

Daytime Sleep and Performance Following a Zolpidem and Melatonin Cocktail

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Study Objectives: Pharmacologic enhancement of daytime sleep may help sustain optimal cognitive performance. At effective doses, zolpidem induces sleep but also impairs performance. Combining melatonin with low-dose zolpidem may promote daytime sleep without exacerbating performance impairments seen with high-dose zolpidem alone.

Design and Methods: Following an 8-hour undisturbed nighttime sleep period, 80 subjects (50 men, 30 women) were administered oral zolpidem 0, 5, 10, or 20 mg at 10:00 am ($n = 20$ per group) and then oral melatonin 0 or 5 mg at 10:30 am (thus, $n = 10$ per drug combination) in a double-blind randomized fashion. Subjects napped from 10:00 am to 11:30 am, at which time they were awakened and cognitive tests administered (Restricted Reminding, Paired-Associates, and Psychomotor Vigilance). A second nap ensued from 12:45 pm to 4:00 pm, followed immediately by further testing.

Results: Melatonin 5 mg plus zolpidem 0 mg enhanced daytime sleep ($P < .05$) with no memory or performance impairment ($P > .05$). Zolpidem 20 mg plus melatonin 0 mg also enhanced daytime sleep (albeit nonsignificantly), but memory and vigilance were impaired ($P < .05$). Melatonin's sleep-promoting effects were not evident until the second nap.

Conclusions: No advantages to administering melatonin plus zolpidem "cocktails" were evident. Unlike zolpidem, melatonin 5 mg alone improved daytime sleep without impairing memory and vigilance. Functional coupling of sleep-inducing and memory-impairing effects may be specific to benzodiazepine-receptor agonists such as zolpidem, suggesting potential advantages to using melatonin in the operational environment. That melatonin's sleep-promoting effects were delayed for several hours presents a practical consideration that may limit melatonin's usefulness when daytime sleep periods cannot be reliably anticipated or planned in advance.

Key Words: zolpidem, melatonin, memory, Psychomotor Vigilance Test, benzodiazepine receptor

Abbreviations: BZR, benzodiazepine receptor; PVT, psychomotor vigilance test; RRT, Restricted Reminding task; P-A, Paired-Associates task; PSG, Polysomnography; TST, total sleep time; SWS, slow-wave sleep; REM, rapid eye-movement sleep; CV, coefficient of variation; ANOVA, analysis of variance; HSD, Tukey Honestly Significant Difference (HSD) tests.

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INTRODUCTION

UNDER CONDITIONS NONCONDUCTIVE TO SLEEP (EG, ATTEMPTING TO SLEEP DURING DAYTIME HOURS), PHARMACOLOGIC SLEEP ENHANCEMENT MAY BE useful to ensure sleep durations adequate for sustaining nominal cognitive performance during subsequent waking hours. For operational use, the ideal sleep-inducing agent would increase recuperative sleep time (via rapid onset and possibly short duration of action) without impairing subsequent operational readiness. Benzodiazepine-receptor (BZR) agonists such as zolpidem, triazolam, and temazepam induce daytime sleep under non-sleep-conductive conditions.¹⁻³ However, zolpidem and other BZR agonists also dose-dependently impair memory at their peak sleep-inducing effects,^{1,2} thus limiting their usefulness in operational settings where individuals are likely to be called upon to respond rapidly and unexpectedly or remain on call for extended periods of time (eg, firefighters, medical

personnel, military personnel).

Synthetic versions of the pineal hormone melatonin also promote daytime sleep.⁴⁻⁷ Although the sleep-promoting effects of melatonin may be weaker than those of zolpidem, use of melatonin might be preferable if it does not impair memory to the same extent as somnogenically equivalent doses of zolpidem. Daytime melatonin administration slows response speed^{8,9} and, at doses above 5 mg, also reduces accuracy.^{4,10} However, its effects on memory have not been adequately studied.

Alternatively, combining melatonin with zolpidem (particularly low doses of zolpidem) might take advantage of the unique properties of both: that is, combining melatonin (which possesses mild hypnotic properties) with low-dose zolpidem may promote daytime sleep without exacerbating performance impairments seen with high-dose zolpidem alone—particularly if melatonin does not impair memory. Melatonin has previously been administered in combination with subhypnotic doses of triazolam for inducing sleep but only for nighttime sleep in normal healthy subjects.¹¹ Whether such a combination would be effective for inducing daytime sleep under nonconductive conditions was addressed in the present study.

The first goal of the present study was to determine whether a cocktail of melatonin and zolpidem would be efficacious for inducing daytime sleep under nonconductive conditions. The second goal was to determine whether combinations of zolpidem and melatonin (particularly melatonin in combination with low doses of zolpidem) would induce sleep without exacerbating the memory impairment or other side effects seen previously with 20

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This is not an industry supported study. Drs. Belenky, Balkin, Kautz, Saviolakis, Reichardt, and Wessensten have indicated no financial conflicts of interest.

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mg of zolpidem. A 5-mg dose of melatonin was selected because previous results suggest that doses at or near this amount promote daytime sleep (either by increasing sleep time or decreasing sleep latency^{4,6,7,12}); attempts to establish a dose-response curve for melatonin's sleep-inducing effects beyond this dosage have yielded mixed results. Thus, only this single dosage of melatonin was examined in the present study. Five and 10 mg of zolpidem were selected for combination with melatonin because these doses are not sufficient for inducing daytime sleep when administered alone.^{2,14-16} Zolpidem 20 mg was included (both alone and in combination with 5 mg of melatonin) as a positive control and to determine whether dose-dependency of zolpidem was maintained when given in combination with melatonin.

METHODS

Subjects

Subjects were 80 healthy nonsmoking men ($n = 50$) and women ($n = 30$) (age range 18-35 years; mean = 23.04 years) who responded to advertisements posted at local universities. Informed consent was obtained and included an explanation of all procedures as well as possible side effects of drug. Subjects were screened for past and current physical health problems (complete blood cell count, blood chemistry, urinalysis, 12-lead electrocardiogram, medical history, and physical examination), mental health problems (state-trait anxiety inventory [cutoff = 40], Beck Depression Inventory [cutoff = 9], and medical history), sleep problems (sleep habits questionnaire), and drug use. They were instructed to abstain from alcohol and psychoactive drugs starting 48 hours prior to the study. Compliance was determined with a urine drug screen on samples collected on the morning of the study. All subjects selected for participation reported nightly sleep-onset times between 10 PM and 2 AM and total daily sleep time (nocturnal sleep plus daytime naps) of approximately 6 to 9 hours.

