ELSEVIER

# Mood and Performance Changes in Women with Premenstrual Dysphoric Disorder: Acute Effects of Alprazolam

*Suzette M. Evans, Ph.D., Margaret Haney, Ph.D., Frances R. Levin, M.D., Richard W. Foltin, Ph.D., and Marian W. Fischman, Ph.D.*

*This study determined if women with premenstrual dysphoric disorder (PMS) showed impaired mood and performance when they were experiencing their premenstrual symptoms, and if the effects of alprazolam varied as a function of menstrual cycle phase. Under double-blind conditions, the acute effects of placebo and alprazolam (0.25, 0.50, 0.75 mg) were tested during both luteal and follicular phases. Women with confirmed PMS experienced substantial changes in mood as a function of menstrual cycle phase. However, under controlled laboratory conditions, acute doses of alprazolam did not improve negative premenstrual mood, but rather increased negative mood in the follicular phase. Alprazolam impaired task performance, although this impairment was generally similar in both phases when baseline phase differences were taken into consideration. Consistent with the failure of alprazolam to improve mood premenstrually, subjective measures indicative of abuse liability were not increased following alprazolam. Taken together, these data suggest that acute administration of alprazolam doses are not clinically useful for the treatment of PMS.*
***[Neuropsychopharmacology 19:499–516, 1998]***


KEY WORDS: *Alprazolam; Women; Premenstrual dysphoric disorder; Subjective effects; Psychomotor performance; Abuse liability*

Approximately 2–10% of women suffer from premenstrual symptoms to such a degree that it interferes with normal functioning (i.e., premenstrual dysphoric disorder or PMS), and as many as 30% of women have clinically significant premenstrual mood changes (Logue and Moos 1986; American College of Obstetricians and Gynecologists 1989; Rivera-Tovar and Frank 1990). The most common symptoms reported by women seeking treatment for premenstrual symptoms are anxiety, depression, and irritability (Freeman et al. 1985). The benzodiazepine alprazolam has been evaluated for the treatment of PMS in six double-blind placebo-controlled studies. Four of these studies concluded that alprazolam was more effective than placebo in reducing premenstrual mood symptoms (Harrison et al. 1990; Smith et al. 1987; Berger and Presser 1994; Freeman et al. 1995). Across the studies, the mean dose of alprazolam ranged from 0.75 mg/day (Smith et al. 1987) to 2.25 mg/day (Harrison et al. 1990) and the sample size of those who received alprazolam ranged from 14 (Smith et al. 1987) to 45 women (Freeman et al. 1995). In contrast, two other studies failed to support these findings (Dennerstein et al. 1986; Schmidt et al. 1993), which cannot be accounted for by either the dose range of alprazolam or the sample size. In fact, the only study to actually manipulate the dose of alprazolam across cycles (0.75, 1.0,

From the New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, New York.

Address correspondence to: Suzette M. Evans, New York State Psychiatric Institute, 722 West 168th Street, Unit 66, New York, NY 10032. Tel: (212) 543-5895; Fax: (212) 543-6018; E-mail: se18@columbia.edu

Received February 3, 1998; revised June 10, 1998; accepted June 17, 1998.



Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/98/$–see front matter
PII S0893-133X(98)00064-5

and 1.4 mg/day), failed to show that alprazolam had any therapeutic effects for PMS (Schmidt et al. 1993).

Therapeutic doses of alprazolam also produce sedation and impair psychomotor performance and memory (e.g., Aranko et al. 1985; Block and Berchou 1984; Linnoila et al. 1990; Evans et al. 1994). Two recent studies reported that women with PMS had reduced sensitivity to benzodiazepines, which was more pronounced in the luteal phase, compared to women without PMS (Sundström et al. 1997a,b). The extent to which various aspects of psychomotor or cognitive performance are impaired during the luteal phase in women with PMS has not been well studied and the results have been inconsistent (Jensen 1982; Posthuma et al. 1987; Keenan et al. 1995; Rapkin et al. 1989; Morgan et al. 1996; Resnick et al. 1998). Thus, one purpose of this study was to assess the acute effects of alprazolam and placebo on changes in mood and performance as a function of menstrual cycle phase in women with confirmed PMS.

