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The Use of Triazolam in Phase-Advanced Sleep

M.H. Bonnet, Ph.D., J.R. Dexter, M.D., J.C. Gillin, M.D., S.P. James, M.D., D. Kripke, M.D., W. Mendelson, M.D., and M. Mitler, Ph.D.

The need for optimal nocturnal performance continues to increase in our society. Nighttime function is dependent upon the ability to sleep effectively during the day. The current study examined daytime sleep after placebo, 0.125 mg (364 nmol), 0.25 mg (729 nmol), or 0.50 mg (1458 nmol) of triazolam, and nocturnal performance in the work shift that followed. Forty-one normal young adult subjects participated in a repeated-measures design in which each subject received each medication dose level in a separate week. The results indicated that day sleep increased as a linear function of drug dose from 234 to 374 minutes. Nocturnal alertness, as measured by subjective report and objective nap latency test, increased significantly following the use of triazolam, 0.25 and 0.50 mg, for the day sleep period. Nocturnal performance, as measured by auditory vigilance and additions, also increased significantly following the use of triazolam. Marginal evidence for medication hangover was found at the 0.50-mg dose, and it was therefore recommended that the use of the 0.50-mg dose be monitored carefully if performance demand were to follow medication use by less than 12 hours. The results for the study were interpreted as indicating that under certain conditions, triazolam could effectively increase daytime sleep and improve alertness and performance in the following nocturnal work period.

[Neuropsychopharmacology 1:225–234, 1988]

KEY WORDS: Sleep; Benzodiazepine; Psychomotor performance; Triazolam; Circadian rhythm

There is no clear consensus that people who must sleep at inappropriate circadian times on an occasional or a repeated basis will benefit significantly from the use of a hypnotic to consolidate or increase their sleep. At one level, it is not always readily accepted that these people even have a situational “illness,” or that the chronic nature of shifting schedules can be classified as “situational” (Freedman et al. 1984). However, on a more practical level, it is not known whether additional sleep provided by hypnotics will have a positive effect without residual hangover.

It is common practice for individuals moving to a night shift to stay awake for 24 hours before initiating a post–work-shift daytime sleep period. In general, sleep during this day is shortened and fragmented (Kripke et al. 1971; Seidel et al. 1984; Walsh et al. 1981) but can be increased significantly by the use of hypnotics (Seidel et al. 1984; Walsh et al. 1981; Scollo-Lavizzani 1983). In one study of this design (Walsh et al. 1986), nocturnal performance and alertness following the daytime use of triazolam, 0.5 mg, was not significantly improved. However, although Seidel et al. (1984) found performance and alertness following the daytime use of flurazepam, 30 mg, to be significantly decreased and did not report positive effects of triazolam as compared to placebo, a more extensive treatment of those data (Seidel et al. 1986) reported that multiple sleep latency test (MSLT) latencies at 0200, 0800, and 1000 hours were significantly longer in a night shift following the use of triazolam 0.5 mg (but not 0.25 mg) for day sleep than after placebo.

The strategy of prescribing medication following...
a nocturnal work shift ignores the discomfort and performance loss associated with the first nocturnal work period. Recent evidence suggests that a 4-hour evening nap prior to the initial nocturnal work shift can increase nocturnal performance compared to a no-sleep baseline condition (Nicholson et al. 1985). In the same study, the use of a medium-length-acting hypnotic, brotizolam, for the evening nap did not appear to offer additional benefits.

The insertion of significant sleep prior to a required nocturnal work shift appears to be a wise precaution, particularly when the nocturnal work requires highly skilled performance (e.g., health care, police, air traffic control, nuclear power plant control, and so on). However, sleep prior to the first nocturnal shift is very difficult because the period of prior wakefulness has been so short. Without medication, subjects sleep 6 hours or less even when kept in bed for the entire day (Asersinsky 1969). The present study sought to increase daytime sleep prior to a nocturnal work shift by using a short-acting hypnotic, triazolam, to determine (1) if day sleep prior to an initial nocturnal work shift could be significantly and efficiently increased, (2) if such increased day sleep would result in significantly improved nocturnal alertness and performance, and (3) if any detectable increase in nocturnal alertness/performance is related systematically to increased prior sleep.

