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Combined effects of methamphetamine and zolpidem on performance and mood during simulated night shift work

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Abstract

Individuals who work irregular or rotating shifts often use stimulants and sedatives to offset shift-change-related mood and performance decrements. During this simulated shift work study the acute effects of the stimulant, methamphetamine were examined, and the effects of the hypnotic, zolpidem, and the combination were assessed during the shift after drug administration. Eight volunteers completed this 21-day, within-participant, residential laboratory study during which they received a single oral methamphetamine dose (0 or 10 mg) 1 h after waking, i.e., before task performance, and a single oral zolpidem dose (0 or 10 mg) 1 h before bedtime under 2 shift conditions: day shift and night shift. When participants received placebo at both dosing times, performance on some psychomotor tasks (e.g., the digit-symbol substitution task) and on some measures of mood (e.g., ratings of "Energetic") were disrupted during the night shift, relative to the day shift. Methamphetamine alone eliminated virtually all shift-related disruptions, while zolpidem alone and the drug combination produced few effects. These data indicate that shift changes produce performance impairments and mood alterations that are improved by a single low to moderate dose of methamphetamine. Zolpidem, given alone or in combination with methamphetamine, did not alleviate most shift-change mood and performance effects.

Keywords: Mood; Performance; Shift-work; Stimulant; Hypnotic; Humans

1. Introduction

Individuals who are required to work irregular or rotating shifts frequently adjust their sleep–wake cycles, and report sleep disruptions and increased sleepiness while working (U.S. Congress and Office of Technology Assessment, 1991). These conditions may contribute to diminished performance and work-related accidents. Indeed, Ohayon et al. (2002) reported that rotating shift workers were not only more likely to report feeling sleepy at work, but that they were also more likely to have work-related accidents, possibly due to impaired performance. Other researchers have also reported diminished performance among shift workers (e.g., Browne, 1949; Bjerner et al., 1955; Tilley et al., 1982).

Consequently, many shift workers take medications in an effort to counterbalance shift change-associated performance, sleep and mood disruptions, (e.g., Gold et al., 1992; Niedhammer et al., 1995). A growing number of studies have examined the effects of short-acting non-benzodiazepine hypnotics on daytime sleep and nighttime performance. A recent study from this laboratory, for example, investigated the effects of zolpidem (a short-acting nonbenzodiazepine hypnotic), administered for 3 consecutive days, on psychomotor task performance and mood during simulated shift work (Hart et al., 2003b). While zolpidem improved subjective reports of sleep quality and, to a lesser extent, next-day performance,

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next-day mood was worsened by zolpidem, particularly by the third night of zolpidem administration. These data suggest that short-term zolpidem treatment effectively attenuated some shift-change-related disruptions, but that some residual drug effects on mood emerge over several days of drug administration.

Stimulants have also been shown to be beneficial under conditions during which performance and/or mood are compromised by circadian rhythm misalignment, sleep loss, or fatigue. Caffeine and modafinil both have been reported to be useful countermeasures (e.g., Walsh et al., 1990; Caldwell et al., 2000a). Amphetamines have also been demonstrated to attenuate performance and mood decrements (Baranski and Pigeau, 1997; Magill et al., 2003). Indeed, a large body of empirical evidence indicates that amphetamines are efficacious for lessening performance and mood decrements caused by sleep-deprivation (e.g., Wiegmann et al., 1996; Baranski and Pigeau, 1997; Caldwell et al., 2000b). Furthermore, methamphetamine has been demonstrated to attenuate many shift-change-related disruptions in performance and mood. Hart et al. (2003a) administered methamphetamine for 3 consecutive days to individuals undergoing abrupt work shift schedule changes, and reported that methamphetamine reduced virtually all night shift-related performance and mood impairments, and improved performance on some measures that were not disrupted.

While the above describes data indicating that hypnotics and stimulants when administered alone can function as effective countermeasures to performance and mood decrements caused by circadian rhythm misalignment, sleep loss, and/or fatigue, it is likely that many shift workers use both sleeping medications and stimulants when working irregular shifts. Given that zolpidem has been reported to produce negative effects on the next-day mood of individuals subjected to simulated shift work, one concern is that the combination of zolpidem and methamphetamine might produce greater negative effects than either drug alone. The purpose of this study was to examine the acute effects of methamphetamine and the next-day effects of zolpidem alone and in combination with methamphetamine on behaviors of individuals undergoing simulated shift work. Participants received a single oral methamphetamine dose (0 or 10 mg) 1 h after waking before doing performance tasks and a single oral zolpidem dose (0 or 10 mg) 1 h before bedtime under two shift conditions: (a) During the day shift, participants performed computerized psychomotor tasks from 0830 to 1730 and went to bed at 2400, and (b) during the night shift, participants performed tasks from 0030 to 0930 and went to bed at 1600. We hypothesized that (1) the drug combination would be well tolerated, (2) but next-day performance and mood would be disrupted relative to placebo or zolpidem alone, and (3) disruptions would be greater during the night shift than during the day shift.

