
	SE	8.65	8.59	9.81	8.96	10.46	9.40	9.84	9.57	4.50	4.73
Digit symbol substitution test	Mean	104.00	106.13	**106.25**	**107.81**	**106.19**	**109.31**	108.06	111.31	107.38	**107.39**
	SE	5.57	4.65	4.51	6.05	4.58	3.97	6.44	6.23	2.83	2.37
Latency measures											
Latency to stage 1	Mean	57.50	28.66[b]	**19.31**	**16.38**	**24.03**	**18.66**	55.78[b]	40.74	45.67	**19.59**[c]
	SE	11.43	5.06	4.43	3.58	5.88	3.84	16.36	8.41	5.63	2.23
Latency to stage 2	Mean	67.41	40.88	**24.03**	**24.16**	**23.22**	**22.25**	61.63	43.69	53.40	**23.41**[c]
	SE	13.03	6.88	4.83	4.71	4.37	3.74	16.34	8.25	5.91	2.16
Latency to persistent sleep	Mean	71.91	48.44[b]	**22.91**	**23.16**	**24.84**	**23.75**	81.88[b]	45.50	61.93	**23.66**[c]
	SE	12.90	7.55	4.69	4.90	4.81	4.00	19.65	8.71	6.68	2.25
Wake before persistent sleep	Mean	68.19	41.75[b]	**20.78**	**21.19**	**21.28**	**20.28**	74.59[b]	42.97	56.88	**20.88**[c]
	SE	12.65	6.30	4.60	4.62	4.53	3.71	18.32	8.54	6.30	2.14
Latency to REM	Mean	79.22	72.28	**88.81**	**85.59**	**94.56**	**95.03**	75.95	63.94	72.85	**91.00**[c]
	SE	6.92	8.47	9.97	10.52	11.34	9.83	12.43	4.73	4.26	5.12
Latency to SWS	Mean	18.09	21.59	**17.88**	**16.72**	**23.81**	**15.47**	20.44	14.63	18.69	**18.47**
	SE	1.32	4.21	2.03	2.23	5.53	1.76	3.26	1.86	1.45	1.65
Latency to nonwake	Mean	57.50	28.66[b]	**19.31**	**16.38**	**17.78**	**18.66**	55.78[b]	40.56	45.63	**18.03**[c]
	SE	11.43	5.06	4.43	3.58	3.98	3.84	16.36	8.45	5.63	1.94
Maintenance measures											
Awakenings	Mean	6.38	5.63	**5.88**	**5.19**	**5.69**	**6.63**	6.00	5.00	5.75	**5.84**
	SE	1.24	1.18	1.10	0.89	0.79	1.00	0.84	0.82	0.51	0.47
Entries to wake	Mean	11.94	10.88	**11.19**	**9.63**	**12.56**	**12.69**	11.88	10.19	11.22	**11.52**
	SE	2.17	1.87	1.88	1.48	1.65	**2.05**	1.89	1.66	0.94	0.88
Wake during sleep	Mean	50.88	24.88	**36.81**	**40.59**	**45.97**	**40.00**	49.53	47.66	43.23	**40.84**
	SE	14.64	5.48	10.56	12.06	12.14	10.28	11.28	15.77	6.22	5.53
Wake after sleep	Mean	2.84	17.31	**5.09**	**5.91**	**13.66**	**6.50**	2.88	10.69	8.43	**7.79**
	SE	1.43	9.74	1.93	2.68	10.17	2.68	1.78	6.46	3.00	2.72
Entries to stage 1	Mean	7.19	7.75	**8.09**	**6.44**	**7.31**	**6.88**	7.38	6.25	7.14	**7.18**
	SE	1.35	1.08	1.14	0.93	0.96	0.90	1.25	1.19	0.60	0.49
Sleep efficiency (%)											
Hour 1	Mean	25.63	36.93	**64.53**	**64.15**	**63.33**	**67.61**	27.76	40.15	32.61	**64.90**[c]
	SE	8.18	7.73	7.54	7.02	7.28	6.55	7.39	7.92	3.89	3.47
Hour 2	Mean	67.17	87.45	**98.24**	**95.58**	**89.32**	**95.52**	71.83	84.74	77.80	**94.66**[c]
	SE	9.24	4.36	0.73	2.47	6.07	1.54	9.47	6.89	3.94	1.70
Hour 3	Mean	79.63	90.58	**95.78**	**98.69**	**96.04**	**91.67**	78.44	85.93	83.64	**95.55**[c]
	SE	6.98	4.60	1.79	0.55	1.48	5.22	7.44	6.63	3.23	1.43
Hour 4	Mean	90.05	95.73	**91.31**	**94.74**	**96.51**	**92.56**	80.36	79.38	86.38	**93.78**[c]
	SE	4.36	1.71	4.54	1.64	1.33	4.51	7.85	8.62	3.18	1.66
Hour 5	Mean	84.59	96.93	**86.73**	**87.87**	**91.03**	**92.34**	76.82	86.11	86.11	**89.49**
	SE	7.26	1.14	6.43	6.56	2.08	2.28	8.49	6.80	3.33	2.38
Hour 6	Mean	81.25	91.72	**90.01**	**82.61**	**78.54**	**85.83**	73.70	87.04	83.43	**84.25**
	SE	8.27	3.17	3.75	7.46	8.59	6.93	8.65	6.84	3.55	3.42
Hour 7	Mean	83.18	83.50	**85.84**	**84.79**	**74.07**	**83.39**	89.85	86.04	85.64	**82.02**
	SE	7.53	7.47	7.24	7.16	10.17	7.19	2.90	5.48	3.02	3.97
Hour 8	Mean	85.45	78.01	**83.68**	**78.68**	**75.83**	**82.06**	89.41	81.48	83.59	**80.06**
	SE	4.72	7.74	5.54	6.86	7.55	5.00	4.35	8.17	3.21	3.11
Staging (minutes)											
Stage 1	Mean	28.44	33.50	**30.06**	**24.03**	**29.00**	**26.34**	35.00	19.34	29.07	**27.36**
	SE	5.97	6.52	6.15	3.68	4.86	4.44	9.42	3.64	3.36	2.39
Stage 2	Mean	177.00	184.81	**216.00**	208.88	**213.47**	**217.38**	182.25	186.25	182.58	**213.93**[c]
	SE	14.43	10.56	14.89	11.96	14.15	13.55	14.23	12.79	6.40	6.69
Stages 3/4	Mean	72.13	87.88[b]	**89.44**	**91.72**	**80.28**	**83.63**	58.38[b]	85.34	75.93	**86.27**[c]
	SE	7.59	8.81	6.65	5.82	6.20	6.87	8.10	7.99	4.24	3.17
Stage REM	Mean	74.25	83.88	**75.97**	**81.78**	**69.13**	**79.16**	71.50	79.44	77.27	**76.51**
	SE	5.34	5.84	5.34	5.15	7.13	4.83	7.13	6.34	3.08	2.84
Movement	Mean	5.78	5.66	**5.84**	**5.97**	**7.31**	**6.63**	5.69	5.09	5.55	**6.44**
	SE	0.99	0.90	0.86	0.94	0.86	0.92	0.92	0.80	0.44	0.44