Payment was \$300 for successful completion of the study and adherence to all study procedures. This study was approved by the Walter Reed Army Institute of Research Human Use Committee and the United States Army Medical Research and Materiel Command Human Subjects Review Board of the Army Surgeon General and was performed in accordance with current ethical standards of the United States of America and with the ethical standards laid down in the 1964 Declaration of Helsinki.

Memory and Vigilance Testing

The following tasks were selected for performance assessment based on their demonstrated sensitivity to zolpidem (restricted reminding, paired-associates^{2,14}) or to melatonin (psychomotor vigilance test^{8,9}).

Restricted Reminding Task

Subjects attempted to recall 20 words (from a single semantic category) that had been presented verbally.¹⁷ On each successive trial, subjects were read only those words not recalled during the preceding trial and were asked to produce the entire list of 20 words. The test was ended when the entire list of 20 words had been recalled on 2 successive trials or after 8 trials. Five equivalent forms of the test were randomly assigned across subjects and

sessions. The Restricted Reminding Task (RRT) was scored for number of correctly recalled words.

Paired-Associates Task

Immediate Recall

Forms A and B of the Wechsler Memory Scale Associative Learning subtest were used in the Paired-Associates Task (P-A task). Subjects were verbally presented with a list of 10 word pairs, 6 congruent (eg, "knife – sharp") and 4 noncongruent (eg, "in – although"). Subjects were presented with the first word of each pair and asked to recall the second word of the pair (ie, the "associate"). Errors were corrected by presenting the subject with the correct associate. The same procedure was repeated for 2 more trials using the same 10 word pairs, with the order of word-pair presentation and recall varied on each trial. Immediate recall sessions occurred at 9 AM and 11:30 AM, with a different form administered at each session (forms A and B counterbalanced across subjects).

Delayed Recall

Subjects were presented with each first word of a previously presented pair and tried to recall the associate. To prevent new learning on this recall trial, errors were not corrected. Delayed recall sessions occurred at 11:30 AM (for the list originally presented at 9 AM) and at 4:00 PM (for list originally presented at 9 AM and the list originally presented at 11:30 AM).

Immediate and delayed recall trials were scored for number of correctly recalled associates. Order of presentation of forms A and B were counterbalanced across groups.

Psychomotor Vigilance Test

In the psychomotor vigilance test (PVT), a time display appeared (initially set to "000"), and subjects pressed a response key as soon as the time display began to increase.¹⁸ A response stopped the time display and initiated the next trial. The delay between the subject's response and the next stimulus presentation was 2, 4, 6, 8, or 10 seconds. The delay was pseudorandomly assigned across trials so that each of the 5 response/stimulus intervals was presented an equivalent number of times during each 10-minute test session. The PVT was analyzed for mean speed (reciprocal reaction time, $1/\text{reaction time} \times 1000$).

Symptom Checklist

The experimenter asked each subject individually whether any of the following symptoms was currently being experienced: headache, dizziness, nervousness, lightheadedness, incoordination, nausea, and vomiting. If the subject responded *Yes* to an item, she or he was then asked whether the symptom was mild, moderate, or severe. The list of symptoms includes those most commonly reported for zolpidem as listed on the product insert. Responses were scored as follows: No = 0; Yes/mild = 1; Yes/moderate = 2; Yes/severe = 3. The Symptom Checklist was administered at 9:00 AM, 11:30 AM, and 4:00 PM.

Polysomnography

Polysomnographic (PSG) signals (electrooculogram and electroencephalogram from C3 and C4 referenced to contralateral

mastoids; mental and submental electromyogram) were recorded using Oxford Medilog MR95 digital recording units (Oxford Medical Systems, Oxon, England) in 45 subjects. The remaining PSG data from 35 subjects were recorded using Compumedics Siesta recording units (Compumedics USA, El Paso, Tex). A research associate who remained blinded to drug condition scored daytime nap sleep offline in 30-second epochs according to published criteria.¹⁹ Scoring reliability was within 90% of scoring conducted by a diplomate of the American Board of Sleep Medicine. The following dependent variables were analyzed for both naps: total sleep time without stage 1 ([TST-1] calculated as minutes of stages 2, slow-wave sleep [SWS] and rapid eye-movement [REM] sleep combined); minutes of stage 1 sleep; latency to onset of stage 2 sleep (first epoch of stage 2); and number of subjects who had to be awakened from sleep (defined as stage 2, SWS or REM) at the end of the nap (the latter provided an indication of the potential contribution of sleep-inertia effects to postsleep testing). In addition, for Nap 1, the number of subjects who had to be awakened from sleep (defined as stage 2, SWS, or REM) for melatonin administration at 10:30 AM and the return-to-sleep latency (stage 2) following melatonin administration were analyzed.

Tympanic Temperature

Tympanic temperature was recorded using Thermoscan® tympanic temperature probes (Model #LR98474, Thermoscan Inc., San Diego Calif). Temperature was included for comparison with previous results indicating that daytime melatonin administration reduces body temperature.²⁰

Salivary Melatonin

Salivary melatonin was measured by a double-antibody radioimmunoassay using reagents and following procedures recommended by the vendor (Direct Saliva Melatonin RIA, American Laboratory Products Co. Inc, Windham, NH). For direct melatonin assay, minimum detection limit was 0.3 pg/mL; intra-assay coefficients of variation (CV) were 11.2 %, 4.6%, and 2.9%; and interassay CV were 15.0%, 8.8%, and 4.7% for melatonin concentrations of 1.0 pg/mL, 5 pg/mL, and 20 pg/mL, respectively. Saliva samples were collected by having subjects chew on a roll-shaped saliva collector (Salivette®, Sarstedt, Inc., Newton, NC) for 2 minutes. Samples were refrigerated upon collection and then centrifuged at 1,000 × g for 10 minutes to separate saliva from the salivette. Samples were then stored at -80°C until assay. All samples from the same individual were assayed together within 3 months of collection.

Testing Facilities

During testing and sleep/nap periods, each subject was housed individually in a sound-attenuated 10-foot × 10-foot room that included a bed and computer test station. Ambient temperature was approximately 23°C, and lighting was approximately 500 lux. Background white noise was 65 dB at all times.

Procedure

A schedule of tests and procedures is outlined in Table 1. Subjects reported to the laboratory at 7:00 PM the evening prior to

drug administration, had electrodes for PSGs attached, and practiced cognitive tasks (1 practice session of RRT and 2 practice sessions of PVT; subjects did not practice the P-A task). Lights out was 11:00 PM. They were awakened the following morning at 7:00 AM. Breakfast was served, but further food and beverage intake was prohibited (except ad libitum water) until lunch (approximately 4 hours without food).