In addition to the undesirable side effects of benzodiazepines, the misuse or abuse of these drugs can be a significant problem for certain vulnerable individuals (DuPont 1988). The abuse liability of benzodiazepines, particularly diazepam and alprazolam, has been clearly documented among certain subgroups including sedative abusers (e.g., de Wit and Griffiths 1991), methadone-maintained patients (Weddington and Carney 1987; Iguchi et al. 1993), alcoholics (e.g., Ciraulo et al. 1988), and moderate drinkers (de Wit et al. 1989; Evans et al. 1996). Even though benzodiazepines are prescribed to women almost twice as often as to men (Woods et al. 1992), there is relatively little information regarding the effects, including potential abuse liability, of these drugs in women. Several clinical studies and surveys suggest that women with moderate to severe premenstrual symptoms tend to drink more premenstrually, purportedly to self-medicate their dysphoric symptoms, and may be at increased risk for developing alcoholism (e.g., Podolsky 1963; Price et al. 1987; McLeod et al. 1994). Nonalcoholic women with premenstrual symptoms have been shown to increase their alcohol consumption premenstrually under controlled laboratory conditions (Mello et al. 1990). Women with premenstrual symptoms have also been shown to smoke more marijuana or tobacco cigarettes premenstrually, suggesting that this subpopulation of women may be at increased risk to use a variety of drugs (Mello and Mendelson 1985; Mello et al. 1987). Thus, a second purpose of this study was to determine if women who suffered from PMS were at risk to misuse or abuse benzodiazepines.

To assess the full range of behavioral effects of alprazolam in women with PMS, this study used an outpatient laboratory procedure which is sensitive to the acute subjective and performance effects, as well as the abuse potential, of various sedatives/hypnotics in humans (de Wit and Griffiths 1991; Evans et al. 1991, 1995). The doses of alprazolam studied (0.25, 0.50, 0.75 mg) were within the therapeutic range and have been used to treat premenstrual symptoms in women. Women were tested with each dose condition when they were experiencing premenstrual symptoms (late luteal phase) and when they were not (follicular phase). Given that (1) alprazolam may be an effective treatment for PMS; (2) alprazolam impairs performance and memory; and (3) data from other studies that women with PMS tend to drink and/or use other drugs premenstrually, we hypothesized that alprazolam would improve mood and performance in the late luteal phase compared to the follicular phase, and would correspondingly increase other subjective measures used to assess likelihood of abuse, such as ratings of drug liking.

## MATERIALS AND METHODS

### Subjects

Women who participated in this study responded to an advertisement in a local newspaper for female volunteers suffering from PMS. Twenty-four participants met DSM-IV criteria for PMS (or premenstrual dysphoric disorder; American Psychiatric Association 1994), however four participants withdrew their consent after one or two experimental sessions. The mean age of the 20 women who completed the double-blind study was 28.3 ± 1.2 years (range 22 to 39 years) and the mean level of education was 15.5 ± 0.4 years (range 12 to 20 years). The women had a mean menstrual cycle length of 29.4 ± 0.5 days (range 24 to 36 days). Ten women were Caucasian, five were African-American, four were Hispanic, and one was Asian. All were medically and psychiatrically healthy based on a complete physical examination, electrocardiogram, clinical blood chemistries, urinalyses, and a psychiatric interview. All women were within Metropolitan Life Insurance Company (1983) Table standard weight ranges for their heights. None of the participants were taking oral contraceptives, hormones, or any other prescription medications. Also, women were not pregnant based on a plasma test of circulating chorionic gonadotropin hormone (hCG), or nursing, and had not been pregnant or had an abortion within the previous 6 months. Overall, self-reported drug use was minimal. Ten participants currently smoked cigarettes, 14 participants consumed caffeinated beverages daily, and 14 participants consumed alcohol several times each month. In addition, five participants reported occasional use of marijuana and two participants reported occasional use of cocaine (i.e., not more than three times per month); none of these individuals met DSM-IV criteria for drug abuse or dependence.

To initially screen for PMS, women completed the Premenstrual Assessment Form (Halbreich et al. 1982). This is a retrospective 95-item self-report questionnaire

(composite scores on 18 factors) which compares the direction and severity of changes in mood, behavior, and physical symptoms to the normal non-premenstrual state for the previous three menstrual cycles. Women who endorsed scores of 4 or greater on more than five of the 13 mood factors were then screened for PMS prospectively. This involved having women fill out a modified version of the Daily Ratings Form (Endicott et al. 1986) each evening before going to bed for at least two menstrual cycles (see below for details). These forms were returned by mail on a daily basis. To encourage compliance, women were paid $15 each week for completing the forms and they were provided addressed, stamped envelopes. The criterion for moderate to severe premenstrual symptoms was defined as an average increase of at least 2 points (i.e., 30% increase on a 6-point scale; NIH guidelines) for the 5 days immediately preceding the onset of menstruation (late luteal phase) compared to the 5 postmenstrual days (i.e., days 6–10 after the onset of menstruation or the follicular phase). That is, women had to show premenstrual symptoms during the late luteal phase and a symptom-free period of at least 5 days during the follicular phase of the menstrual cycle. Those women with an average score of 3 or greater during the follicular phase (suggestive of other mood disorders) were excluded. During the second menstrual cycle of this screening period, women were medically and psychiatrically evaluated. The Structured Clinical Interview for DSM-IV (SCID I, First et al. 1995) was used to make Axis I diagnoses, including drug abuse, and was conducted by a trained clinical interviewer when the women were in the follicular phase of the menstrual cycle. The major goal of this interview was to make sure that women did not have a current Axis I psychiatric disorder (within the last year), including substance abuse or dependence, and to specifically rule out major depression or a current anxiety disorder. This screening procedure allowed us to clearly document PMS and distinguish it from premenstrual exacerbation of symptoms related to other ongoing psychiatric and/or medical disorders.