2. Methods

2.1. Participants

Eight healthy research volunteers (mean age 31.6 ~ 7.8 [± S.D.]) completed this 21-day residential study: 2 were female (1 Black, 1 Asian) and 6 were male (3 Black, 3 White). Participants were solicited via word-of-mouth referral and newspaper advertisement in New York City. All participants reported previous stimulant use (7 reported using amphetamines at least once, 5 reported using cocaine at least once, 2 reported using both amphetamines and cocaine at least once, 2 reported current cocaine use [2–3 times per week], and 6 reported current caffeine use [1–28 cups per week]). Six participants reported current alcohol use (1–18 drinks per week), 2 reported current marijuana use (1–3 times per month), and 7 smoked 1–15 tobacco cigarettes per day. Note that the individuals who reported current cocaine and current marijuana use were not the same individuals. All participants reported previous experience working irregular shift schedules. During screening, all volunteers passed comprehensive medical and psychological evaluations, and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table (mean weight [± S.D.] = 75.3 ~ 13.2 kg).

Participants were told that the purpose of the study was to evaluate the effects of medications on performance and subjective-effects of shift workers. Before the commencement of any procedures, each participant signed a consent form approved by the New York State Psychiatric Institute's Institutional Review Board. At the end of the study, each participant was fully informed about experimental and drug conditions, and was paid for their participation. For completing the entire study, they were compensated at a rate of $70 per day, which was paid in two weekly installments.

2.2. Laboratory

Two groups of 4 individuals stayed in a residential laboratory in the New York State Psychiatric Institute (Foltin et al., 1996). The laboratory is not equipped with windows, so participants were not exposed to sunlight throughout their study participation. Light intensity (measured by Sekonic Handy Lumi, Elmsford, NY) inside the laboratory ranged from 20 to 200 lux (lx), with an estimated average intensity in most work areas of ~ 100 lx. The laboratory has a common social area, where participants were free to engage in recreation activities. This area contained two couches, chairs, two video-game machines, two television monitors for viewing videotaped films, free-weight exercise equipment, art supplies, reading materials, board games, and two washers/dryers. Each participant had a bedroom with a bed, desk, Macintosh computer system, microwave, toaster, refrigerator, and food preparation space. For the purpose of continuous

observation of behavior, cameras and microphones were located throughout the common social area and in bedrooms. However, no microphones or cameras were located in bathrooms, showers, or private dressing areas. Communication between the staff and participants was kept to a minimum and was primarily accomplished via a continuous on-line computer network system consisting of the computers in each participant's bedroom and a computer in the control room.

2.3. Design

Before beginning the study, participants completed two training sessions (3–4 h per session) on the computerized tasks that would be used during the study. On 2 separate days, they received a methamphetamine capsule (10 mg) and a zolpidem capsule (10 mg) to provide them with experience with the study drug and to detect any adverse reaction. No untoward events were noted.

The study design for the two groups of participants is shown in Table 1. During this study, participants worked (i.e., completing computerized task batteries) on two different shifts. During the day shift, they performed computer tasks from 0830 to 1730 and went to bed at 2400. During the night shift, they performed computer tasks from 0030 to 0930 and went to bed at 1600. Shifts alternated three times during the study, and shift conditions were separated by an "off" day during which participants were not on a schedule and data were not collected. One group of participants started on the night shift, and the other started on the day shift. Placebo or methamphetamine (10 mg) was administered 1 h after waking and placebo or zolpidem (10 mg) was administered 1 h before bedtime. Ten mg was selected as the active dose for both drugs because it reliably attenuates many shift-change-related performance decrements (Hart et al., 2003a,b). During the first 3 in-patient days, participants received placebo capsules at each dosing time while working on the day or night shift. Day 4 was an off day. On Days 5–10, participants began working on a different shift (e.g., participants who started on the night shift were switched to the day shift), and they received active zolpidem alone, methamphetamine alone, and the combination. A placebo day separated each active drug day to allow adequate drug washout. Day 11 was another off day. On Days 12–17, participants began working on a different shift and they received active zolpidem alone, methamphetamine alone, and the combination. Again, a placebo day separated each active drug day. Day 18 was another off day. On the final 3 days (Days 19–21), participants began working on a different shift and they received placebo capsules at each dosing time. Participants moved out of the laboratory on Day 22.