Predrug (baseline) testing occurred at 9:00 AM. At 10:00 AM, the first oral drug (0, 5, 10, or 20 mg zolpidem) was administered in a randomized, double-blind manner. Subjects were instructed to try to sleep in their individual bedrooms while sitting upright in chairs. Lights and background white noise remained on during the nap, thus simulating a non-sleep-conducive situation with an opportunity for sleep during down time (eg, troop transport; passenger in a convoy). At 10:30 AM, subjects were awakened if asleep, and the second oral drug (0 or 5 mg synthetic melatonin – Catalog #370215, Regis Technologies Inc., Morton Grove, Ill) was administered in a randomized double-blind manner. Subjects were then allowed to sleep again until 11:30 AM. This first nap served mainly to fill down time between drug administration and estimated peak drug effect. Thus, a staggered administration of zolpidem at 10:00 AM fol-

Table 1—Schedule of Tests and Procedures

Time	Event	Tests Administered
9:00 AM	Baseline (predrug) Testing	RRT (new list) P-A (new list, 3 trials of immediate recall) PVT Symptom checklist Saliva sample
10:00 AM	Zolpidem administration Start Nap 1	None
10:30 AM	Melatonin administration Continue Nap 1	None
11:30 AM	Awaken from Nap 1 Postdrug Testing	RRT (new list) P-A (list from 9:00 AM; one trial of delayed recall) P-A (new list; 3 trials of immediate recall) PVT Symptom checklist Saliva sample
12:45 PM	Start Nap 2	None
4:00 PM	Awaken from Nap 2	RRT (new list) P-A (list from 9:00 AM, one trial of delayed recall) P-A (list from 11:30 AM; one trial of delayed recall) PVT Symptom checklist Saliva sample

RRT refers to Restricted Reminding Task; P-A, Paired-Associates Task, PVT, Psychomotor Vigilance Test.

lowed by melatonin at 10:30 AM was utilized in order to maximize the chances of awakening subjects when both drugs were at estimated peak plasma concentrations.²¹⁻²⁴ No attempt was made to distribute age or sex equivalently across zolpidem/melatonin combinations.

At 11:30 AM, subjects were awakened if asleep and immediately tested. The latter simulated a “worst case” operational scenario, ie, the need to perform quickly upon awakening when drug effects were estimated to be maximal. Following testing, subjects were allowed to eat and drink noncaffeinated items. They returned to their individual sleep suites to nap from 12:45 PM until 4:00 PM under the same conditions as the first nap. Because it commenced at or near estimated peak drug effects, this second nap served to determine drug efficacy for inducing sleep. At 4:00 PM (when most drug-related effects would have dissipated²), subjects were awakened if asleep and then immediately tested. Thereafter, electrodes were removed, and subjects underwent a brief physical examination. They were given a meal, debriefed, and released at 7:00 PM.

Design and Statistical Analyses

A 3-way mixed design was employed and included factors for zolpidem dose (grouping factor with 4 levels: 0, 5, 10, or 20 mg), melatonin dose (grouping factor with 2 levels: 0 or 5 mg), and session (within-subjects’ factor with 3 levels: 9:00 AM [predrug], 11:30 AM [early postdrug], and 4:00 PM [late postdrug]). Inclusion of the first 2 factors addressed effects of zolpidem, melatonin, or the combination of zolpidem plus melatonin on daytime sleep and performance. Combination of these first 2 factors (zolpidem dosage and melatonin dosage) resulted in 8 possible drug groups with 10 subjects per group. Inclusion of the third factor (session) addressed drug effects across time.

Nap data (latency to stage 2 sleep; minutes of TST-1; minutes of stage 1 sleep) were analyzed using 2-way analysis of variance (ANOVA) for zolpidem dose and melatonin dose. Frequency variables (number of subjects awakened) were analyzed using χ^2 analyses for each drug group versus placebo

(zolpidem 0 mg + melatonin 0 mg group). Because the naps were of unequal duration, they were analyzed separately, and the session factor did not apply. Cognitive performance data (RRT, P-A, PVT) were analyzed using a 3-way mixed ANOVA for zolpidem dose, melatonin dose, and session. Greenhouse-Geisser adjustments were applied to the session factor and its interactions. For all analyses, significant interactions were followed by simple-effects analyses. Posthoc comparisons among means were conducted using Tukey honestly significant difference (HSD) tests.

Symptom checklist data were analyzed using χ^2 analyses for each drug group versus placebo (zolpidem 0 mg + melatonin 0 mg group). For the latter analysis, severity rating was disregarded and symptoms were coded as “present” or “absent.” Unless otherwise noted, statistical significance for all analyses was $P < .05$.

RESULTS

Due to occasional technical difficulties, polysomnographic data from 72 (of the 80) subjects were available for analyses from each nap. Lost data ($n = 8$) were distributed as follows (no differences among groups, $\chi^2 P > .05$): 1 from zolpidem 0 mg + melatonin 0 mg; 1 from zolpidem 5 mg + melatonin 0 mg; 3 from zolpidem 10 mg + melatonin 0 mg; 1 from zolpidem 10 mg + melatonin 5 mg; and 2 from zolpidem 20 mg + melatonin 5 mg.

Nap 1 (10:00 am – 11:30 am)

Table 2 lists the minutes of TST-1, minutes of stage 1, latency to stage 2, number of subjects who had to be awakened from sleep for melatonin administration at 10:30 AM, return-to-sleep latency following melatonin, and number of subjects who had to be awakened from sleep at the end of the nap as a function of zolpidem/melatonin combination.

Minutes of TST-1

A marginal zolpidem \times melatonin interaction suggested that melatonin 5 mg marginally increased minutes of TST-1 at the

Table 2—Polysomnographic Variables for Nap 1

Drug Dose		Nap 1 Variable					
Zolpidem dose, mg	Melatonin dose, mg	TST-1, min*	Stage 1, min†	Latency from start of nap to stage 2 sleep, min	Subjects awakened from stage 2 sleep, SWS, or REM sleep for melatonin at 10:30 AM, no.	Latency from melatonin administration to Stage 2, min‡	Subjects awakened from stage 2 sleep, SWS or REM sleep at end of Nap 1, no.
0	0	15.8 (11.5)	12.4 (11.5)	49.5 (24.9)	2	25.8 (19.7)	3
0	5	27.7 (19.0)	24.4 (11.5)	33.1 (19.0)	3	15.0 (9.9)	6
5	0	25.8 (20.3)	14.1 (8.3)	46.0 (29.0)	3	27.4 (22.1)	3
5	5	33.8 (15.8)	18.6 (11.7)	32.3 (17.2)	2	15.2 (6.0)	5
10	0	29.2 (11.7)	19.4 (11.3)	29.7 (15.9)	2	22.4 (19.6)	4
10	5	26.4 (16.7)	23.0 (14.6)	34.5 (21.7)	1	16.2 (12.8)	5
20	0	22.8 (18.0)	13.6 (11.7)	42.3 (30.4)	3	27.3 (22.1)	4
20	5	20.4 (18.7)	8.4 (7.5)	55.9 (25.6)	0	28.4 (22.5)	2

TST-1 refers to total sleep time, the sum of stages 2, slow-wave sleep (SWS), and rapid eye movement (REM) sleep only.