METHODS

Forty-one male and female volunteers 20 to 45 years old without a history of significant work shift or sleep disturbance served as subjects at one of four study sites. Only those subjects without significant psychopathology and with a normal physical examination and normal blood and urine laboratory test values participated in the study. No subject took or received any psychotropic or sedating medication other than the experimental drugs for 7 days prior to or during the study. Additionally, subjects refrained from naps and alcohol ingestion for 2 days prior to and during the laboratory sessions (except as required in the protocol). Finally, subjects did not ingest caffeine for 8 hours prior to and during the laboratory sessions. All subjects gave their informed consent to these procedures.

Following selection but prior to the study proper, subjects were trained to criterion on the performance tasks used in the study. They were also given a copy of the study schedule and instruction on laboratory rules and the completion of subjective report forms. Each subject participated for 36-hour periods, which were usually scheduled 1 week apart. Each tour began with arrival at the laboratory at 2100 hours. Electrodes were attached for continuous monitoring of the central electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG), and each subject completed a presleep questionnaire. Subjects retired at 2300 hours and were awakened at 0700 hours. They completed a postsleep questionnaire and practiced performance tasks to be used later before being given breakfast at 0900. Following breakfast, subjects completed the Stanford Sleepiness Scale (SSS) and Profile of Mood States (POMS), and baseline performance was tested on Wilkinson Auditory Vigilance, Wilkinson Addition, and Williams Word Memory.

Wilkinson Auditory Vigilance—Subjects listened to tones presented at 2-second intervals for 30 minutes. Randomly, about every 2 minutes, a slightly shorter tone was presented. Subjects responded by pressing a button when they heard the shorter tone. Hit Rate (number of correct detections/number of signals presented) and False Alarm Rate were analyzed.

Wilkinson Addition—Subjects were presented with a book of random, two-digit, five-number addition problems. Subjects completed as many problems as possible in 30 minutes. Number correct and number incorrect were scored.

Williams Word Memory—A list of 15 words was presented via cassette tape recorder. As each word was vocalized, spelled, and again vocalized, the subject wrote the word on a piece of paper. Following word 15, the subject turned the page over and rewrote, in any order, as many words as he could remember. Total number of correct recalls from two lists was recorded.

At 1130 hours medication was administered. Subjects were randomly assigned to one of four orders of four conditions:

1. placebo
2. triazolam, 0.125 mg (364 nmol)
3. triazolam, 0.25 mg (729 nmol)
4. triazolam, 0.50 mg (1458 nmol). Subjects were put to bed at 1200 hours in private, sound-attenuated bedrooms. Subjects were required to remain in bed in the dark until at least 1600 hours without time cues. If, after 1600 subjects remained awake for more than 30 minutes, stated that they did not believe they could sleep any more, and requested to get up, they were allowed to sit up in bed and turn on the room light. Recording continued until 2000 hours, when all subjects were awakened and recordings completed. Subjects completed postsleep forms and were given dinner.

**Table 1**

<table>
<thead>
<tr>
<th>Lat 1 (r)</th>
<th>TST (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%W</td>
<td>%1</td>
</tr>
<tr>
<td>%2</td>
<td>%3</td>
</tr>
<tr>
<td>%4</td>
<td>%REM</td>
</tr>
<tr>
<td>EFA (n)</td>
<td></td>
</tr>
</tbody>
</table>
Starting at 2300, a 10-hour work/nap shift began with a Multiple Sleep Latency (nap) Test. Subjects took five nap tests (2-hour intervals) alternating with performance tasks until 0900 hours when they were allowed to leave the laboratory.

RESULTS

Night Sleep

All sleep recordings were scored using guidelines specified by Rechtschaffen and Kales (1968) by trained scorers at each center. As expected, no significant differences were found on any EEG or subjective report parameter when the data from the four baseline (premedication) nocturnal sleep periods were analyzed. Summary data from the combined night sleep periods are presented in Table 1, however, for comparison purposes.

