The Effect of Two Benzodiazepine Receptor Agonist Hypnotics on Sleep-Dependent Memory Consolidation

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Introduction: Numerous studies have demonstrated that sleep promotes memory consolidation, but there is little research on the effect of hypnotics on sleep-dependent memory consolidation. We compared bedtime administration of zolpidem-ER 12.5 mg (6- to 8-h duration of action), middle-of-the-night administration of zaleplon 10 mg (3- to 4-h duration of action), and placebo to examine the effect of different durations of hypnotic drug exposure on memory consolidation during sleep.

Methods: Twenty-two participants with no sleep complaints underwent 3 conditions in a counterbalanced crossover study: (1) zolpidem-ER 12.5 mg (bedtime dosing), (2) zaleplon 10 mg (middle-of-the-night dosing), and (3) placebo. Memory testing was conducted before and after an 8-h sleep period, using a word pair association task (WPT; declarative memory) and a finger-tapping task (FTT; procedural memory).

Results: ANOVA revealed a significant condition effect for the WPT ($p = 0.025$) and a trend for the FTT ($p = 0.067$), which was significant when sex was added to the model ($p = 0.014$). Improvement in memory performance following sleep was lower with bedtime dosing of zolpidem-ER compared to placebo and middle-of-the-night dosing of zaleplon. There were no differences between placebo and zaleplon.

Conclusions: The results suggest that in some circumstances hypnotics may have the potential to reduce the degree of sleep-dependent memory consolidation and that drug-free sleep early in the night may ameliorate this effect.

Keywords: Hypnotics, memory consolidation, sleep

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A growing body of evidence demonstrates that sleep promotes memory consolidation in healthy individuals.¹⁻³ Numerous studies using various designs and memory tasks have consistently found that memory consolidation (i.e., improvement on a given memory task from initial training/test to retest) is significantly greater after a period of sleep than a period of wake. This is commonly referred to as sleep-dependent memory consolidation (SDMC).⁴ For example, improvements on a procedural memory finger-tapping task were observed after a night of sleep but not after 4-, 8-, or 12-hour daytime periods without sleep.^{5,6} Studies examining declarative memory consolidation, such as with a word pair association task, also demonstrate improvements in performance after sleep.⁷ In addition to improvements in memory following overnight sleep, memory consolidation is also enhanced during naps as short as 45 minutes. Improvements in procedural^{8,9} and declarative¹⁰ memory occur with naps, but not following similar durations of wakefulness. These findings suggest that memory consolidation that occurs during wakefulness is enhanced during sleep.

Synaptic plasticity, which refers to structural or functional neural changes in response to stimuli,² is thought to be the cellular substrate underlying the processes of memory formation and consolidation.¹¹ Sleep has been found to enhance plasticity in animals,¹² which is consistent with the idea that sleep enhances memory consolidation. In humans, fMRI studies have shown that sleep-dependent learning of a motor skill task is accompanied by changes in multiple brain areas,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Few studies have investigated the impact of hypnotic medication on sleep-dependent memory consolidation. This study compared the effect of differing time of exposure to two hypnotics on the sleep-dependent consolidation of declarative and non-declarative memory.

Study Impact: This study contributes to the research surrounding sleep-dependent memory and hypnotics, indicating that hypnotic exposure during most of the night may reduce sleep-dependent memory consolidation; whereas hypnotic exposure only during the second half of the night appears to have no effect.

indicative of large-scale plastic reorganization of memory.¹³ There is evidence that some sleep-promoting medications may affect corticoplasticity negatively. Frank and colleagues found that zolpidem 10 mg/kg (although not triazolam 1-10 mg/kg or ramelteon 0.1-1 mg/kg) reduced cortical plasticity in rats by approximately 50%.¹⁴ They also demonstrated that trazodone 10 mg/kg (but not zaleplon 10 mg/kg or eszopiclone 1-10 mg/kg) impaired sleep-dependent plasticity.¹⁵ Although not all hypnotics studied significantly impaired corticoplasticity, low sample sizes and variable potency might have influenced the results. The finding that plasticity may be negatively affected by hypnotics suggests that hypnotics may also lead to impairments in SDMC.