Table 1
Study design

Study day	Group 1		Group 2	
	Shift condition	Drug condition	Shift condition	Drug condition
1	Day	Pbo/Pbo	Night	Pbo/Pbo
2	Day	Pbo/Pbo	Night	Pbo/Pbo
3	Day	Pbo/Pbo	Night	Pbo/Pbo
4	Off	Off	Off	Off
5	Night	Pbo/Pbo	Day	Pbo/Pbo
6	Night	Pbo/Zol	Day	Pbo/Zol
7	Night	Pbo/Pbo	Day	Pbo/Pbo
8	Night	MA/Zol	Day	MA/Zol
9	Night	Pbo/Pbo	Day	Pbo/Pbo
10	Night	MA/Pbo	Day	MA/Pbo
11	Off	Off	Off	Off
12	Day	Pbo/Pbo	Night	Pbo/Pbo
13	Day	MA/Zol	Night	MA/Zol
14	Day	Pbo/Pbo	Night	Pbo/Pbo
15	Day	Pbo/Zol	Night	Pbo/Zol
16	Day	Pbo/Pbo	Night	Pbo/Pbo
17	Day	MA/Pbo	Night	MA/Pbo
18	Off	Off	Off	Off
19	Night	Pbo/Pbo	Day	Pbo/Pbo
20	Night	Pbo/Pbo	Day	Pbo/Pbo
21	Night	Pbo/Pbo	Day	Pbo/Pbo

Actual shift condition and dosing order for the two groups of participants. Drug dosing times were 0915 and 2300 during the day shift and 0115 and 1500 during the night shift (i.e., 1 h after waking and 1 h before bedtime). Pbo/Pbo=placebo was administered at both dosing times; Pbo/Zol=placebo was administered after waking and zolpidem (10 mg) was administered before bedtime; MA/Zol=methamphetamine (10 mg) was administered after waking and zolpidem (10 mg) was administered before bedtime; MA/Pbo=methamphetamine (10 mg) was administered after waking and placebo was administered before bedtime. Off=off day.

2.4. Procedure

Participants moved into the laboratory on the day before the study, at which time they received additional training on tasks and experimental procedures. The 1st experimental day began at 0015 (i.e., the night shift) for 4 participants and at 0815 (i.e., the day shift) for 4 participants the following morning. Participants first completed baseline psychomotor tasks, a 50-item subjective-effects visual analog questionnaire, and a visual analog sleep questionnaire. They were then weighed (but were not informed of their weight) and given time to eat breakfast. Following breakfast, participants completed eight 30-min computerized task batteries, composed of the subjective-effects questionnaire and psychomotor tasks, each day. Note that task batteries were performed in the participants' individual bedrooms. Each task battery was separated by a 15-min break. From 1000 to 1245 (0200 to 0445), participants completed four task batteries and, after a 1-h break period, they completed four additional task batteries from 1430 to 1715 (0630 to 0915). Beginning at 1730 (0930), participants had access to activities available in the social area. Two videotaped films were shown daily, beginning at 1900 and 2130 (1100 and 1330). Lights were turned out at 2400 (1600) for an 8.25-h sleep period.

2.5. Subjective-effects and psychomotor battery

The computerized visual analog questionnaire consisted of a series of 100-mm lines labeled "not at all" at one end and "extremely" at the other end (Haney et al., 1999). The lines were labeled with words describing a mood (e.g., "Anxious," "Angry," "Frustrated"), a drug effect (e.g., "High," "Good Drug Effect," "Bad Drug Effect"), or a physical symptom (e.g., "Headache," "Stomach Upset," "Muscle Pain"). Participants completed a visual analog sleep questionnaire each morning. This questionnaire consisted of a series of 100-mm lines labeled "not at all" at one end and "extremely" at the other end. The lines were labeled "I slept well last night," "I woke up early this morning," "I fell asleep easily last night," "I feel clear-headed this morning," "I woke up often last night," and "I am satisfied with my sleep last night," and a fill-in question asking for an estimate of how many hours participants thought they slept the previous night was included (Haney et al., 2001).