Day Sleep

A total of 44 recordings were terminated prior to 460 minutes of total time in bed by subjects who had been awake for at least 30 minutes and requested to sit up. As these episodes were evenly distributed among conditions [13, 11, 12, and 8 episodes across placebo and the three increasing medication doses, respectively (χ² = 1.27, NS)], wakefulness prior to 460 minutes in terminated recordings was added to early final wake for analysis. Seventy-three percent of early termination came from one center, but data from each center are representative of the reported findings. Table 1 summarizes daytime EEG sleep values as a function of medication dose. For each sleep variable, a repeated-measures analysis of variance (ANOVA) was performed with a within-subjects term for drug dose and a between-subjects term for study center. A term for study center by drug dose interaction was also calculated. However, since these interaction terms were low (p > 0.25), the interaction variance was pooled to test the main effects for drug dose and study center. Significance was based on Greenhouse-Geisser p, and significant F and p values appear in the tables. Pairwise comparisons for significant drug dose effects were performed with the Neuman-Keuls procedure using the Greenhouse-Geisser df. Significant medication dose differences are presented in the column labeled “differences.”

Triazolam significantly reduced stage W (F = 37.28, p < 0.0001) in a dose-related fashion with each drug condition different from all others. Significant dose-related effects were also found for stage 2, which was increased in a dose-related fashion with all conditions differing from all others, and stage 3, with an increase at the 0.25-mg dose as compared to placebo, and rapid eye movement stage (REM), with an increase at 0.25 mg and 0.5 mg as compared to placebo. Significant dose effects were not found for stage 1 or stage 4.

Total sleep time and sleep efficiency were both significantly increased as a function of drug dose. For both variables all dose conditions differed significantly from all others. Awakenings greater than 10 minutes were also reduced as a function of medication dose. Significant drug-related differences were not found for latency to stage 1, which was in the 9- to 20-minute range for these normal sleepers in all conditions, or for latency to REM, or for awakenings greater than 1 minute.

Early final wake (EFA) data were examined in more detail because it was hoped that they might give an indication of the time course of triazolam activity as a function of dose for the day sleep period. Overall, the analysis of EFA indicated a significant effect for medication dose (F = 15.8), with EFA significantly reduced at the 0.5-mg dose as compared to

<table>
<thead>
<tr>
<th>Table 1. Study Sleep Parameters</th>
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<tbody>
<tr>
<td>Night sleep</td>
</tr>
<tr>
<td>Lat 1 (min)</td>
</tr>
<tr>
<td>TST (min)</td>
</tr>
<tr>
<td>%W</td>
</tr>
<tr>
<td>%1</td>
</tr>
<tr>
<td>%2</td>
</tr>
<tr>
<td>%3</td>
</tr>
<tr>
<td>%4</td>
</tr>
<tr>
<td>%REM</td>
</tr>
<tr>
<td>EFA (min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day sleep</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lat 1 (min)</td>
<td>10</td>
<td>7.5</td>
<td>7.6</td>
<td>9.0</td>
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<td>TST (min)</td>
<td>443</td>
<td>234</td>
<td>275</td>
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<td>50</td>
<td>40</td>
<td>33</td>
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<td>%1</td>
<td>6.8</td>
<td>6.2</td>
<td>5.8</td>
<td>5.2</td>
</tr>
<tr>
<td>%2</td>
<td>56</td>
<td>28</td>
<td>35</td>
<td>41</td>
</tr>
<tr>
<td>%3</td>
<td>5.6</td>
<td>2.4</td>
<td>3.2</td>
<td>4.2</td>
</tr>
<tr>
<td>%4</td>
<td>4.6</td>
<td>2.0</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>%REM</td>
<td>20</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>EFA (min)</td>
<td>4.6</td>
<td>155</td>
<td>140</td>
<td>122</td>
</tr>
</tbody>
</table>