Because 10%-20% of the population is estimated to have insomnia¹⁶⁻¹⁸ and hypnotics remain a commonly used treatment,

it is important to determine if memory consolidation during sleep is negatively affected by these drugs. Few studies have investigated the effect of hypnotics on sleep-dependent memory in humans. Melendez et al. reported no effect of either zolpidem immediate release (10 mg) or triazolam (0.25 mg) on SDMC in normal sleepers.¹⁹ However, subjects were trained to 100% on the memory tasks prior to the sleep period precluding a demonstration that the tests used were sensitive to SDMC with placebo. Other investigators found that zopiclone (7.5 mg), but not brotizolam (0.25 mg), impaired SDMC in normals.²⁰ The small sample ($N = 8$) may have been insufficient to detect an effect with brotizolam. Finally, Morgan et al. reported significant impairment of sleep-dependent memory on a motor task with triazolam (0.375 mg), but not with zolpidem immediate release (10 mg).²¹ However, the dose of triazolam is rather high and the detected effect may be a direct influence of drug on motor performance during the morning testing period, rather than interference with SDMC. Additionally, the small sample ($N = 12$) may have provided insufficient power to detect an effect with the dose of zolpidem employed.

In sum, these studies provide some evidence that hypnotic drugs may impair SDMC, but further investigation is clearly needed to confirm these findings and assess possible contributing factors. One such factor may be duration of drug exposure. Given that memory consolidation improves after sleep periods (without medication) that are as brief as 1-2 hours,⁸⁻¹⁰ limiting drug exposure to a portion of the sleep period may result in less interference with SDMC, compared to drug exposure for the majority of the sleep period.

The objective of the present study was to determine the effect of different durations of hypnotic drug exposure on SDMC. To do this, we used hypnotics with different durations of action and administered them at different times of the night. We compared the effects of bedtime administration of zolpidem extended-release (zolpidem-ER) 12.5 mg, middle-of-the-night administration of zaleplon 10 mg, and placebo on procedural and declarative memory consolidation. The two hypnotics have similar mechanisms of action, both binding preferentially to the α -1 benzodiazepine receptor subunit,²² although their durations of action differ. Zolpidem-ER has an estimated duration of action of 6-8 h, with a $t_{1/2}$ of 2.8 h and a t_{max} of 1.5 h.²³ In contrast, zaleplon has an estimated duration of action of 3-4 h due to rapid absorption and elimination, with $t_{1/2}$ and t_{max} both approximately one h.²⁴ These doses were chosen because, at the time of study, they were the recommended therapeutic doses for treatment of insomnia. In addition, residual morning sedation has not been detected with either drug at these doses when administered at bedtime,^{25,26} or with zaleplon 10 mg when administered as little as 4 h before wake time (middle-of-the-night dosing).^{27,28} Normal subjects were studied to avoid potential influence of the inherent sleep disruption of insomnia patients.

We predicted that SDMC would be impaired following a period of sleep with drug activity during most or all of the night, but not after a period during which approximately half of the sleep is drug-free. Specifically, we hypothesized that bedtime administration of zolpidem-ER 12.5 mg would result in lower SDMC—measured as the percent change in memory performance from before sleep to after sleep—compared to placebo and middle-of-the-night zaleplon 10 mg. In addition

we predicted that SDMC would not be lower following zaleplon 10 mg compared to placebo.

METHODS

Subjects

Healthy individuals with no sleep complaints were recruited via media advertisements and telephone contacts. Participants were required to have a Pittsburgh Sleep Quality Index²⁹ global score ≤ 5 and report nightly total sleep time between 7 and 10 h with time in bed between 7 and 10.5 h. Exclusionary criteria included the presence of any clinically significant unstable medical condition; a DSM-IV axis-I psychiatric disorder during the past 2 years; a prior diagnosis of, or symptoms suggesting risk for, sleep apnea, restless legs syndrome, or other sleep disorder; a history of substance abuse in the past year; use within the prior 2 weeks of prescription hypnotic medication, over-the-counter sleep aid, or any psychotropic medication; a history of adverse reaction to benzodiazepines or similar medications; and a body mass index ≥ 36 . In addition, participants could not be night or rotating shift workers; consume ≥ 700 mg per day of xanthine-containing food or beverages; consume > 14 units of alcohol per week; or smoke ≥ 1 pack of cigarettes per day, use chewing tobacco > 3 times per day, or be unable to refrain from smoking or chewing without distress or discomfort while in the sleep laboratory. Female subjects could not be pregnant or nursing and were required to use adequate contraceptive procedures throughout the study.