The study was approved by the Institutional Review Board of the New York State Psychiatric Institute. Participants gave their written informed consent before beginning the study and were paid for their participation. They were informed that they could receive placebo, as well as various sedatives, stimulants, or antihistamines. Participants were told that the purpose of the study was to determine the effects of these drugs on mood and ability to perform certain tasks at different phases of the menstrual cycle.

### Design and Experimental Procedures

The women participated as outpatients at the New York State Psychiatric Institute for a total of 10 experimental sessions. Data were collected on a range of subject-rated, observer-rated, and performance measures before drug administration and over a 4-h time course following drug administration. After participants had passed all study entry criteria, two practice sessions were conducted (usually during the late follicular or early luteal phase of the menstrual cycle). The purpose of these practice sessions was to familiarize participants with the routines to be followed and to provide training on the performance tasks. Medication was not administered on these practice sessions and these data were not analyzed. Participants then started the double-blind testing phase which consisted of eight testing sessions. Four sessions were scheduled during the luteal phase (1–5 days before the onset of menstruation) to correspond to the days of maximal premenstrual symptoms and the other four sessions were scheduled during the follicular phase (6–10 days after the onset of menstruation). During each phase, four doses were tested (placebo and 0.25, 0.50, and 0.75 mg of alprazolam). The dose order within each phase was randomized with the restriction that the two highest doses were not administered on consecutive days and the dose order for the two phases was not identical for a given individual.

The scheduling of sessions was based upon the changes in mood premenstrually, menstrual cycle length, and the onset of menstruation. Luteal sessions were scheduled based on changes in mood symptoms in the current cycle; the time-frame of these sessions were later confirmed based on the onset of menstruation. All of this information was obtained from the Daily Ratings Form, which participants filled out each evening for two menstrual cycles before the study and throughout the study. Women were also instructed to record their basal body temperature each morning on the Daily Ratings From to predict the time of ovulation. Attempts were made to conduct all sessions for a given phase consecutively. In the event that a session could not be scheduled (e.g., menstruation began earlier than expected, illness, holiday), missed sessions were rescheduled during the correct phase of the next menstrual cycle. Six out of 20 women had to have some sessions rescheduled during the correct phase of the next menstrual cycle; for only three of these women, this was due to menstruation starting a day or two earlier than predicted, based on our knowledge of a given woman's cycle length.

### Experimental Session

Participants reported to the laboratory at approximately 9:00 A.M. and remained until approximately 2:30 P.M. They were instructed not to eat breakfast before reporting to the laboratory and to refrain from using all psychoactive drugs (with the exception of tobacco, caffeinated products, and alcohol) for the duration of their

participation in the study. Each session, before drug administration, a urine specimen was collected and a breath-alcohol test was conducted to test for the presence of alcohol in expired air. Urine specimens were analyzed for the presence of illicit drugs (benzodiazepines, barbiturates, morphine and morphine derivatives, amphetamines, cannabinols, and cocaine). During sessions, the women were only allowed to smoke cigarettes after each assessment battery (including vital signs) was completed. They were instructed not to drink alcohol 24 h prior to or following a session.

Participants were served a light breakfast which consisted of either a bagel, cereal or waffles, juice and a caffeinated beverage (for those women who regularly consumed caffeine). Participants selected their breakfasts during the practice sessions and were given the same breakfast on all subsequent sessions. They were given 15 min to eat breakfast, which was consumed approximately 45 min before drug administration. Following breakfast, participants completed the baseline (i.e., before drug administration) assessment battery which consisted of computerized questionnaires and performance tasks. Table 1 illustrates the assessment measures and the time(s) that each was conducted during the experimental session. Immediately following the baseline assessment battery (approximately 10:00 A.M.), two blue capsules were administered to participants. The assessment battery was repeated at 0.5, 1, 2, 3, and 4 h after drug administration. After the 3-h assessment battery, the women were given 30 min to eat the lunch they had selected earlier that morning. Between breakfast and lunch the women were not allowed to consume anything except water.