private, acquired at 1600 maintained; they did numerous at 0 to 2000 and rested the rest sleep
the 0.25-mg dose, which was reduced compared to the placebo. A frequency plot of the cumulative percent of subjects awake from 5 hours postmedication or placebo can be seen in Figure 1. It can be seen in Figure 1 that the number of subjects awake increases as the sleep period progresses. At 5 hours postmedication, the same number of subjects are awake in the placebo and triazolam 0.125-mg conditions. By 7.5 hours postmedication, 80% and 78% of subjects are awake in the placebo or 0.125-mg condition and 0.25-mg conditions, respectively. At the end of the sleep period, 30% of subjects were still asleep in the 0.50-mg condition as compared to 15%, 10%, and 8% in the other three conditions. To determine the consistency of EFA (i.e., the tendency for the subjects who slept well in one condition to sleep well in other conditions), Pearson $r$ correlations were computed between EFA following placebo and each of the three medication conditions. Correlations for EFA for the nocturnal sleep periods were also computed for comparison purposes (Table 2). The correlations indicate that there is a highly significant relationship (usually $p < 0.001$) between length of early awakening following placebo and length of early awakening following each dose of medication. These correlations are of a similar magnitude to those found in length of early awakening when the night sleep were compared in the same fashion (Table 2).

In summary, strong drug-dose related increases in total sleep of up to 140 minutes were found. The increases were primarily in stage 2 sleep, but small increases in stage 3 and REM were also seen.

Subjective ratings of daytime sleep agreed closely with the objective EEG parameters (Table 3). Subjects estimated that their sleep latency was shorter after 0.5 mg of triazolam than after placebo. They also estimated their total sleep as longer after 0.25 and 0.50 mg of triazolam. Awakenings were estimated to be more frequent after placebo than all medication conditions, and sleep quality the worst.

**Table 2. Pearson Correlations for Early Final Wake Between Placebo and Medication Administration Sleep Periods ($n = 41$)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nocturnal sleep</th>
<th>Placebo day sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125 mg</td>
<td>0.52$^a$</td>
<td>0.56$^a$</td>
</tr>
<tr>
<td>0.25 mg</td>
<td>0.52$^a$</td>
<td>0.55$^a$</td>
</tr>
<tr>
<td>0.50 mg</td>
<td>0.37$^b$</td>
<td>0.45$^b$</td>
</tr>
</tbody>
</table>

$^a p < 0.001.$

$^b p < 0.05.$
Table 3. Subjective Day Sleep Values

<table>
<thead>
<tr>
<th>Day sleep questions</th>
<th>Placebo</th>
<th>0.125 mg</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
<th>F&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective latency</td>
<td>25.6</td>
<td>22.3</td>
<td>19.8</td>
<td>16.5</td>
<td>3.47</td>
<td>0.05</td>
<td>Pl &gt; 0.5</td>
</tr>
<tr>
<td>Subjective awakenings</td>
<td>4.6</td>
<td>2.2</td>
<td>1.9</td>
<td>1.6</td>
<td>3.65</td>
<td>0.05</td>
<td>Pl &gt; All</td>
</tr>
<tr>
<td>Subjective sleep length</td>
<td>4.2</td>
<td>4.6</td>
<td>5.4</td>
<td>6.3</td>
<td>14.86</td>
<td>0.05</td>
<td>Pl = 0.1 &lt; 0.25 &lt; 0.5</td>
</tr>
<tr>
<td>Sound sleep</td>
<td>3.3</td>
<td>4.0</td>
<td>4.4</td>
<td>4.8</td>
<td>12.26</td>
<td>0.05</td>
<td>Pl &lt; 0.1 = 0.25</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>3.5</td>
<td>4.3</td>
<td>4.5</td>
<td>4.7</td>
<td>7.84</td>
<td>0.05</td>
<td>Pl &lt; 0.1 &lt; 0.5</td>
</tr>
<tr>
<td>Sleepy now</td>
<td>1.4</td>
<td>1.4</td>
<td>1.8</td>
<td>1.8</td>
<td>2.58</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Refreshed</td>
<td>3.4</td>
<td>3.7</td>
<td>3.8</td>
<td>3.8</td>
<td>1.48</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tense</td>
<td>1.4</td>
<td>1.2</td>
<td>1.4</td>
<td>1.2</td>
<td>2.33</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Subjective scales were 1–7 ratings from “Not at all” to “Very.”
<sup>b</sup> df = 3,108.

Sleep was more sound after all doses of medication as compared to placebo. No significant differences were found in ratings of tenseness at awakening, feeling refreshed at awakening, or sleepiness at awakening.