Experimental Design and Procedure

The protocol was approved by the Institutional Review Board of St. Luke's Hospital. All subjects provided written informed consent and were compensated for their participation.

A randomized, counterbalanced, double-blind, placebo-controlled, crossover design was used to compare overnight memory consolidation during three drug conditions: (1) zolpidem-ER 12.5 mg (bedtime dosing), (2) zaleplon 10 mg (middle-of-the-night dosing), and (3) placebo (**Figure 1**). To provide blinding, capsules containing drug or placebo were administered twice each night: 30 min before bedtime and 3.5 h after bedtime during a brief experimental awakening. Thus placebo was given in the middle of the night during the zolpidem-ER condition, before bedtime in the zaleplon condition, and at both times in the placebo condition. Subjects were randomly assigned to a study condition sequence using a Latin Square design and had a 1- to 2-week interval between visits to allow for adequate wash-out.

Declarative memory and procedural memory tasks were administered 90 min before bedtime (60 min before drug administration) and 60 min after wake time, with the time between testing held constant at 10.5 h. The order of the tasks was counterbalanced within each study condition and held constant across conditions for each subject. Ninety minutes was chosen for the evening interval to allow time for memory testing and electrode placement prior to drug administration which occurred 30 min before bedtime. Sixty min was chosen for the morning interval so that testing occurred at a time when drug levels were undetectable or minimal. Thus

morning testing occurred 9.5 h after zolpidem-ER dosing and 5.5 h after zaleplon dosing which is approximately 1.5 h after drug should have been eliminated based on pharmacokinetic data.^{23,24} Both time intervals are consistent with prior studies of SDMC involving overnight sleep.^{5,6}

Polysomnography (PSG) was conducted at each of the 3 overnight visits with bedtime at the subject's reported typical bedtime and time in bed held constant at 8 hours. Sleep was recorded and scored according to standard criteria,³⁰ using C_3 - A_2 or C_4 - A_1 EEG derivations by experienced staff blind to the experimental condition.

Subjects were instructed to cease caffeine consumption at 12:00 p.m., and to refrain from napping and consuming alcohol, on the days they were scheduled to arrive in the laboratory for overnight testing. In addition, use of nicotine products was prohibited while subjects were in the laboratory. Subjects were studied in private rooms without access to other subjects. During brief periods when testing was not conducted, subjects were permitted to engage in quiet activities such as reading or watching television. Breakfast was provided in the morning after awakening.

Double-blind study drug was prepared by a compounding pharmacy (Foundation Care, St. Louis, MO). Zolpidem-ER and zaleplon were over-encapsulated in identical #000-sized white opaque capsules and back-filled with an excipient (lactose). Identical placebo capsules contained only lactose. A dissolution test documented that there was less than a two-minute difference in dissolution of the outer capsule between the two active drug preparations.

Dependent Measures

Declarative memory was assessed with a word pair association task (WPT), modeled after that of Plihal and Born.^{31,32} Approximately 90 min prior to bedtime, 46 word pairs (23 related and 23 unrelated word pairs) were presented on a computer screen, one pair at a time for 3 sec each. Immediately following presentation of all 46 word pairs, an initial test of recall (WPT-Pre) was conducted. Participants were presented with the first (cue) word of each pair, one at a time and in a different order, and were asked to recall the second (target) word for each cue word. Immediately after each response, the correct word pairing—both cue word and target word—was displayed on the computer screen for 2 sec, regardless of whether the response was correct. Approximately 60 min after wake time, a second recall test (WPT-Post) was conducted during which subjects were again presented with the cue words, one at a time in yet a different order, and asked to recall the target words. Three unique versions of the test were utilized, with a different version administered during each of the 3 overnight conditions. Order of the test versions was randomly assigned and counterbalanced. SDMC was measured as the percent change in the number of correctly recalled word pairs from WPT-Pre to WPT-Post.