TABLE 3. *Continued*

		PSG night								Treatment	
		1	2	3	4	8	9	10	11	P	D
Staging (percent)											
Stage 1	Mean	8.57	9.07	**7.71**	**6.09**	**7.54**	**6.61**	10.70	6.24	8.65	**6.99**
	SE	1.67	2.02	1.74	0.99	1.27	1.21	2.68	1.10	0.97	0.66
Stage 2	Mean	48.81	46.60	**51.08**	**50.31**	**52.76**	**52.13**	52.04	49.27	49.18	**51.57**
	SE	1.98	1.97	2.43	1.82	2.03	2.30	2.73	2.04	1.10	1.06
Stages 3/4	Mean	19.81	22.09[b]	**21.66**	**22.48**	**20.91**	**20.48**	16.18[b]	22.78	20.21	**21.38**
	SE	1.46	2.03	1.66	1.48	2.08	1.69	1.95	1.74	0.94	0.86
Stage REM	Mean	21.16	20.81	**18.20**	**19.68**	**16.96**	**19.11**	19.38	20.29	20.41	**18.49**
	SE	1.01	1.21	1.15	1.02	1.54	1.03	1.43	1.26	0.61	0.60
Movement	Mean	1.68	1.43	**1.39**	**1.43**	**1.82**	**1.64**	1.70	1.43	1.56	**1.57**
	SE	0.26	0.22	0.20	0.23	0.20	0.25	0.28	0.22	0.12	0.11

[a] PSG = sleep study; P = placebo; D = drug; SE = standard error, REM = rapid eye movement sleep, SWS = slow-wave sleep. Bold entries indicate treatment with drug.
[b] Night 1, 2 or both are significantly different from night 10 using Newman/Keul's range test.
[c] Drug night is significantly different from placebo night using Newman/Keul's range test.

agreed subjectively that sleep latency was decreased, total sleep time increased and the number of awakenings was the same or less on treatment.