Data are presented as mean (SD).

*Zolpidem \times Melatonin interaction, $P = .076$

†Zolpidem main effect, $P = .064$

‡Melatonin main effect, $P = .098$

zolpidem 0-mg dose only (TST-1 for melatonin 5 mg + zolpidem 0 mg = 27.7 minutes; TST-1 for melatonin 0 mg + zolpidem 0 mg = 15.8 minutes) (interaction $F_{3,64} = 2.40, P = .076$; melatonin simple effect at zolpidem 0 mg, $F_{1,64} = 7.55, P = 0.008$). Neither the melatonin nor zolpidem main effects were significant ($P > .05$).

Minutes of Stage 1

A marginal main effect for zolpidem suggested that the zolpidem 20-mg group obtained less stage 1 sleep than the zolpidem 10-mg group (means = 10.72 and 21.43 minutes of stage 1 sleep, respectively, zolpidem main effect $F_{3,64} = 2.55, P = 0.064$; Tukey HSD = 10.44, $P < .05$). Neither the main effect for melatonin nor the zolpidem x melatonin interaction were significant ($P > .05$).

Latency (in Minutes) to Stage 2

No significant effects were found for latency to stage 2 (main effects and interaction, $P > .05$).

Number of Subjects Awakened for Melatonin Administration

For each drug group, the number of subjects who had to be awakened for melatonin administration did not differ from placebo ($\chi^2, P > .05$).

Return to Sleep Latency Following Melatonin Administration

A marginal main effect for melatonin suggested that melatonin 5 mg reduced return-to-sleep latency compared to melatonin 0 mg (means = 25.7 and 18.7 minutes, respectively; melatonin main effect $F_{1,64} = 2.82, P = 0.098$). Neither the main effect for zolpidem nor the Zolpidem x Melatonin interaction were significant ($P > .05$).

Number of Subjects Awakened at End of Nap 1

For each drug group, the number of subjects who had to be awakened for testing at the end of Nap 1 did not differ from

placebo ($\chi^2, P > .05$).

Nap 2 (12:45 PM – 4:00 PM)

Table 3 lists minutes of TST-1, minutes of stage 1, latency to stage 2, and number of subjects who had to be awakened from sleep at the end of the nap as a function of zolpidem/melatonin combination.

Minutes of TST-1

A main effect for melatonin indicated that melatonin 5 mg increased TST-1 (mean = 92.79 minutes) compared to melatonin 0 mg (mean = 63.25 minutes) ($F_{1,64} = 13.15, P = 0.001$). Neither the zolpidem main effect nor the Zolpidem x Melatonin interaction was significant ($P > .05$).

Minutes of Stage 1

No significant effects were found for minutes of stage 1 (main effects and interaction, $P > .05$).

Latency to Stage 2

A melatonin main effect indicated that melatonin 5 mg decreased latency to stage 2 compared to melatonin 0 mg (latency to stage 2 = 21.14 and 36.22 minutes respectively; $F_{1,64} = 10.67, P = 0.002$). A zolpidem main effect indicated that zolpidem 20 and 10 mg decreased latency to stage 2 compared to zolpidem 0 mg (latency to stage 2 = 19.46, 22.12, and 42.27 minutes respectively; zolpidem main effect $F_{3,64} = 5.21, P = 0.003$; posthoc Tukey HSD = 18.20, $P < .05$). The Zolpidem x Melatonin interaction was not significant ($P > .05$).

Number of Subjects Awakened at End of Nap 2

For each drug group, the number of subjects who had to be awakened for testing at the end of Nap 2 did not differ from placebo (Chi-squares, $P > .05$).

Table 3—Polysomnographic variables for Nap 2

Drug Dose		Nap 2 Variable			
Zolpidem dose, mg	Melatonin dose, mg	TST-1, min*	Stage 1, min†	Latency from start of nap to stage 2 sleep, min	Subjects awakened from stage 2 sleep, SWS, or REM sleep at end of Nap 2, no.
0	0	50.8 (23.5)	31.4 (22.2)	56.9 (40.9)	1
0	5	92.8 (36.9)	36.1 (17.9)	29.1 (12.0)	3
5	0	60.6 (49.4)	22.0 (13.5)	39.6 (23.3)	1
5	5	97.5 (33.6)	29.5 (13.7)	20.9 (11.9)	2
10	0	57.3 (26.9)	35.3 (12.2)	26.2 (11.0)	1
10	5	80.0 (34.7)	40.2 (15.3)	18.5 (12.7)	3
20	0	81.0 (39.9)	36.1 (27.0)	23.3 (20.6)	2
20	5	100.4 (32.6)	39.2 (20.5)	15.2 (8.8)	4

TST-1 refers to total sleep time, the sum of stages 2, slow-wave sleep (SWS), and rapid eye movement (REM) sleep only.

Data are presented as mean (SD).

*Melatonin main effect, $P = .001$

†Melatonin main effect, $P = .002$; zolpidem main effect, $P = .003$

Restricted Reminding

Number of Correctly Recalled Words

Figure 1 shows mean number of correctly recalled words across sessions (9:00 AM, 11:30 AM, and 4:00 PM) as a function of zolpidem and melatonin dose. A significant Zolpidem x Session interaction ($F_{6,138} = 14.42, P = 0.000$) indicated that at 11:30 AM (estimated peak plasma concentration of zolpidem and melatonin) zolpidem 10 and 20 mg reduced the number of words recalled compared to zolpidem 5 and 0 mg (zolpidem simple effect at 11:30 AM session $F_{3,69} = 15.02, P = 0.000$; Tukey HSD = 31.05, $P < .05$). At 4:00 PM, the mean number of words recalled was still reduced in the zolpidem 20 mg group, but only compared to the zolpidem 10 mg group (zolpidem simple effect at 4:00 PM session $F_{3,69} = 3.41, P = 0.0222$; Tukey HSD = 15.54, $P < .05$). Neither the melatonin main effect nor the Zolpidem x Melatonin interaction was significant ($p > .05$).