Procedural memory was assessed with a finger-tapping task (FTT), a test frequently used to demonstrate sleep-dependent memory.^{5,21} In this test, subjects are asked to type a 5-digit number sequence as quickly and as accurately as possible with the fingers of the nondominant hand by pressing 4 adjacent numeric keys on a standard computer keyboard. Subjects

Figure 1—Study design

Each subject underwent three conditions with order counterbalanced: zolpidem-ER (bedtime dosing), zaleplon (middle-of-the-night dosing), and placebo. Capsules containing drug or placebo were administered twice each night: 30 min before bedtime and 3.5 h after bedtime. Placebo was administered in the middle of the night in the zolpidem-ER condition, before bedtime in the zaleplon condition, and both times in the placebo condition. Memory tests were conducted 90 min before bedtime and 60 min after wake time. Time in bed (dark bar) was 8 h with bedtime at the subject's usual bedtime.

are instructed to look at the number sequence displayed on the computer screen while typing. No feedback on performance is given. Each test consists of twelve 30-sec tapping trials alternating with twelve 30-sec rest periods. The FTT was administered approximately 90 min prior to bedtime (FTT-Pre) and approximately 60 min after wake time (FTT-Post) using the same number sequence. Three versions of the test were utilized (2-4-3-1-2, 3-1-4-2-3, and 4-2-3-1-4), with a different version administered during each condition. Order of the test versions was randomly assigned and counterbalanced across conditions. SDMC was measured as the percent change in the number of correctly typed sequences from FTT-Pre (mean of the last 3 trials) to FTT-Post (mean of the first 3 trials).

Residual morning sedation was evaluated with the Digit Symbol Substitution Task (DSST), a measure of information processing, psychomotor performance, visuomotor coordination, and concentration. This test is commonly used as an indicator of psychomotor impairment and residual sedation following administration of hypnotics.³³ The 90-sec test requires subjects to substitute digits (between 0 and 9) with different nonsense symbols according to a key which links symbols and

digits. The DSST was administered 60 min after wake time and just prior to the FTT-Post and WPT-Post. Three unique versions of the test were utilized, with a different version administered each morning and order randomly assigned and counterbalanced. The primary performance measure was the number of correct substitutions.

Statistical Analysis

Statistical analyses were conducted with SYSTAT 13, using repeated-measures ANOVAs followed by paired comparisons to examine condition differences. Age was used as a covariate for WPT analyses because it has been shown to affect declarative memory performance.^{34,35} PSG measures were examined for the entire 8 h, the first 3.5 h of the night, and the last 4.5 h of the night.

RESULTS

Study Sample

Twenty-six individuals gave written informed consent and were randomized to the study. Two subjects withdrew due to scheduling conflicts, and 2 subjects were excluded from data analysis because of unusual sleep patterns while on placebo (one subject's total sleep time was 263 min; one subject's percent of REM sleep was 41%). The final sample ($N = 22$) consisted of 14 females and 8 males, with a mean age of 29.4 ± 6.7 years. Subjects had mean body mass index of 25.4 ± 4.3 , and reported consuming an average of 1.0 ± 0.8 caffeinated beverages per day and 1.9 ± 1.7 alcoholic beverages per week. All but one of the subjects were nonsmokers; that subject consumed an average of 8 cigarettes per day. Two extreme outliers (≥ 3 standard deviations from the mean) were noted on the WPT and excluded from analyses involving this task. This sample ($N = 20$) consisted of 14 females and 6 males, with a mean age of 30.1 ± 6.6 years.

Polysomnography

Polysomnography data in minutes and percents are shown in **Table 1**. Because time in bed was constant at 8 h, comparisons are similar for minutes and percents. Significant differences in the paired comparisons for both measures are presented in the table but data in minutes are reported here.

Comparing zolpidem-ER and placebo conditions, several predictable differences of minor magnitude reached statistical significance. For the entire night, zolpidem-ER had a shorter latency to persistent sleep ($p = 0.007$), less wake after sleep onset (WASO; $p = 0.026$) and stage 1 ($p = 0.003$), as well as more total sleep time (TST; $p = 0.010$), stage 2 ($p = 0.012$), and slow wave sleep (SWS; $p < 0.001$). Most of these differences occurred in the first 3.5 h, with zolpidem-ER demonstrating less WASO ($p = 0.001$), stage 1 ($p = 0.001$), and REM ($p = 0.005$), as well as more TST ($p = 0.004$), stage 2 ($p = 0.035$), and SWS ($p = 0.001$) during this time period. During the last 4.5 h the only difference was less stage 1 with zolpidem-ER ($p = 0.015$).