Subjective changes

Few studies have examined the relationship between subjective and objective measures of sleep. Carskadon et al. (7) compared objective and subjective findings in untreated insomniacs and their findings were similar to ours: subjects underestimated total sleep time and the number of arousals and consistently overestimated sleep latency. As did we, they found a highly significant correlation between subjective and objective measures for total sleep time and sleep latency, but no correlation for nocturnal arousals. Lewis (8) found that normals underestimated total sleep time but overestimated sleep latency and the number of awakenings. We found that our insomnia patients also underestimated total sleep time and overestimated sleep latency, but in contrast to the above study the subjects also underestimated the number of awakenings. These differences may be

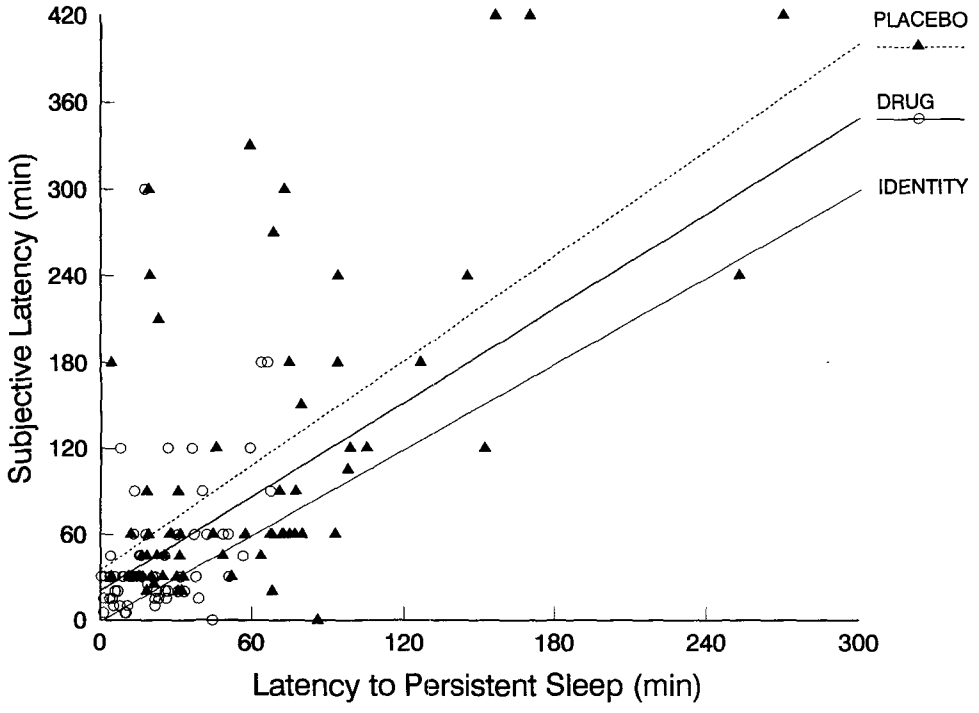

FIG. 1. Subjective and objective sleep latency in 16 patients on drug and placebo.

TABLE 4. *Correlation grid of subjective vs. objective findings*[a]