Paired Associates

Immediate Recall

Figure 2 shows number of associates correctly recalled at 9:00 AM and 11:30 AM sessions as a function of zolpidem and melatonin dose (means collapsed across the three immediate recall trials). A significant Zolpidem Dose x Session interaction ($F_{3,72} = 11.01, P = 0.000$) indicated that zolpidem 20 mg impaired immediate recall at estimated peak plasma concentration compared to all other zolpidem doses (zolpidem simple effect at 11:30 AM, $F_{3,72} = 10.68, P = 0.000$; Tukey HSD = 1.82, $P < .05$). A significant 3-way Zolpidem x Session x Trial inter-

action [$F(6, 144) = 2.63, P = 0.019$] indicated that at 11:30 AM, zolpidem 20 mg impaired recall across all three immediate recall trials. Neither the melatonin main effect nor the Zolpidem x Zolpidem interaction was significant ($P > .05$).

Delayed Recall

A significant Zolpidem x Session interaction indicated that delayed recall of the list originally presented at 9:00 AM (predrug) was impaired by zolpidem 20 mg at 11:30 AM although the impairment was small (9.3 versus 9.8 correctly recalled associates, respectively; interaction $F_{3,72} = 3.39, P = 0.023$). Neither the melatonin nor zolpidem main effect was significant for delayed recall of the 9:00 AM list ($P > .05$). A significant main effect for zolpidem was found for delayed recall at 4:00 PM for the list originally presented at 11:30 AM (estimated peak drug effect) (zolpidem main effect $F_{3,71} = 14.94, P = 0.000$); delayed recall was impaired by zolpidem 20 mg (mean = 4.45 correct) compared to all other zolpidem doses (mean = 9.05, 8.05, and 7.16 correct for zolpidem 0, 5, and 10 mg, respectively; Tukey HSD = 1.96, $P < .05$). Neither the melatonin main effect nor the Zolpidem x Melatonin interaction was significant ($P > .05$).

Psychomotor Vigilance

Figure 3 shows mean response speed on the PVT across sessions as a function of zolpidem/melatonin dose. A significant Zolpidem x Session interaction indicated that at 11:30 AM, zolpidem 20 mg impaired speed compared to all other zolpidem doses (interaction $F[6, 142] = 16.54, P = 0.000$; zolpidem simple effect at 11:30 AM $F_{3,71} = 16.02, P = 0.000$; Tukey HSD = 0.57, $p < .05$). At 4:00 PM, zolpidem 20 mg impaired speed compared to zolpi-

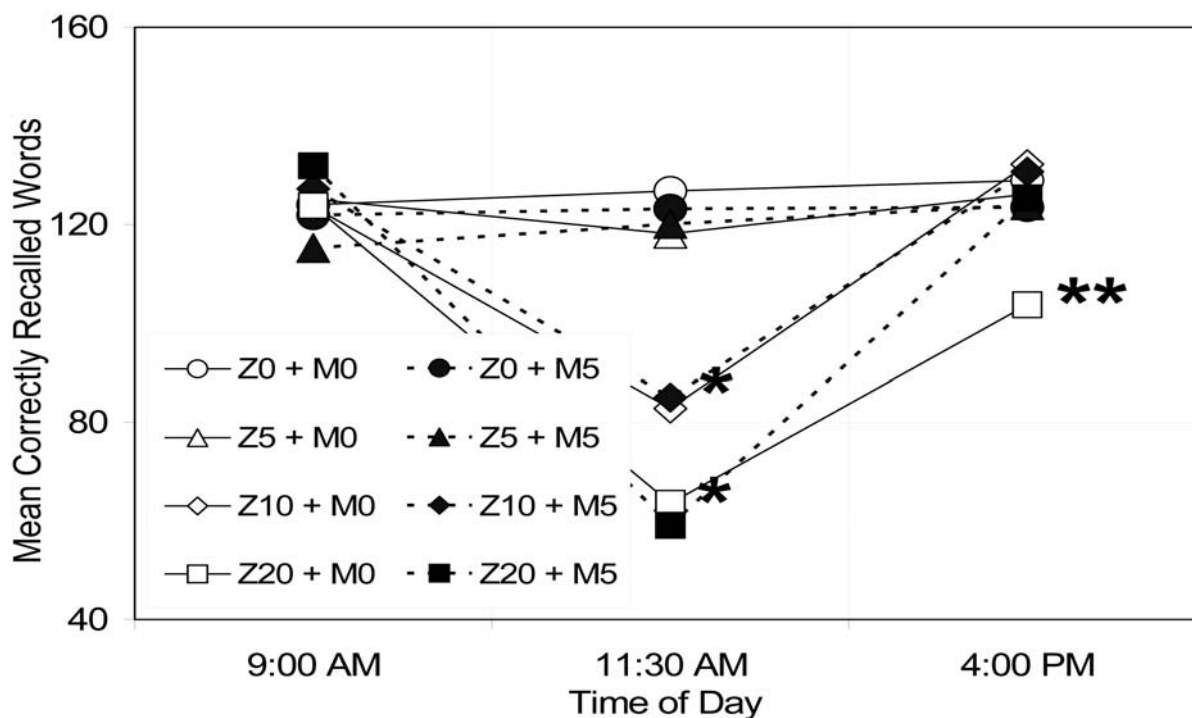


Figure 1—Mean number of correctly recalled words for the Restricted Reminding Task across sessions (9:00 AM, 11:30 AM, and 4:00 PM) as a function of zolpidem/melatonin dose. In the legend, Z denotes zolpidem and 0, 5, 10, or 20 denotes zolpidem dose; M denotes melatonin and 0 or 5 denotes melatonin dose. *Significantly different from zolpidem 0 and 5 mg (with or without melatonin 5 mg) at 11:30 AM. **Significantly different from zolpidem 10 mg (with or without melatonin 5 mg) at 4:00 PM.

dem 5 and 10 mg (zolpidem simple effect at 4:00 PM $F_{3,71} = 6.99$, $P = .000$; Tukey HSD = 0.30, $P < .05$). A marginal main effect for melatonin ($F_{3,71} = 3.74$, $P = .057$) suggested that melatonin 5 mg slowed PVT speed compared to melatonin 0 mg (means = 2.85 and 3.01, respectively). The Zolpidem x Melatonin interaction was not significant ($P > .05$).

Salivary Melatonin Levels

Due to technical problems with sample collection and processing prior to assay, reliable salivary melatonin samples were available for 67 (of the 80) subjects.