Nocturnal Performance, Sleepiness, and Mood

The performance, sleepiness, and mood tests were repeated over the course of the nocturnal performance periods. As a result, additional repeated-measures ANOVA terms for test time and time by drug dose interaction were included in the analyses. Otherwise, analysis for these variables was analogous to that for the sleep variables. Highly significant time of night effects were found for most variables. These effects, which were not related to medication efficacy, are not detailed here. No drug dose by time of night interactions were significant. Therefore main effects for medication dose are described. Trend analyses for sleepiness and performance across the night were computed for each drug dose. Also, trend analyses across dose levels were computed at the nocturnal test points. However, these latter trend analyses did not differ as a function of test point and are therefore not reported.

Multiple Sleep Latency Test (MSLT) data are presented in Figure 2. Significant overall medication effects were found (F = 10.61, p < 0.001). Latencies averaged 1.6 to 2.2 minutes longer (both significant) following daytime triazolam use (0.25 and 0.50 mg, respectively). Trend analyses revealed strong linear components in all conditions. Only one higher-order fit, a cubic trend in only the 0.50-mg condition, was statistically significant [F(1,119) = 5.58, p < 0.05]. This component reflects the dip in nap latency in the 0.50-mg condition at the 2300-hour nap.

Because learning effects are frequently found in performance data, weekly predrug baseline performance values were subtracted from nocturnal performance values prior to the standard ANOVA. Wilkinson Addition data indicated an overall significant increase in both correctly completed problems after all drug doses (Figure 3; F = 5.40, p < 0.001) and a significant increase in incorrect additions (F = 6.52, p < 0.001). About nine more correct additions and about two more incorrect problems were completed (which resulted in the percent of correct addition problems changing from 95% to 94%). Trend analyses differed between conditions primarily by indicating a significant quadratic component in only the placebo condition [F(1,119) = 10.6, p < 0.01]. This component probably reflected the steeper decline in placebo performance between 0130 and 0530 and the steeper increase in performance at 0730. Wilkinson Vigilance Hit Rate was significantly increased after all medication conditions as compared to placebo (Figure 4; F = 5.82, p < 0.001). Trend analyses differed primarily in the presence of a significant quadratic effect in only the 0.25-mg condition [F(1,119) = 11.8, p < 0.01]. Significant differences were found in Wilkinson Vigilance False Alarm Rate. A significant effect for condition was found for the Williams Word Memory Test (F = 3.26, p < 0.05), but Neuman–Keuls pairwise comparisons revealed no significant drug condition differences.

Mood data are presented in Table 4. As with the performance data, no significant time of night by drug dose interactions were found. Therefore, only overall medication effects will be presented. On the Standard Sleepiness Scale, subjects reported being overall less sleepy during the night following day sleep that had been increased by triazolam 0.5 mg as compared to placebo. Similar results were seen on...
the POMS Fatigue Scale (Table 4 and Fig. 5), where significantly less fatigue was reported following triazolam 0.5-mg sleep than all other conditions. The POMS Vigor Scale was significantly increased following the 0.5-mg dose, and POMS Confusion was reduced. No significant drug-related differences were found for POMS Depression, Anger, or Tension Scales.

In summary, overall increases in objective and subjective nocturnal alertness were found, particularly following sleep lengthened by triazolam 0.5 mg. Improvement was also seen in correctly completed addition problems and vigilance hit rate following increased day sleep. However, an increase in incorrect additions was also found.

**DISCUSSION**

Subjects entered the study with similar amounts of prior sleep on each week. This implies that the strong drug-related increases in total day sleep time can be directly attributed to the medication. Total day sleep times showed an increase of about 40 minutes with each increase in drug dose. Stage 2 sleep, stage 3 sleep, and REM sleep were increased after triazolam use as compared to placebo. The SWS and REM findings are not usually reported for triazolam and probably reflect the increase and consolidation of sleep in the medication conditions. Subjective ratings were generally consistent with the objective EEG data. When subjects arose at 2200 hours, they did not report being any sleepier, less refreshed, or more tense in any medication condition. The sleep data indicate that the day sleep was improved by the medication, but that even at the 0.5-mg dose, 20% of the sleep period was spent awake. The early final wake data, which document inability to return to sleep at the end of the recording period, further clarify the day sleep period and demonstrate the medication dose effects. The data indicate that many subjects had difficulty in returning to sleep in the second half of the recording period and that the inability to return to sleep was related to medication dose.