	Subjective							
	Latency	Time awake after sleep	Sleep time	Sleep quality	Ease falling asleep	Refreshing quality of sleep	Morning sleepiness	Able to concentrate
Overall measures								
Total sleep time	−0.5535		0.6623	−0.5005	−0.4300	−0.4274		−0.2641
Total wake time	0.5575		−0.6724	0.5228	0.4297	−0.4682		0.2731
Sleep efficiency	−0.5581		0.6730	−0.5232	−0.4301	−0.4686		−0.2731
Latency measures								
Latency to stage 1	0.5481		−0.3418	0.2838	0.4591	0.3351	−0.3505	0.3304
Latency to stage 2	0.5747		−0.3480		0.5113	0.3550	−0.3277	0.2997
Persistent sleep	0.6411		−0.4018	0.3112	0.5492	0.3808	−0.2984	0.3480
Wake before persistent sleep	0.6388		−0.3986	0.3155	0.5461	0.3831	−0.3070	0.3300
Latency to REM								
Latency to SWS								
Latency to nonwake	0.5464		−0.3107		0.4683	0.3278	−0.3138	0.2922
Maintenance measures								
Awakenings		0.4525						
Entries to wake		0.5280	−0.2930	0.3164				
Wake during sleep		0.3604	−0.5379	0.4256		0.3516		
Entries to stage 1		0.3449						
Sleep efficiency								
Hour 1	−0.4659				−0.5625	−0.3025	0.3582	−0.2719
Hour 2	−0.5971		0.4042	−0.2890	−0.4701	−0.3252	0.2455	−0.2650
Hour 3	−0.4528		0.4023	−0.3468	−0.4185	−0.3287		
Hour 4			0.3841	−0.3223		0.2848		
Hour 5	−0.4070		0.4208	−0.3337				
Hour 6	−0.3313	−0.3238	0.5221	−0.4203		−0.3043		
Hour 7		−0.3887	0.3719	−0.2978		−0.2341		
Hour 8		−0.4803	0.3133					
Staging (minutes)								
Stage 1		0.4493		0.3376		0.2596		
Stage 2	−0.3720		0.5236	−0.3873	−0.3294	−0.3732		
Stages 3/4	−0.3112		0.3349	−0.3938	−0.3252			
Stage REM	−0.3527	−0.4142	0.5526	−0.4574		0.3592		−0.2686
Movement								
Staging (%)								
Stage 1		0.4437	−0.4294	0.4610		0.3712		
Stage 2								
Stages 3/4								
Stage REM		−0.3671	0.2888					
Movement								

[a] Numbers represent regression coefficients. Only values for $p < 0.01$ are included.

r	p
0.2269	=0.01
0.3	$<6.0 \times 10^{-4}$
0.4	$<2.9 \times 10^{-6}$
0.5	$<1.0 \times 10^{-8}$

related to the fact that Lewis only examined awake periods exceeding 1 minute, whereas our epoch length was 30 seconds.

Of interest, Lewis showed that when his normals withdrew from various hypnotics they exaggerated the extent of the "poorness" of sleep. Our patients demonstrated a similar phenomenon. The differences between subjective and objective estimation of sleep latency (to persistent sleep) were 70.9 vs. 48.4 minutes for the last pretreatment night and 170.0 vs. 81.9 minutes for the first withdrawal night.

CONCLUSION

Both the objective and subjective results show that 10 mg zolpidem is an effective hypnotic whose clinical effect is consistent with predictions from its pharmacokinetics. The lack of effects on the morning measurements, low incidence of side effects, lack of effect on the distribution of sleep stages and relatively minor effects in the postdrug nights makes this agent an attractive one for the use in short-term management of insomnia in patients whose main difficulty is in falling

asleep. The objective evaluations paralleled the subjective ones suggesting that compliance would be good for patients using this agent.

In addition, for several of the subjective measures there was correlation with objective findings. This is in spite of the well-known observation that individual subjective measures may be notoriously inaccurate. Figure 1 shows an example. Although there is a high correlation between the subjective sleep latency and the objective latency to persistent sleep, notice in individual cases the huge discrepancy between subjective and objective results. The fact that many of the data points for the placebo nights deviate markedly above the line of identity suggests that subjective evaluation tends to overshoot; estimated latency was usually longer than measured latency. Similar findings were made with the other measures; for example on placebo, estimated sleep time tended to be much less than measured total sleep time. Perhaps one of the reasons why subjective evaluation correlated so well with objective evaluation is that on placebo many subjective measures overshoot, by overestimation of the poor quality of sleep and return toward measured values as sleep improves. Thus the intrinsic noise of subjective measurement seems to be counterbalanced by the increased signal. The utility of subjective evaluation probably also requires a large number of subjects and nights because of the large intersubject variability and intrasubject variability, especially for measures such as the visual analog scale. We agree with Lewis that some useful information of hypnotic effect can be done using subjective measures because for the important variables (total sleep time and sleep latency), the correlations are both significant and positive. However, because the subjective maintenance variables were not reliably correlated with objective ones and because patients cannot give any useful information about sleep architecture, we believe PSG remains the keystone in the evaluation of hypnotic efficacy.