Computerized psychomotor tasks consisted of a digit recall task, digit-symbol substitution task (DSST), divided attention task (DAT), rapid information task (RIT), and repeated acquisition task. *Digit Recall Task*. During this task, an 8-digit number was displayed for 3 sec on the computer screen. Participants were instructed to enter the number correctly while it was on the screen and again after it had disappeared from the screen. They were also told that they would be asked to reproduce and recognize the number near the end of the battery. This task was designed to assess changes in immediate and delayed recall. *DSST*. This 3-min task (McLeod et al., 1982) consisted of 9 random 3-row X 3-column squares (one square blackened/row) displayed across the top of the computer screen. Each array was associated with a number (1–9). A randomly-generated number appeared at the bottom of the screen, indicating which of the arrays should be reproduced on the 9-key keypad attached to the computer. Participants were instructed to reproduce as many patterns as possible by entering the patterns associated with the randomly generated numbers. This task was designed to assess changes in visuospatial processing. *DAT*. This 5-min task consisted of concurrent pursuit-tracking and vigilance tasks (Miller et al., 1988). Participants tracked a moving circle on the video screen using the mouse, and also had to signal when a small black square appeared at any of the four corners of the screen. Accurate tracking of the moving stimulus increased its speed proportionately. This task was designed to assess changes in vigilance and inhibitory control. *RIT.* During this 10-min task (Wesnes and Warburton, 1983) a series of digits was displayed rapidly on the computer screen (100 digits/min), and participants were instructed to press a key as quickly as possible after three consecutive odd or even digits have appeared. This task was designed to assess changes in sustained concentration and inhibitory control. *Repeated Acquisition Task*. At the start of this 3-min learning task, 4 buttons were illuminated, and participants were instructed to learn a 10-response sequence of button presses (Kelly et al., 1993). A position counter incremented by one each time a correct button was pressed, and remained unchanged after an incorrect response. The points counter increased by 1 each time the 10-response sequence was correctly completed. The sequence remained the same throughout the task, but a new random sequence was generated when the task occurred again. Participants were instructed to earn as many points during the task as possible by pressing the buttons in the correct sequence. This task was designed to assess changes in learning and memory. It should be noted that cognitive/psychomotor task performance was maintained by instructional control rather than explicit reinforcement.

2.6. Medications

The Pharmacy Department of the New York State Psychiatric Institute repackaged tablets of methamphetamine hydrochloride (5 mg; Desoxyn®, Abbott Laboratories, North Chicago, IL) and tablets of zolpidem hydrochloride (5 mg; Ambien®, G.D. Searle and Company, Chicago, IL) by placing tablets into a white #00 opaque capsule and adding lactose filler. Placebo consisted of white #00 opaque capsules containing only lactose. Methamphetamine dosing times were upon waking at 0915 (day shift) and 0115 (night shift), and zolpidem dosing times were prior to bedtime at 2300 (day shift) and 1500 (night shift). All capsules were administered double-blind.

2.7. Data analysis

The area-under-the-curve (AUC) for the subjective-effects visual analog questionnaire and psychomotor performance measure was determined using the trapezoidal method (Tallarida and Murray, 1981). AUC was used instead of peak effect data to detect effects that occurred throughout the entire day, instead of only one time point. Peak effect data were also analyzed, but for the sake of brevity, only AUC data are presented, as the results were similar.

Data were analyzed using a three-factor repeated measures analyses of variance (ANOVA): the first factor was drug condition (placebo or active methamphetamine or zolpidem), the second factor was shift condition (day, night), and the third factor was day within condition (1, 2, 3). Data from off days (Days 4, 11, and 18) were not included in the analyses. For all analyses, ANOVAs provided the error terms needed to calculate planned comparisons that were designed to answer two questions: (1) are psychomotor task performance and subjective-effects ratings disrupted during the night shift, and (2) are there interactive effects of shift condition and drug condition? To evaluate night shift-related disruptions, each day of placebo was compared to the corresponding night of placebo (e.g., the first day of placebo during the day shift versus the first night of placebo during the night shift). To evaluate the effects of methamphetamine alone on night shift-related

disruptions, the night during which participants received methamphetamine after waking and placebo before bedtime was compared to the second night of placebo (e.g., Day 10 versus Day 20; see Table 1—Group 1). To evaluate the effects of zolpidem alone on next-night shift-related disruptions, the night following zolpidem administration at bedtime was compared to the second night of placebo (e.g., Day 7 versus Day 20; see Table 1–Group 1). To evaluate the effects of the methamphetamine–zolpidem combination on next-night shift-related disruptions, the night following administration of the drug combination was compared to the second night of placebo (e.g., Day 9 versus Day 20; see Table 1–Group 1). The second night was used as the comparator because shift-change-related disruptions are more pronounced on the first night of shift work and abates by the third night of shift work (Hart et al., 2003a). Drug-related effects during day shift work were evaluated similarly. Only those p values < 0.05 were considered statistically significant and Hunyh–Feldt corrections were used.

3. Results

3.1. Effects of shift condition

The upper panel of Fig. 1 shows how selected psychomotor performance varied between the day and night shift when participants received placebo. As expected, performance was disrupted during night shift work. The tracking speed on the DAT, the number of digits entered (data not shown), the number of trials attempted (DSST; data not shown), and the number of correct responses (DSST) all were decreased during at least two of the three nights that participants worked on the night shift compared to corresponding days of the day shift ($p<0.05$). On average, the AUC for mean number of digits entered decreased from 90 during day shift days to 67 during night shift nights. Other measures were also disrupted during the night shift. For example, the AUC for mean number of misses on the RIT and the AUC for mean hit latency on the DAT (a measure of complex reaction time) increased during at least two of the three nights that participants worked on the night shift compared to corresponding days of the day shift ($p<0.05$). On average, the AUC for mean number of misses on the RIT during day shift days was 180, compared to 225 during night shift nights. In addition, the AUC for mean number of errors made on the repeated-acquisition task was significantly higher during the second night of night shift work, relative to the second day of day shift work ($p<0.05$; data not shown).