Sleep architecture was similar between the zaleplon and placebo conditions. Comparisons between these conditions showed only one significant difference, an increase (by

10.5 min) in SWS in the zaleplon condition for the entire night ($p = 0.003$). There were no other differences for the entire night, the first 3.5 h (when placebo was present during both conditions), or the last 4.5 h (following middle-of-the-night dosing).

Because zolpidem-ER was taken at bedtime and zaleplon was dosed in the middle of the night, we performed comparisons between these conditions for the entire night as well as the last 4.5 h. In addition, the first 3.5 hours were compared to demonstrate that the sleep architecture differences between zolpidem-ER and zaleplon conditions were parallel, as expected, to the differences between the first 3.5 h of the zolpidem-ER and placebo conditions. Comparisons between the two active drug conditions for the entire night demonstrated less WASO ($p = 0.022$) and stage 1 ($p = 0.005$), as well as more TST ($p = 0.006$) and stage 2 ($p = 0.003$) with zolpidem-ER compared to zaleplon. For the first 3.5 h when placebo was present in the zaleplon condition, zolpidem-ER had less WASO ($p = 0.001$), stage 1 ($p = 0.001$), and REM ($p = 0.031$), as well as more TST ($p = 0.008$), stage 2 ($p = 0.023$), and SWS ($p = 0.004$), consistent with the zolpidem-ER/placebo comparisons for the same time period. During the last 4.5 h, zolpidem-ER had more stage 2 ($p = 0.016$) than zaleplon.

DSST

The DSST means (number of correct substitutions) were: zaleplon = 67.4 ± 11.7 , placebo = 68.0 ± 11.9 , and zolpidem-ER = 64.5 ± 11.1 . Repeated-measures ANOVA indicated a trend for a condition effect ($F_{(2,20)} = 3.095$, $p = 0.067$). Follow-up paired comparisons showed lower DSST scores with zolpidem-ER compared to placebo ($p = 0.029$) and a trend for lower scores compared to zaleplon ($p = 0.052$). Correlational analyses were thus conducted to determine if residual sedation might be responsible for poorer SDMC in the zolpidem-ER condition. These analyses revealed no significant correlations between DSST and memory measures.

SDMC: Declarative

Pre-sleep learning (the number of correctly-recalled word pairs on the WPT-Pre) was similar among the conditions: zaleplon = 24.5 ± 8.9 , placebo = 25.1 ± 6.9 , and zolpidem-ER = 25.8 ± 8.1 ($F_{(2,17)} = 1.725$, $p = 0.208$). There was evidence of an overnight improvement in memory for each condition, measured as raw score change in correctly recalled word pairs from WPT-Pre to WPT-Post (zaleplon: 4.15 ± 3.6 , placebo: 4.20 ± 3.8 , and zolpidem-ER: 3.35 ± 3.7). Repeated-measures ANOVA, including age as a covariate, demonstrated a significant effect of condition for the percent change from WPT-Pre to WPT-Post ($F_{(2,17)} = 4.619$, $p = 0.025$; **Figure 2**). Pairwise comparisons revealed significantly lower overnight improvement on WPT in the zolpidem-ER condition compared to both the placebo ($p = 0.015$) and zaleplon ($p = 0.031$) conditions. There was no difference between zaleplon and placebo ($p = 0.58$).

SDMC: Procedural

Pre-sleep learning (the average number of correctly typed number sequences on the FTT-Pre) was similar among conditions: zaleplon = 19.3 ± 5.2 , placebo = 20.0 ± 5.4 , and zolpidem-ER = 20.2 ± 6.2 ($F_{(2,20)} = 1.52$, $p = 0.243$). There was evidence of an overnight improvement in memory for each

Table 1—Polysomnography data for each condition (N = 22)