A 3-way Zolpidem x Melatonin x Session interaction ($F_{6,118} = 3.12$, $P = 0.009$) indicated that melatonin 5 mg increased salivary melatonin levels at the 11:30 AM session regardless of zolpidem dose (salivary melatonin levels for melatonin 5 mg group = 115.78 pg/mL; for melatonin 0 mg group = 1.76 pg/mL); at 4:00 PM, salivary melatonin levels for the melatonin 5 mg group were still elevated for zolpidem 0 and 20 mg (means = 71.87 and 72.00 pg/mL respectively) compared to zolpidem 5 and 10 mg (means = 35.29 and 38.91 pg/mL, respectively) (zolpidem simple effect at 4:00 PM $F_{3,59} = 3.01$, $P = 0.037$). For the melatonin 0 mg group, salivary melatonin levels remained below 4.0 pg/mL across all sessions regardless of zolpidem dose.

Tympanic Temperature

To control for substantial inter- and intra-group variations in tympanic temperature at 9:00 AM, tympanic temperature values at 11:30 AM and 4:00 PM were converted to an absolute change from the 9:00 AM value (temperature at 11:30 AM or 4:00 PM minus temperature at 9:00 AM). All values are reported in degrees Celsius.

A significant main effect for zolpidem indicated that the change in tympanic temperature from 9:00 AM to 11:30 AM and 4:00 PM was greater for the zolpidem 20-mg group (in which tympanic temperature decreased by 0.29°C [SM = 0.12°C])

compared to other zolpidem doses (mean [SEM] increases of 0.05°C [0.12°C], 0.16°C [0.12°C], and 0.21°C [0.12°C] for 0-, 5-, and 10-mg doses, respectively; $F [3,71] = 3.54$, $P = 0.019$). Main effects for melatonin and session were not significant ($P > .05$), nor were any interactions significant ($P > .05$).

Symptom Checklist

At 9:00 AM (prior to drug administration), rates of symptom reporting were uniformly low across all groups (no more than 1 subject per group reporting a particular symptom; χ^2 for all symptoms, $P > .05$).

Table 4 summarizes symptom reports from 11:30 AM (estimated peak drug effect) and 4:00 PM. At 11:30 AM, subjects administered zolpidem 10 or 20 mg (with or without melatonin 5 mg) reported dizziness, incoordination, nausea, lightheadedness, and vomiting more frequently than did subjects in the placebo group (zolpidem 0 mg + melatonin 0 mg). One of the subjects from the zolpidem 20 mg + melatonin 5 mg group also experienced auditory and visual hallucinations during the first nap period. Otherwise, no serious or untoward side effects were noted. At 4:00 PM, more subjects in the zolpidem 20 mg + melatonin 5 mg group reported dizziness, lightheadedness, nausea, and vomiting compared to those receiving placebo.

DISCUSSION

Effects on Daytime Sleep

The first goal of the present study was to determine whether the efficacy of zolpidem, administered at doses previously shown to be insufficient for promoting daytime sleep² (ie, zolpidem 5 and 10 mg), could be enhanced by administering it in combination with melatonin 5 mg. Contrary to our predictions, the present findings suggest that no somnogenic benefits are realized from combining melatonin 5 mg with low doses of zolpidem (5 and 10 mg), ie, TST-1 was not increased nor was latency to stage 2

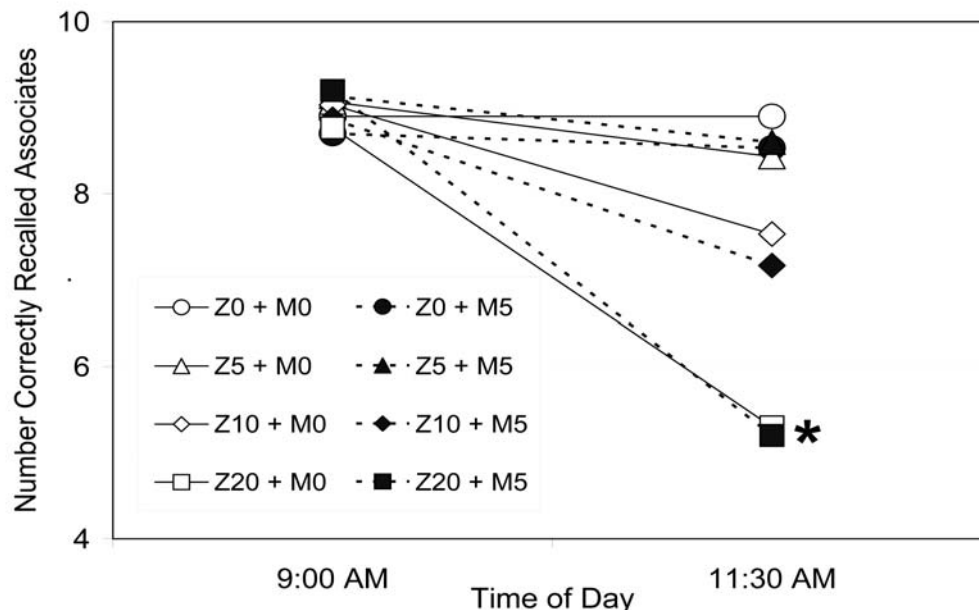


Figure 2—Mean number of correctly recalled associates (collapsed across immediate recall Trials 1-3) for the Paired-Associates Task (immediate recall phase) at 9:00 AM (before drug) and 11:30 AM (after drug) as a function of zolpidem/melatonin dose. Legend abbreviations are identical to Figure 1. *Significantly different from zolpidem 0, 5, and 10 mg (with or without melatonin 5 mg) at 11:30 AM.

decreased by the combination of zolpidem (5 or 10 mg) and melatonin 5 mg. Consistent with previous studies, the present results indicate that melatonin 5 mg *alone* is effective for induction of daytime sleep—during the second daytime nap (12:45 PM to 4:00 PM), melatonin 5 mg alone increased TST-1 and decreased latency to stage 2 sleep. Although results of previous studies have suggested only mild somnogenic effects (eg, slightly decreased sleep latencies) of melatonin,⁴⁻⁷ results from the present study suggest that melatonin 5 mg alone is effective for increasing daytime sleep amounts in normal healthy adults. Also in contrast to previous studies,^{2,14} in the present study, zolpidem 20 mg failed to significantly increase TST-1 during nap 2. Nonetheless, the trend for increased TST-1 with increasing doses of zolpidem is consistent with results of previous studies,^{2,14} suggesting a dose-dependent effect of zolpidem on daytime sleep.