The bottom panels of Fig. 1 show how selected subjective-effects ratings varied between the day and night shift when participants received placebo. Ratings of "Alert" (data not shown), "Energetic," and "Stimulated" (data not shown) were decreased during at least two of the three

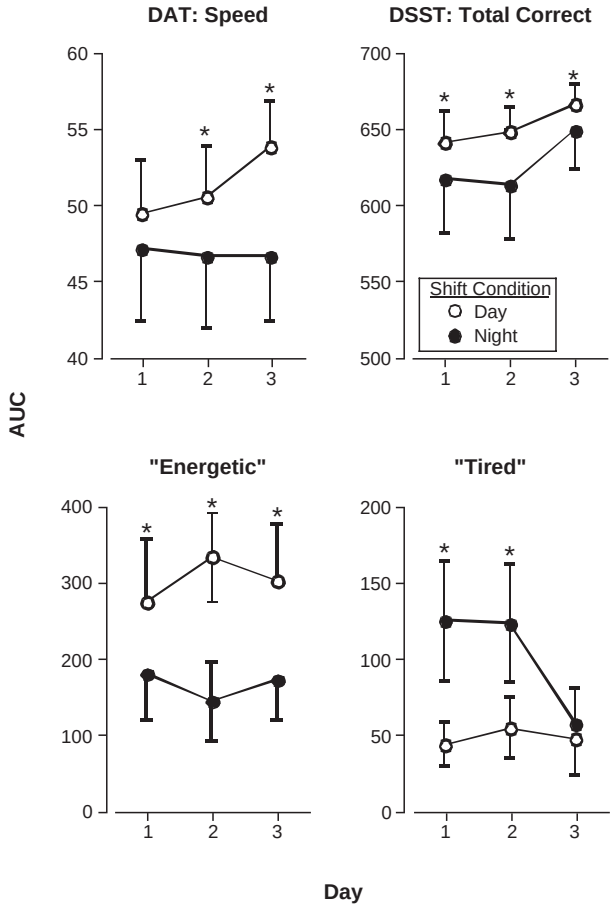

Fig. 1. Upper panel: Area-under-the-curve (AUC) values for tracking speed (DAT) and total correct (DSST) following placebo administration as a function of shift condition and day within condition. Bottom panel: Area-under-the-curve (AUC) values for visual analog scale ratings of "Energetic" and "Tired" following placebo administration as a function of shift condition and day within condition. *Significant difference between the day and night shift conditions for that day following placebo administration ($p<0.05$). Error bars represent one S.E.M. Overlapping error bars were omitted for clarity.

nights that participants were on the night shift compared to the corresponding day shift days ($p<0.05$). On average, the mean AUC for the rating "Stimulated" during day shift days was 101, compared to 43 during night shift nights. In contrast, ratings of "Tired" were increased during the first two nights that participants worked on the night shift, relative to the corresponding day shift days ($p<0.05$ for both days of the condition). Additionally, participants estimated that they had slept approximately 2 fewer hours on the evening preceding the first night shift night, relative to the first day of the day shift ($p<0.05$; day shift = 7 versus night shift = 5).

3.2. Effects of acute methamphetamine alone

The top panels of Fig. 2 show how each drug condition affected psychomotor performance during the night shift condition. As can be seen, methamphetamine alone signifi-