	Zaleplon (middle-of-the-night dosing)	Zolpidem-ER (bedtime dosing)	Placebo
Entire Night			
Latency to persistent sleep (min)	15.2 (14.6)	10.2 (8.2)	21.4 (15.4) ^b
Total sleep time (min)	434.6 (26.1) ^b	449.0 (15.4)	431.8 (23.9) ^b
Sleep efficiency (%)	90.6 (5.4) ^b	93.6 (3.2)	89.9 (5.0) ^b
Wake after sleep onset (min)	32.2 (20.4) ^b	22.0 (13.1)	31.8 (17.7) ^b
Stage 1 (min)	49.7 (16.9) ^b	37.0 (18.2)	50.9 (19.1) ^b
Stage 1 (%)	11.5 (4.1) ^b	8.3 (4.3)	11.9 (4.7) ^b
Stage 2 (min)	237.6 (26.4) ^b	264.8 (34.3)	244.7 (34.7) ^b
Stage 2 (%)	54.9 (7.2) ^b	59.0 (8.0)	56.7 (7.6) ^b
SWS (min)	57.8 (31.6)	64.9 (39.1)	47.2 (28.2) ^{a,b}
SWS (%)	13.2 (7.2)	14.3 (8.5)	10.9 (6.3) ^{a,b}
REM (min)	89.5 (22.4)	82.3 (21.4)	89.0 (21.1)
REM (%)	20.5 (4.4)	18.3 (4.5)	20.5 (4.3) ^b
First 3.5 hours			
Total sleep time (min)	185.4 (17.0) ^b	194.9 (9.0)	183.8 (13.5) ^b
Wake after sleep onset (min)	21.0 (16.1) ^b	9.4 (5.6)	19.0 (11.1) ^b
Stage 1 (min)	22.5 (9.1) ^b	13.3 (8.0)	21.0 (9.4) ^b
Stage 1 (%)	12.3 (5.3) ^b	6.9 (4.3)	11.6 (5.5) ^b
Stage 2 (min)	97.6 (20.4) ^b	108.8 (26.3)	100.9 (17.6) ^b
Stage 2 (%)	53.2 (13.1)	56.2 (15.0)	55.1 (9.9)
SWS (min)	44.6 (27.4) ^b	57.6 (33.3)	38.6 (22.9) ^b
SWS (%)	23.5 (14.0) ^b	29.2 (16.8)	20.8 (11.9) ^b
REM (min)	20.8 (11.9) ^b	15.1 (9.1)	23.3 (10.7) ^b
REM (%)	10.9 (6.0) ^b	7.7 (4.6)	12.5 (5.3) ^b
Last 4.5 hours			
Total sleep time (min)	248.9 (12.5)	250.4 (20.3)	247.7 (14.2)
Wake after sleep onset (min)	10.2 (7.2)	11.8 (10.5)	12.4 (10.3)
Stage 1 (min)	27.2 (10.4)	22.8 (12.3)	29.8 (12.5) ^b
Stage 1 (%)	11.0 (4.4)	9.3 (5.5)	12.2 (5.3) ^b
Stage 2 (min)	139.8 (17.1) ^b	153.9 (22.2)	143.7 (23.0)
Stage 2 (%)	56.2 (6.7) ^b	61.6 (8.2)	57.9 (8.0)
SWS (min)	13.2 (15.2)	7.3 (11.0)	8.5 (9.8)
SWS (%)	5.2 (6.1)	2.8 (4.2)	3.5 (4.0)
REM (min)	68.7 (15.0)	66.4 (20.6)	65.6 (15.9)
REM (%)	27.5 (5.5)	26.3 (7.6)	26.4 (5.9)

Data are presented as mean (standard deviation). ^ap < 0.05, paired comparison vs. zaleplon. ^bp < 0.05, paired comparison vs. zolpidem-ER.

condition, measured as raw score change in correctly typed sequences from FTT-Pre to FTT-Post (zaleplon: 2.77 ± 2.0 , placebo: 2.59 ± 3.0 , and zolpidem-ER: 1.53 ± 2.8). Repeated measures ANOVA showed a trend towards a condition effect for the percent change from FTT-Pre to FTT-Post ($F_{(2,20)} = 3.097$, $p = 0.067$). Pairwise comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to placebo ($p = 0.035$), a trend for less improvement with zolpidem-ER compared to zaleplon ($p = 0.057$), and no difference between zaleplon and placebo ($p = 0.78$). Because plots of the data indicated sex may have differentially affected performance on the FTT, we added sex to the ANOVA model for a secondary analysis of percent change. This analysis revealed a condition effect ($F_{(2,19)} = 5.446$, $p = 0.014$) and a trend for a condition by sex interaction ($F_{(2,19)} = 3.028$, $p = 0.072$). Paired comparisons revealed significantly lower overnight improvement on FTT for zolpidem-ER compared to both placebo ($p = 0.014$) and zaleplon ($p = 0.012$), and no difference between zaleplon and placebo ($p = 0.88$; **Figure 3**).