Memory and Vigilance Effects

The second goal of the present study was to determine whether sleep-inducing doses of melatonin plus zolpidem would cause postsleep performance impairment. Specifically of interest was whether the melatonin/low-dose zolpidem combinations would cause less postsleep performance impairment than zolpidem 20 mg alone (a dose previously shown to be sleep inducing and memory impairing). Because results showed no sleep-promoting advantages of melatonin plus zolpidem 5 or 10 mg (whereas melatonin 5 mg alone did promote sleep), the relevant question is whether melatonin 5 mg alone caused less memory and performance impairment than did zolpidem 20 mg.

Specifically, melatonin's effects on memory were of interest given the substantial memory-impairing effects of zolpidem 20 mg.^{2,14} Results showed that melatonin 5 mg did not impair post-sleep performance on memory tasks, which were affected by zolpidem 20 mg (confirming that melatonin's lack of effect was not due to insensitive tests). Thus, melatonin 5 mg appears to have some advantages over zolpidem 20 mg (and perhaps other BZR agonists) in terms of postsleep performance effects. Further, although results for zolpidem are consistent with the view that the sleep-inducing and memory-impairing effects of BZR agonists are functionally coupled, the present results for melatonin suggest that this functional coupling does not generalize to all sleep-inducing agents.

Stage of sleep upon awakening from naps was not controlled in the present study; therefore, sleep inertia and drug effects could be confounded. Thus, an alternative explanation for postsleep performance differences among drug groups is sleep inertia. The latter does not appear to be the case, however, because our results indicate that the number of volunteers who had to be awakened from Nap 1 as well as Nap 2 for testing did not differ as a function of zolpidem or melatonin.

A final question addressed was whether the previously demonstrated dose dependency of zolpidem² was maintained when given in combination with melatonin. Although not statistically significant, results for all 3 performance tasks suggested dose dependency across the 3 doses of zolpidem tested in the present study—and no interaction of this effect with melatonin.

In the present study, melatonin impaired speed on the PVT. Although these effects were marginal, they are consistent with

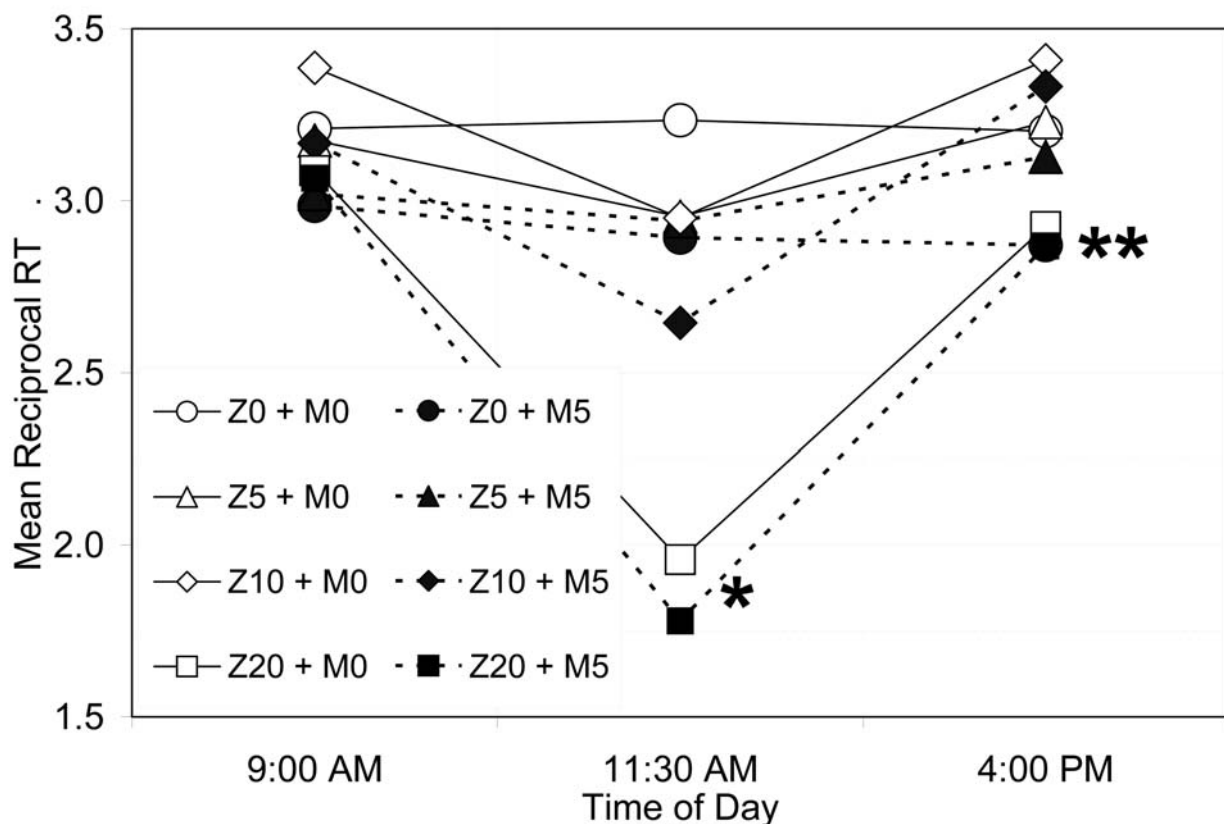


Figure 3—Mean speed for the psychomotor vigilance test across sessions (9:00 AM, 11:30 AM, and 4:00 PM) as a function of zolpidem/melatonin dose. Legend abbreviations are identical to Figure 1, except RT refers to reaction time.

*Significantly different from zolpidem 0, 5, and 10 mg (with or without melatonin 5 mg) at 11:30 AM. **Significantly different from zolpidem 5 and 10 mg (with or without melatonin 5 mg) at 4:00 PM.

previous studies in which psychomotor performance impairment was found following daytime administration of melatonin 5 mg.^{25,9} Like the present study, in previous studies, melatonin only impaired psychomotor performance (impaired tracking,²⁵ slowed PVT speed⁹), while other aspects of performance remained relatively preserved. The duration of the psychomotor performance-impairing effects of melatonin (1 hour after the dose but no effect at 5 hours after the dose) appeared to be shorter than those found in a previous study (in which melatonin 5 mg impaired PVT speed for up to 3.5 hours after the dose⁹); however, in the present study, performance was not tested between 1 and 5 hours after the dose, so the temporal pattern of the performance-impairing effects of melatonin was not evaluated. Taken together, these findings indicate that melatonin 5 mg exert performance-impairing effects that are restricted to reduced response speed—effects that contrast to those of zolpidem, which also include significant memory impairment.