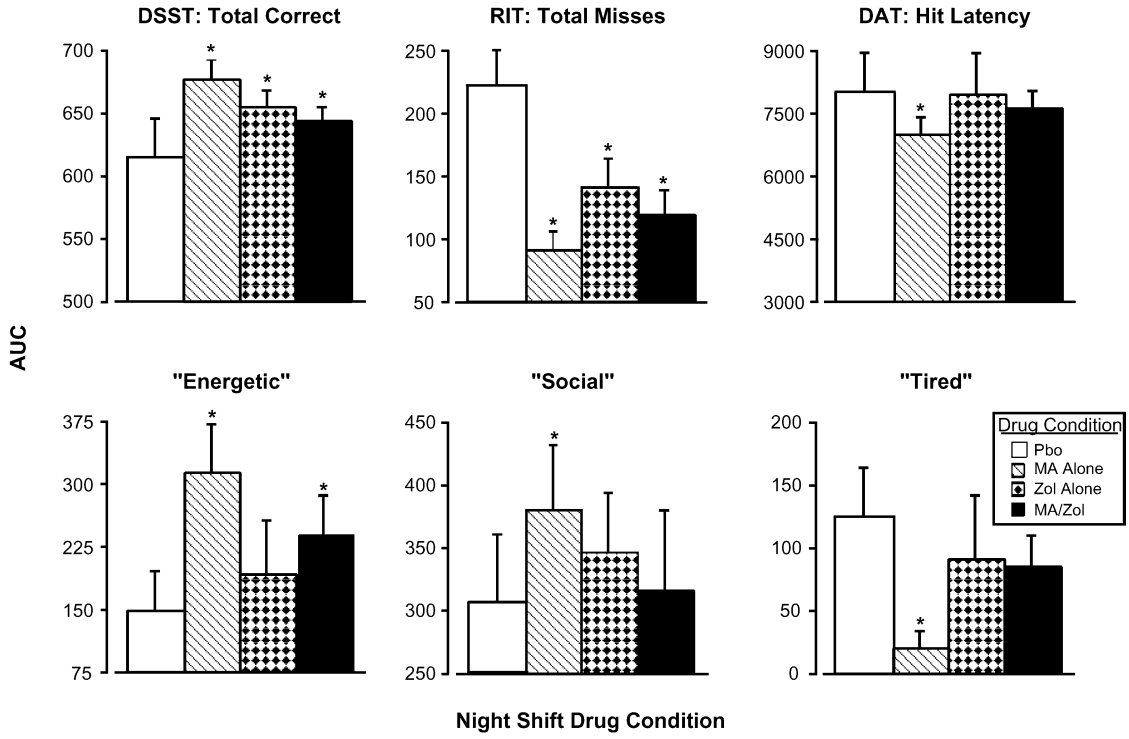

Fig. 2. Upper panel: Area-under-the-curve (AUC) values for total correct (DSST), total misses (RA), and mean hit latency (DAT) as a function of drug condition during the night shift. Bottom panel: Area-under-the-curve (AUC) values for visual analog scale ratings of "Energetic," "Social," and "Tired" as a function of drug condition during the night shift. *Significant difference between placebo and active drug ($p<0.05$). Error bars represent one S.E.M. Overlapping error bars were omitted for clarity.

cantly improved performance on all three of the selected tasks. Specifically, methamphetamine *increased* the total number of hits made and tracking speed on the repeated-acquisition task ($p<0.05$; data not shown), the total number of trial attempts and correct responses on the DSST ($p<0.05$; some data not shown), and the total number of hits made on the RIT ($p<0.05$; the AUC for mean number of hits: placebo=1038 versus 1184). In addition, methamphetamine *decreased* the mean hit latency on the DAT ($p<0.05$) and the number of false alarms and hits made on the RIT ($p<0.05$; some data not shown). Administration of methamphetamine during the *day shift* also produced significant effects on performance, although fewer than those observed during the night shift. Methamphetamine *increased* the total number of attempts and correct responses on the DSST ($p<0.05$; data not shown), the total number of hits made on the RIT ($p<0.05$; AUC for mean number of hits: placebos=1040 versus 1214) and *decreased* the mean hit latency on the DAT ($p<0.05$; data not shown) and the number of misses made on the RIT ($p<0.05$; data not shown).

The bottom panels of Fig. 2 show how each drug condition affected subjective-effects ratings during the night shift condition. Methamphetamine *increased* ratings of "Energetic," "Good Drug Effect," "Self Confident," "Social," and "Stimulated," while it *decreased* ratings of "Sleepy" and "Tired" ($p<0.05$; some data not shown). On average, the mean AUC rating of "Self Confident" was 538 under active methamphetamine, compared to 450 under the placebo condition; the mean AUC rating of "Sleepy" was 5 under active methamphetamine, compared to 90 under the placebo condition. During the *day shift*, methamphetamine produced effects on subjective-effects ratings that were similar but not identical to those observed during the night shift. For instance, ratings of "Good Drug Effect" and "Stimulated" were increased in a similar manner as seen during the night shift, whereas ratings of "High" and "Jittery" were also increased, effects not observed when participants worked on the night shift ($p<0.05$; data not shown).

3.3. Next-day effects of zolpidem alone

As is shown in the upper panels of Fig. 2, administration of zolpidem the evening before participants worked on the night shift significantly improved performance on the DSST (increasing the total number of trial attempts and correct responses: $p<0.05$; some data not shown) and on the RIT (decreasing the number of misses: $p<0.05$). In contrast, zolpidem disrupted performance on the DAT by decreasing the total tracking distance ($p<0.05$; data not shown). This effect was also observed when participants received zolpidem while working on the *day shift*. Zolpidem produced only two other significant effects during the *day*

shift condition: the number of errors made on the repeated-acquisition task was *increased* (performance disruption) as well as the total number of hits made on the RIT (performance improvement: $p<0.05$; data not shown).