Correlation between Sleep Parameters and SDMC

Exploratory correlation analyses were conducted for each condition to determine if improvements in memory were related to specific all-night PSG measures (TST, Stage 1%, Stage 2%, SWS%, and REM%). In the placebo condition, WPT percent change was positively correlated with REM% ($r = 0.520$, $p = 0.019$) and FTT percent change was negatively correlated with stage 2% ($r = -0.432$, $p = 0.044$). In the zolpidem-ER condition, WPT percent change correlated negatively with SWS% ($r = -0.524$, $p = 0.018$).

DISCUSSION

The objective of the present study was to determine the effect of different durations of hypnotic drug exposure on SDMC. We compared bedtime administration of zolpidem-ER 12.5 mg (6- to 8-h duration of action) with middle-of-the-night administration of zaleplon 10 mg (3 to 4-h duration of action) and placebo. ANOVAs revealed a significant condition

Figure 2

WPT: Mean percent change from pre-sleep (WPT-Pre) to post-sleep (WPT-Post). Means and standard deviations are adjusted for age. *placebo vs. zolpidem-ER, $p = 0.015$; ‡zaleplon vs. zolpidem-ER, $p = 0.031$.

Figure 3

FTT: Mean percent change from pre-sleep (FTT-Pre) to post-sleep (FTT-Post). Error bars are standard errors. *placebo vs. zolpidem-ER, $p = 0.035$; ‡zaleplon vs. zolpidem-ER, $p = 0.057$.

effect for the WPT and a trend for the FTT, which was significant when sex was added to the model. The results suggest that bedtime administration of zolpidem-ER reduces the magnitude of SDMC while middle-of-the-night dosing with zaleplon does not.

One interpretation of these data is that the 3.5-h drug-free period of sleep prior to zaleplon ingestion was sufficient to allow SDMC to occur to the same degree as in the placebo condition, whereas having drug active in the brain for most of the sleep period, as in the zolpidem-ER condition, reduces SDMC. Observations from nap studies that as little as 45 minutes of sleep allows SDMC to occur is consistent with this interpretation.^{8,10} Our data do not address whether the timing of drug-free sleep is important. Similar results with zaleplon administered at bedtime (allowing a period of drug-free sleep in the latter part of the night) would suggest that some minimal period of drug-free sleep any time of night is sufficient to maximize SDMC. On the other hand, a decrement in SDMC in this circumstance would suggest that drug exposure early in the sleep period is a critical factor in diminishing SDMC.

Alternative explanations include differences specific to the two drugs or to the doses employed (affecting peak plasma and duration of action). Zaleplon and zolpidem-ER have different chemical structures. However, both are GABAA receptor agonists with preferential binding to the α -1 subunit, which is believed to be responsible for the drugs' sedative properties as well as for anterograde amnesic effects.³⁶

We do not believe residual sedation accounts for the reduced SDMC with zolpidem-ER 12.5 mg. since testing was done 9.5 hours post-dose and studies of this drug as a hypnotic indicate no residual sedation 8.5 to 9.5 hours post dosing.^{25,26,37} Although DSST scores with zolpidem-ER were slightly lower

than those with zaleplon and placebo, follow-up correlational analyses between DSST and WPT/FTT performance showed no significant findings, indicating that any residual sedation present in the zolpidem-ER condition did not predict performance on the memory tests. We also visually examined the data to determine if residual sedation was more likely to occur in females, since the FDA has recently lowered the recommended dosage of zolpidem-ER for women based on reports that some women eliminate zolpidem more slowly than men.³⁸ Our females did have lower DSST scores in the zolpidem-ER condition than in the other conditions, while males showed equivalent DSST scores in all three conditions. However, these scores were not correlated with WPT/FTT performance. In fact, males (in contrast to females) appeared to perform more poorly on the memory tests in the zolpidem-ER condition than in the other conditions.

It is important to note that although SDMC was reduced in the zolpidem-ER condition, memory improvement across the sleep period was present in all three conditions. The overnight percent change in FTT performance in the zaleplon and placebo conditions (14.4% to 15.4%) is similar to the improvement seen in published studies using the same test with overnight sleep ranging from 3.5 to 7.5 hours (14% to 18%).^{5,39} In comparison, the percent change with zolpidem-ER was only 8%. It is difficult to compare the WPT data (which show overnight improvements of 16% to 19%) with published studies because of variability of methodology, particularly in type and number of word pairs used in those studies. Nonetheless, these data suggest that sleep with a hypnotic does not prevent SDMC from occurring, but may reduce its magnitude.