The data from the nocturnal work shift are in general agreement with the day sleep data. The data consistently showed increased alertness (longer MSLT latencies), increased vigilance and correct addition performance, and decreased subjective fatigue and sleepiness in a general drug dose-related fashion. However, although total sleep was in-
increased 60% at the 0.5-mg dose, performance and alertness increased only 10%–20% on most tasks. It was also found that there was an increase in incorrect addition problems in the medication conditions compared to placebo. This finding can be explained by the fact that following placebo, total additions (and incorrect additions) were reduced as compared to baseline. Following medication, total additions were slightly above predrug baseline level and incorrect additions, although increased as compared to placebo, were still below predrug baseline. Statistical analysis showed no significant time of night by triazolam dose interactions, and performance generally was best after the 0.5-mg dose. However, trend analyses for the MSLT data (Fig. 2) indicated from a cubic component that at the first nocturnal testing point, sleepiness may have been slightly greater after the 0.5-mg dose than it would have been expected to be after that dose based on later data. Inspection of individual data revealed that 5 of the 41 subjects had decreased nap latencies compared to the 0.25-mg dose at the initial nap. As this testing point occurred about 12 hours after medication administration, and other work has shown hangover effects lasting 10 to 16 hours after administration of triazolam 0.5 mg (Veldkamp et al. 1974; Nicholson and Stone 1980), it is possible that some hangover from the 0.5-mg dose might have existed in the 8- to 12-hour postdrug time period.

Performance, which was analyzed with respect to predrug baseline, appeared to be maintained throughout the night except for normal circadian influences. Performance was at predrug baseline levels at the completion of the nocturnal work shift in the 0.5-mg condition but was about 15% decreased in the placebo condition. This can be compared with about a 30% performance decrease on these tasks with no prior afternoon nap (Bonnet 1986). Subjective fatigue, although significantly reduced by triazolam 0.5 mg throughout the night, nonetheless remained elevated above predrug baseline in all conditions at the end of the nocturnal work shift (Fig. 5). The MSLT values, although increased postmedication, still were in the range that might be considered "pathologically sleepy." The 2-minute increase in nap latency following medication does not appear to be a large difference. However, it is clear that sleepiness as measured by MSLT is not a linear relationship at low values. These values can be compared with nap latencies of about 2 minutes (Bonnet 1986) after sleep loss with no prior nap.

The most parsimonious view of the data is that triazolam was successful in increasing daytime sleep and that this increased sleep helped to maintain nocturnal alertness. This explanation is strengthened by Nicholson et al. (1985), who found that a 4-hour evening sleep resulted in increased nocturnal performance as compared to a nonsleep condition. How-
ever, only one previous study that has used hypnotics to facilitate daytime sleep has shown significantly improved nocturnal alertness as compared to placebo conditions (Seidel et al. 1984, 1986; Schweitzer et al. 1986). One factor that may account for this is the fact that subjects in those studies have typically slept very little in the 24 hours before beginning their daytime drug or placebo sleep period (i.e., sleep deprivation and phase advance as opposed to sleep satiation and phase advance in the current study). As a result, total daytime sleep was not greatly increased (Seidel et al. 1984; Schweitzer et al. 1986) in medication as compared to placebo conditions because sleep propensity was greater in the placebo conditions and probably masked some of the medication effects.

Nicholson et al. (1985) allowed a 4-hour evening nap facilitated by brotizolam 0.125 mg or placebo prior to a nocturnal work period. Although evening sleep was improved by the medication, residual performance decrement was found after medication-associated sleep. Such hangover probably resulted from performance demand 4 to 5 hours after the use of the intermediate half-life brotizolam.