APPENDIX: DEFINITION OF TERMS

Sleep staging was done by using routine criteria (9), and the following definitions were used:

Awakenings. The number of times, after onset of persistent sleep, that there is a wake entry of at least two epochs duration. Each awakening must be separated by a stage 2, 3, 4 or REM.

Entries to stage 1. The number of times, after the onset of persistent sleep, that there is a stage 1 epoch preceded by a stage 2, 3, 4 or REM epoch; or a movement epoch preceded by an epoch of sleep.

Entries to wake. The number of times, after the onset of persistent sleep, that a wake epoch is preceded by a nonwake epoch.

Latency to nonwake (minutes). The number of epochs from the beginning of the recording to the first epoch of nonwake (stage 1, 2, 3, 4 or REM), divided by two.

Latency to persistent sleep (minutes). The number of epochs from the beginning of the recording to the beginning of the first continuous 20 epochs of nonwake divided by two.

Latency to slow-wave sleep without wake (minutes). The number of nonwake epochs from beginning of recording to the first stage 3 or 4, divided by two.

Latency to REM without wake (minutes). The number of nonwake epochs from beginning of recording to the first stage REM, divided by two.

Latency to stage 1 or 2 (minutes). The number of epochs from the beginning of recording to the first epoch of stage 1 or 2 sleep, divided by two.

Percent stage X. The total number of stage X epochs divided by the total number of sleep epochs (includes stages 1, 2, 3, 4, REM and movement), multiplied by 100.

Sleep efficiency (percent). Total sleep time divided by time in bed, multiplied by 100.

Sleep efficiency by hour (percent). The number of sleep epochs (stages 1, 2, 3, 4, REM and movement) divided by number of epochs recorded in the hour, multiplied by 100.

Time in bed (minutes). The number of epochs from beginning of recording to last entry, divided by two.

Total sleep time (minutes). The sum of all the epochs from beginning of recording to last entry, divided by two.

Total wake time (minutes). The sum of all the epochs of stage wake from beginning of recording to last entry divided by two.

Wake time before persistent sleep (minutes). The number of epochs of stage wake that occurred before the onset of persistent sleep divided by two.

Wake time during sleep (minutes). The number of wake epochs after the onset of persistent sleep prior to the last stage 2, 3, 4 or REM, divided by two. (If there is no stage 2, 3, 4, or REM, any wake time after onset of persistent sleep will be counted as wake after sleep.)

Wake time after sleep (minutes). The number of wake epochs from the last stage 2, 3, 4 or REM to the end of the recording, divided by two. (If there is no stage 2, 3, 4 or REM, wake after sleep will include all wake epochs after onset of persistent sleep divided by two.)

REFERENCES

1. Biggio G, Concas A, Corda MG, Serra M. Enhancements of GABAergic transmission by zolpidem, an imidazopyridine with preferential affinity for type I benzodiazepine receptors. *Eur J Pharmacol* 1989;167:173–80.
2. Langer SZ, Arbilla S, Scatton B et al. Receptors involved in the mechanics of action of zolpidem. In: Sauvanet JP, Langer SZ, Morselli P, eds. *Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach.* New York: Raven Press, 1987:55–72.
3. Nicholson AN. Hypnotics: clinical pharmacology and therapeutics. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine,* Philadelphia: WB Saunders, 1989.
4. Thenot JP, Hermann P, Durand A et al. Pharmacokinetics and metabolism of zolpidem in various animal species and in humans. In: Sauvanet JP, Langer SZ, Morselli PL, eds. *Imidazo-*

pyridines in sleep disorders: a novel experimental and therapeutic approach. New York: Raven Press, 1987:149–54.
5. Monti JM. Effect of zolpidem on sleep in insomniac patients. Eur J Clin Pharmacol 1989;36:461–6.
6. Merlotti L, Roehrs T, Koshorek G, Zorick F, Lampere J, Roth T. The dose effects of zolpidem on the sleep of healthy normals. J Clin Psychopharmacol 1989;9(1):9–14.
7. Carskadon MA, Dement WC, Mitler MM, Guilleminault C, Zarcone VP, Spiegel R. Self-reports versus sleep laboratory findings in 122 drug-free subjects with complaints of chronic insomnia. Am J Psychiatry 1976;133:12.
8. Lewis SA. Subjective estimates of sleep: an EEG evaluation. *Br J Psychol* 1969;60:203–8.
9. Rechtshaffen A, Kales A, eds. *A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects.* Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.