Previous research has shown that certain aspects of sleep architecture may be associated with SDMC,³¹ although there is inconsistency among studies. In our exploratory analyses

(subject to type 1 error given the number of tests performed) we found only three significant correlations. In the placebo condition, FTT improvement correlated negatively with stage 2%. This conflicts with prior reports linking performance on this task with increased stage 2 or spindling.^{6,9,40} Also unexpected was the positive correlation between WPT improvement and REM%, as this task has been associated with SWS and/or stage 2.^{7,31,41,42} The single significant correlation in the drug conditions was a negative correlation between WPT percent change and SWS% in the zolpidem-ER condition, which also conflicts with previous findings that increases in SDMC are associated with increases in SWS.^{31,42,43} Perhaps the increase in SWS with zolpidem-ER does not have the same functional benefit as naturally occurring SWS. The fact that zolpidem increases slow wave activity only in frequencies ≤ 1 Hz^{44,45} provides some indication that the functional effect of increased SWS with zolpidem-ER may be different than naturally occurring SWS. The inconsistencies among studies suggest that many variables influence SDMC, so that there does not appear to be a simple relationship between gross measures of sleep and SDMC. Spectral analysis of the EEG may provide more insight into whether there is a relationship between sleep stages and memory consolidation with these hypnotics. Spindle detection analysis may also be beneficial since spindles have been linked with declarative^{7,46} and procedural memory.^{6,9,40,47}

Our findings, if confirmed, may have implications for the treatment of insomnia. If hypnotics negatively affect SDMC, cognitive-behavioral treatment should be considered instead of or prior to pharmacological treatment of chronic insomnia, assuming no other compelling reasons to favor pharmacotherapy. When pharmacological treatment is considered, there may be an advantage for *pro re nata* treatment of insomnia, rather than prophylactic treatment in anticipation of sleep disturbance. In other words, taking a drug routinely to prevent insomnia might be less preferable than intermittent use so that SDMC can be optimized on nights when drug is not needed. Similarly, short-acting drugs, which allow some drug-free sleep to occur, may interfere less with SDMC than longer-acting drugs. Use of short-acting drugs or a drug with delayed release could be particularly advantageous for patients with sleep maintenance insomnia, the most frequent insomnia phenotype, with a population prevalence reported to be 16.1% to 23.5%.^{18,48} However, a much better understanding of SDMC in insomnia patients is needed before making such recommendations. A modest amount of evidence suggests that SDMC may be impaired in primary insomnia.^{49,50} Whether use of hypnotic medication in this population worsens this impairment is unknown. The clinical significance of SDMC impairment, whether caused by insomnia, hypnotic use, or their combination must also be taken into consideration. Understanding the effects of hypnotics on SDMC in normal individuals without sleep problems or medical comorbidities is an important first step in this evaluation.

In conclusion, the findings of this study advance our knowledge of the effects of hypnotics on SDMC, an area with little research to date. The results suggest that in some circumstances hypnotics may have the potential to reduce the degree of SDMC and that drug-free sleep early in the night may ameliorate this effect. Future studies of SDMC would benefit from comparisons

of specific drugs administered at different doses and times as well as study of drugs with different mechanisms of action in individuals with insomnia as well as normal controls.

ABBREVIATIONS

ANOVA, analysis of variance; statistical test
 DSST, Digit Symbol Substitution Task
 EEG, electroencephalogram
 ER, extended-release drug
 FTT, finger-tapping task
 FTT-Pre, number of correctly-typed number sequences on the FTT test given before each sleep period
 FTT-Post, number of correctly-typed number sequences on the FTT test given after each sleep period
 PSG, polysomnography
 SDMC, sleep-dependent memory consolidation; the improvement in memory from pre-sleep to post-sleep
 SWS, slow wave sleep
 TST, total sleep time
 WASO, wake after sleep onset
 WPT, word pair task
 WPT-Pre, number of correctly-recalled word pairs on the WPT test given before each sleep period
 WPT-Post, number of correctly-recalled word pairs on the WPT test given after each sleep period

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