The beneficial effects of the medication reported in the current study were presumably related to (1) the placement of the nap period at a time when the natural propensity to sleep was relatively low, (2) the

Table 4. Profile of Mood States and Stanford Sleepiness Scale (SSS) Mean Data

<table>
<thead>
<tr>
<th>POMS variable</th>
<th>Placebo</th>
<th>0.125 mg</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
<th>F^b</th>
<th>p</th>
<th>Diff^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension</td>
<td>4.4</td>
<td>4.2</td>
<td>4.3</td>
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<tr>
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<td>1.51</td>
<td>NS</td>
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<tr>
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<td>1.6</td>
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<td>1.88</td>
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<tr>
<td>Vigor</td>
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<td>7.9</td>
<td>8.6</td>
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<td>0.05</td>
<td>0.5 &gt; .25 = Pl</td>
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<tr>
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<td>7.93</td>
<td>0.01</td>
<td>0.5 &lt; All</td>
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<td>6.8</td>
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<td>3.6</td>
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<td>5.50</td>
<td>0.01</td>
<td>0.5 &lt; 0.25 = Pl</td>
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</table>

^a Subjective scales all rate from low to high.

^b df = 3,108.

^c p < 0.05.
short metabolic half-life of triazolam, (3) the evaluation of a relatively large number of subjects, and (4) allowance of sufficient time for the medication to metabolize prior to work demand.

The current study was designed primarily as a dose-finding study, and the results may therefore not be directly applicable to individuals shifting to night work or traveling across time zones. As such, some cautions are appropriate. Although the sleep data indicate that the ability to maintain sleep returned to placebo levels 5 hours after administration of triazolam 0.125 mg and 7.5 hours after administration of triazolam 0.25 mg, extended mood and performance testing did not begin in the current study until 11.5 hours after medication administration. Also, the current study clearly cannot describe the effects of chronic or frequent medication use.

With these caveats in mind, the early final wake data do indicate continuing sleep-producing activity of the 0.125-mg dose for 4 to 5 hours after administration (Fig. 1). No evidence of idiosyncratic responding (much longer or shorter length of activity in some subjects) was seen, although the subject group was carefully chosen to be young and healthy. Other data from midazolam, a benzodiazepine with similar half-life, indicate little hangover when that medication was administered at a 15-mg dose 5 hours before morning testing (Roth et al. 1985). Possible continuing activity of the 0.25-mg dose in producing sleep was seen until 6.5 to 7.5 hours following medication administration in the current study, and the 0.5-mg dose appeared to be maintaining activity even at the 2000 hours “lights on” time. These data agree well with those presented by Seidel et al. (1986), who showed that triazolam 0.5 mg significantly decreased wakefulness within sleep through the fourth quarter of the day sleep period (%W being 20% in the fourth quarter after triazolam 0.5 mg versus 43% after placebo). Triazolam 0.25 mg reduced wake during the third quarter of the sleep period (%W being 14% in the third quarter after triazolam 0.25 mg versus 30% after placebo), although this was not statistically significant, but was much less effective in the fourth quarter (%W being 37% after triazolam 0.25 mg versus 43% after placebo). Although other studies have not shown evidence of
hangover from the 0.25-mg dose more than 8.5 hours after administration, hangover effects from the 0.5-mg dose have been reported for as long as 16 hours after administration (Veldkamp et al. 1974; Nicholson and Stone 1980). In general, these studies confirm the potency of triazolam during 5 to 6 hours after administration and suggest that alertness may be impaired if subjects must be aroused and perform tasks during this period. Clearly, individual sensitivity to the medication may exist such that some individuals on lower doses of medication may be impaired for longer periods of time while other individuals may not be impaired after higher doses.

In summary, phase-advanced total sleep was increased in a dose-related fashion in the current study. Similarly, subsequent nocturnal alertness, performance and mood were increased in a dose-related fashion. Evidence for significant hangover effects was not found. This study presents the first evidence that the use of a benzodiazepine hypnotic may under certain circumstances result both in significantly improved post-sleep objective alertness and performance as compared to placebo. The use of a nocturnal prophylactic nap prior to an initial all-night work shift appears to improve nocturnal performance and alertness by 30% to 50%, and the use of triazolam to extend that nap may improve alertness and performance an additional 15% to 40%.

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