Symptoms, Tympanic Temperature, and Salivary Melatonin

Results from the present study suggest a favorable side-effect profile with melatonin 5 mg (alone or in combination with zolpidem)—only the melatonin 5 mg + zolpidem 10 mg group experienced an increased incidence of incoordination. Otherwise, melatonin 5 mg did not increase those symptoms that are associated with zolpidem use. One subject who was given a combination of zolpidem 20 mg + melatonin 5 mg experienced auditory and visual hallucinations during the first nap. These side effects have been reported previously for zolpidem and appear to be dose related.²⁶ As reported previously,² zolpidem 20 mg may cause vomiting. Although it has been hypothesized that zolpidem-induced vomiting was due to subjects being required to stand up and walk at peak drug effect,² in the present study, subjects vomited even though they were not required to stand up or

otherwise move. Thus, the emesis-inducing effects of zolpidem appear to be a direct effect of the drug and not an interaction effect of zolpidem and physical activity. Vomiting may have reduced TST in the zolpidem 20-mg group during the first nap by interfering with sleep directly or by effectively lowering the actual zolpidem dose absorbed—however, the greater memory impairment seen in the zolpidem 20-mg group (compared to zolpidem 5 and 10-mg groups) would argue against the latter hypothesis.

In the present study, melatonin 5 mg did not reduce tympanic temperature. This contrasts with previous results for temperature-reducing effect of melatonin whether measured rectally,⁷ orally,¹² or tympanically.⁵ The substantial variability in tympanic temperature readings found in the present study may have been due to improper seating of the tympanic unit within the ear canal. This in turn may have caused a failure to obtain an accurate reading of infrared energy emitted by the deep auditory ear canal (which is the basis for tympanic temperature).

Melatonin 5 mg increased salivary melatonin levels consistently across all doses of zolpidem at 11:30 AM, indicating no dose-related interactions with zolpidem on salivary melatonin. At 4:00 PM, zolpidem effects on salivary melatonin levels were inconsistent, with lower levels at zolpidem 5 and 10 mg compared to zolpidem 0 and 20 mg. However, the latter did not appear to translate into behavioral effects, since zolpidem dose-ordered effects on memory were still evident at that time.

Melatonin and Daytime Sleep—Mechanism of Action

In the present study, melatonin 5 mg increased TST and reduced sleep latency (stage 2) during the second daytime nap, which commenced 135 minutes after melatonin administration. This finding was consistent with a previously published study,⁵ in which it was reported that melatonin administered at 10:00

Table 4—Number of subjects reporting symptoms at 11:30 AM and 4:00 PM sessions as a function of zolpidem/melatonin combination

Symptom	Session Time	Zolpidem Dose		0		5		10		20	
		0	5	0	5	0	5	0	5		
Headache	11:30 AM	1	0	0	0	2	2	1	2		
	4:00 PM	1	0	0	0	1	1	0	0		
Dizziness	11:30 AM	0	0	1	1	5*	4*	3*	9*		
	4:00 PM	0	0	0	0	2	1	2	4*		
Nervousness	11:30 AM	1	0	0	0	0	0	0	1		
	4:00 PM	0	0	0	0	0	0	0	0		
Lightheadedness	11:30 AM	3	0	1	2	4	2	2	7*		
	4:00 PM	0	0	0	0	1	1	1	6*		
Incoordination	11:30 AM	0	0	1	1	3*	4*	7*	6*		
	4:00 PM	1	0	0	0	0	0	3	3		
Nausea	11:30 AM	0	0	1	0	1	2	6*	5*		
	4:00 PM	0	0	0	0	0	1	2	3*		
Vomiting	11:30 AM	0	0	0	0	1	2	2	3*		
	4:00 PM	0	0	0	0	0	0	2	3*		

*Indicates a significant difference from placebo (zolpidem 0 mg + melatonin 0 mg).

AM increased TST but only during the fourth hour (3:00-4:00 PM) of a 4-hour nap (ie, 5 hours after drug administration). Subjective sleepiness also lags melatonin administration by several hours: subjective sleepiness peaks at 3 to 4 hours after melatonin (5 mg) administration.^{25,27} In contrast, fastest latencies to stage 2 sleep lagged melatonin administration by only 1 hour (and actually preceded the maximum drop in core temperature by 2 hours).⁶ Although the latter would appear to be inconsistent with other findings, other results from that study indicated a secondary reduction in sleep-onset latency that occurred four hours post-melatonin — and one hour after maximum decline in body temperature.⁶ These results suggest that another factor, in addition to time of day, is affecting the daytime sleep-promoting efficacy of melatonin¹²: that is, latency from melatonin administration to onset of somnogenic action. In other words, the sleep-inducing effects of melatonin appear to require several hours to emerge.

This time lag between daytime melatonin administration (ie, exogenous melatonin) and its daytime sleep-promoting effects suggests that a similar mechanism may account for the effects of endogenous melatonin on nighttime sleep in diurnal animals—and that this mechanism may relate more to nocturnal sleep maintenance than to nocturnal sleep initiation. That is, endogenous melatonin secretion peaks early in the nocturnal sleep period. This coincides with peak homeostatic pressure for sleep (which is likely sufficient for maintaining sleep). At this time of night, secondary sleep-promoting mechanisms (such as melatonin) would be unnecessary. However, later in the nocturnal sleep period, homeostatic pressure for sleep has decreased—and at this point, the earlier melatonin peak may have the delayed effect of promoting sleep maintenance via effects on brain temperature⁶—that is, the downstream (delayed) result of a slow cascade of brain temperature-dependent changes that were initially triggered by melatonin secretion early in the sleep period and that later in the sleep period culminate in changes in brain metabolic activity. As discussed previously,²⁸ high-affinity melatonin-binding sites in the suprachiasmatic nucleus make this brain region a candidate for control of the effects of melatonin. Regardless of mechanism, the apparent lag between melatonin availability at target receptor sites and onset of sleep promotion limits the potential usefulness of melatonin as a sleep inducer in operational environments characterized by narrow or unpredictable opportunities for sleep.

CONCLUSIONS

It has been suggested that the sedative and hypnotic properties of zolpidem and other BZR agonists are related^{29,30} or functionally coupled¹⁴ to the central BZR. Prescription sleep-inducing agents that act at the central BZR (even those that are not benzodiazepines, such as zolpidem and zaleplon) possess the potential to impair memory at peak sleep-inducing effect. The search for sleep-inducing agents that do not act at the central BZR (and it appears that the sleep-promoting effects of melatonin are not exerted at the BZR³¹) may yield drugs that improve sleep without impairing performance.

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