Zolpidem administered the evening before assessing next-day subjective-effects ratings produced significant "negative" effects during both shift conditions, although more effects were produced during the day shift. When participants worked on the night shift, administration of zolpidem the evening before increased ratings of "Confused," "Can't Concentrate," and "Irritable" ($p<0.05$; data not shown). On average, the mean AUC for the rating of "Can't Concentrate" was 123 under the zolpidem condition, compared to 7 under the placebo condition. When participants worked on the *day shift*, administration of zolpidem the evening before *increased* ratings of "Irritable," "Miserable," "Tired," and "Yawning," and *decreased* ratings of "Energetic" ($p<0.05$; data not shown). On average, the mean AUC for the rating of "Tired" was 137 under the zolpidem condition, compared to 54 under the placebo condition; the mean AUC for the rating of "Energetic" was 250 under the zolpidem condition, compared to 334 under the placebo condition.

3.4. Next-day effects of methamphetamine–zolpidem combination

As is shown in Fig. 2 (upper panel), administration of both methamphetamine and zolpidem produced modest effects on next-day psychomotor performance when participants worked on the night shift. Performance was improved significantly on the DSST (the total number of trial attempts and correct responses were increased: $p<0.05$; some data not shown) and RIT (the total number of hits made increased, while the total number of misses decreased: $p<0.05$; some data not shown). When *day shift* performance was assessed, the drug combination produced only one significant effect: the number of hits made on the RIT was increased, relative to placebo ($p<0.05$; data not shown).

The bottom panels of Fig. 2 shows that the methamphetamine–zolpidem combination *increased* next-day ratings of "Energetic" during the night shift condition ($p<0.05$). This was the only significant effect of the drug combination on subjective-effects ratings.

4. Discussion

Results from the current study show that psychomotor performance and subjective-effects ratings were altered during the night shift: psychomotor performance and some subjective ratings were decreased (e.g., "Alert"), while other ratings were increased (e.g., "Tired"). These data are congruent with data from other investigations that assessed the effects of changing work shifts in research participants (e.g., Reid and Dawson, 2001; Sharkey et al., 2001; Hart et al., 2003a,b). The drug conditions produced differential effects on night shift-related disruptions: 1) methamphetamine alone improved night time performance and mood; 2) zolpidem alone improved some next-day performance, while disrupting mood and one measure of performance; and 3) the methamphetamine–zolpidem combination produced few improvements of next-day performance and mood. The data showing that methamphetamine attenuated virtually all night shift-related disruptions and those showing that zolpidem produced mixed effects correspond well to those reported earlier (Hart et al., 2003a,b). The findings that the drug combination modestly improved night shift-related disruptions without producing deleterious effects, however, have not been reported previously in individuals working on rotating shifts under controlled laboratory conditions.

When participants received placebo at both dosing times and performance was compared between day shift and night shift work, participants' nighttime performance was markedly poorer on several tasks measuring diverse domains including visuospatial processing (e.g., DSST: total corrects), reaction time (e.g., DAT: mean hit latency), and vigilance (e.g., RA: total errors). In general, night shift-related impairments persisted for two of the three nights. Other researchers have observed that performance of night shift workers is poorer on the initial nights than performance on subsequent nights (Tilley et al., 1981; Knauth and Rutenfranz, 1981; Reid and Dawson, 2001). In addition, previous data from this laboratory, collected under similar conditions as those employed in the current study, are in agreement with the present findings, i.e., night shift-related performance disruptions were noted for the majority of the nights that participants worked on the night shift (Hart et al., 2003a,b). Given that participants were provided a day off immediately before working on the night shift, the data suggest that an adjustment period of 1 day is insufficient and an adjustment period consisting of several nights without working may be necessary when individuals rotate to night shift work. This point is particularly relevant in view of evidence showing that night shift workers are more susceptible to work-related accidents and automobile accidents while driving home from the night shift (Mitler et al., 1988; Leger, 1994).

One potential explanation for the performance decrements observed during night shift work under placebo conditions is that participants experienced greater sleep disruptions the preceding evening and thus were less mentally and physically responsive during the work period. Participants' subjective sleep reports partially support this view. On the evening preceding the first night of the night shift, for example, participants reported sleep durations approximately 2 h less than those reported on Day 1 of the day shift. Reported sleep durations on subsequent nights, however, were similar to sleep durations reported during the day shift, and no other measure on the sleep questionnaire (e.g., sleep satisfaction) varied as a function

of shift condition. In contrast, subjective-effects ratings during waking hours indicated that participants were less alert, energetic, and stimulated and were more tired for the majority of the nights that they worked on the night shift. While it is possible that the sleep questionnaire employed in this study was not sufficiently sensitive, data from our previous shift-change investigations indicate otherwise (Hart et al., 2003a,b). In those studies, participants reported consistently shorter sleep durations and reduced sleep quality on evenings preceding night shift work, suggesting that the sleep questionnaire used in the current study is sensitive to shift-change-related sleep disruptions. Nevertheless, in future studies subjective sleep reports should be used in conjunction with objective measures of sleep.

Methamphetamine administered shortly after waking offset virtually all night shift-related performance impairments, e.g., the number of correct responses made on the DSST was decreased markedly during the night shift and methamphetamine counterbalanced this effect returning performance to baseline levels (i.e., day shift levels). Several other performance measures and subjective-effects ratings showed a similar pattern. Methamphetamine, for instance, increased subjective reports of energetic and self-confident. These findings are congruent with data from other studies that assessed the effects of amphetamines on performance of fatigued and sleep-deprived individuals (Caldwell et al., 1995, 2000b; Wiegmann et al., 1996), and provide further evidence that administration of a single, low dose of methamphetamine can temper night shift-related performance and mood disruptions. The use of methamphetamine, however, raises concern that night shift workers may be susceptible to methamphetamine abuse. A potential alternative therapeutic medication is the alerting-agent modafinil, which has been shown to reduce night shift-related cognitive/psychomotor deficits and sleepiness during work periods (Walsh et al., 2004).

Administration of zolpidem on the evening preceding night shift work resulted in mixed effects on next-day performance and mood, producing improvements on some measures while causing disruptions on other measures. Zolpidem the evening before, like methamphetamine the day of, for example, improved visuospatial processing (as measured by performance on the DSST); in contrast, it worsened DAT performance as well as mood, as measured by subjective-effects ratings, e.g., zolpidem increased ratings of "Can't Concentrate" and "Irritable." These findings are in agreement with previous data from this laboratory (Hart et al., 2003b). While data from other laboratories also indicate the emergence of some residual effects following zolpidem, these effects have not been reported 7 h post-administration (e.g., Allain et al., 1995; Danjou et al., 1999). Together, these observations suggest that some residual drug effects may occur when zolpidem (10 mg) is administered the preceding evening. Other researchers, however, have reported data indicating the absence of such effects (e.g., Scharf et al., 1994; Dockhorn and Dockhorn, 1996). Although the reason for this apparent discrepancy is unclear, one possible explanation is that investigators reporting a lack of residual drug effects conducted studies in a patient population (i.e., insomniacs) whereas investigators reporting the presence of residual drug effects conducted studies using healthy volunteers.

The methamphetamine–zolpidem combination produced some modest beneficial effects on night shift-related performance and mood disruptions: visuospatial processing (e.g., DSST: total trial attempts and correct responses) and attention (e.g., RIT: total number of hits) were improved, and ratings of "Energetic" were increased. While the number of impaired performance measures that were attenuated by the drug combination were fewer than those improved by methamphetamine alone, unlike zolpidem alone, the drug combination produced no negative residual drug effects on performance or mood. This observation does not support our hypothesis that the methamphetamine–zolpidem combination would produce greater next-day performance and mood disruption relative to zolpidem alone. We reasoned that because zolpidem alone had been shown to produce residual drug effects on mood (Hart et al., 2003b), administration of the drug combination during simulated shift work would have worsened mood and performance. A possible explanation for this inconsistency is that the Hart et al. (2003b) study assessed drug effects following consecutive days of administration, whereas in the current study the methamphetamine–zolpidem combination was administered only once during each shift condition. It is likely that shift workers in the natural ecology administer the combination of stimulants and sedative on consecutive days, thereby limiting the generalizability of this finding. One reason the administration of the drug combination was limited to 1 day per shift condition in the current study is because of safety/drug interaction concerns. Because this was the first controlled study to examine the effects of methamphetamine in combination with zolpidem in human research participants, the safety and tolerability of the medication combination was unknown. An important finding from the present study is that drug combination was well tolerated. This observation suggests that testing of consecutive daily dosing of the drug combination under simulated shift work conditions is warranted.

A potential limitation of the present study is that unlike shift workers in the natural ecology, study participants were not exposed to the external light/dark cycle. Because the external light/dark cycle is thought to affect circadian rhythm alignment, which has been suggested to be an important mediator of shift-change-related performance decrements and sleep disruptions (Eastman and Martin, 1999), it is possible that the generalizability of current results to most shift workers may be limited. Nevertheless,

the data showing that performance and mood were disrupted as a function of the night shift condition argue that the current procedures provide a useful model to simulate work shift change conditions, and that medication-related effects can be sensitively detected within this model.

In conclusion, the current data demonstrate that performance and mood are disrupted during simulated night shift work under controlled conditions. The effects occurred during the majority of nights participants worked on the night shift, despite the inclusion of a 1-day acclimation period. This finding may be of particular significance in occupations that require abrupt changes in work schedules, e.g., police officers and military personnel. The data further show that a single, low dose of methamphetamine can attenuate most night shift-related performance and mood disruptions, while a single, low dose of zolpidem improved performance to a lesser degree and worsened next-day mood. The combination of methamphetamine and zolpidem produced few effects. Because shift workers may use the combination of stimulants and sedative on consecutive days, future studies should assess the combined effects of amphetamine-like drugs and zolpidem administered over consecutive days.

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