At the end of each session, participants were evaluated prior to discharge for signs of intoxication and were required to pass a field sobriety test. As a safety precaution, they were not allowed to drive to and from the laboratory: they were provided subway tokens at the end of each session. If the research staff or the participant felt that the participant was still impaired, she either remained at the laboratory until the drug effects subsided or she was transported home in a taxi cab. Participants were also instructed that they should not drive a car for 8 hours after drug administration and should not take any medications or alcohol. Upon completion of the study, they were informed about possible PMS treatment options and given a referral if interested.

## Mood Scales and Questionnaires

***Daily Ratings Form.*** This rating scale (Endicott et al. 1986) is used to diagnose whether a woman has clinically meaningful premenstrual mood changes and to document the onset and duration of menstruation. The form consists of 21 items describing problems with mood, behavior, and physical symptoms. Three additional items determined if any of these problems interfered with work or school, social activities, or interpersonal relationships. Once each day, in the evening before going to bed, women rated the severity of each

**Table 1.** Dependent Measures and Time(s) of Each Assessment During an Experimental Session

| Dependent Measures | Baseline (Predrug) | Hours After Drug Administration | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0.5 | 1 | 2 | 3 | 4 | 12 |
| Subject-rated questionnaires | | | | | | | |
| Beck Depression Inventory | X | | | | | | |
| Trait Anxiety | X | | | | | | |
| State Anxiety | X | | | X | | X | |
| VAS Questionnaire | X | X | X | X | X | X | |
| Profile of Mood States (POMS) | X | X | X | X | X | X | |
| Drug-Effect Questionnaire | | X | X | X | X | X | |
| Daily Ratings Form | | | | | | | X[a] |
| Performance tasks | | | | | | | |
| Balance | X | X | X | X | X | X | |
| DSST | X | X | X | X | X | X | |
| Divided Attention Task | X | X | X | X | X | X | |
| Repeated Acquistion | X | X | X | X | X | X | |
| Word Recall/Recognition Task | | | | | | | |
| Immediate Recall | | | | X | | | |
| Delayed Recall | | | | | | X | |
| Delayed Recognition | | | | | | X | |
| Observer-rated questionnaire | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | |

[a]Participants completed this questionnaire once a day, in the evening before going to bed.

of the symptoms based on what they experienced that day on a 6-point scale, from 1 ("not at all") to 6 ("extreme"). This form was modified to comprise ratings for a single day, rather than for an entire week, to prevent any bias in ratings viewed from previous days. The measure used to determine the level of premenstrual symptoms each day was the mean score of all 24 items. This questionnaire was completed daily for at least two menstrual cycles before participation in the experimental sessions, as well each evening until the participant completed the study.

Participants completed all of the other subject-rated measures during the experimental sessions and they were instructed to answer the questions based on how they felt at that time (with the exception of the Trait Anxiety Inventory).

***Beck Depression Inventory.*** This 21-item self-report questionnaire was completed at baseline (i.e., before drug administration) each session (Beck et al. 1961). A score of 16 or greater is indicative of clinical depression.

***State-Trait Anxiety Inventory.*** This self-report questionnaire (Spielberger et al. 1970) consists of two self-rated subscales, 20 items each, one rating trait anxiety and the other state anxiety. The Trait Anxiety Inventory was completed at baseline each session, whereas the State Anxiety Inventory was completed at baseline, 2 h (approximate peak time of drug effect) and 4 h after drug administration.

***Profile of Mood States (POMS).*** This 72-item computerized version of the POMS, including the original 65 items (McNair et al. 1971) and an additional seven items, yields scores on eight mood subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, Confusion, Friendliness, and Elation. A ninth score, Arousal, is obtained by adding together the scores for Vigor and Tension-Anxiety and subtracting the scores for Confusion and Fatigue, and a tenth score, Positive Mood, is obtained by subtracting the Depression-Dejection score from the Elation score. The questionnaire was presented on the participant's computer screen and individual items were presented one at a time. Participants rated each item on a 5-point scale from 0 ("not at all") to 4 ("extremely") by pressing keys on a keypad. To have all subscales on a similar 5-point scale, total scores for each of the eight major subscales were divided by the number of items used to determine the subscale score.

***Visual Analog Scales (VAS).*** A series of 50 statements was presented on the computer screen, one at a time. The participant rated each statement by placing a mark on a 100-point visual analog line, with the left extreme labeled "not at all" and the right extreme labeled "extremely." The statements presented were: I feel stimulated; I feel anxious; I feel depressed; I feel sedated; I feel high; I feel hungry; I feel friendly; I feel miserable; I feel on edge; I feel alert; I feel tired; I feel talkative; I feel self-confident; I feel social; I feel irritable; I feel confused; I feel a good drug effect; I feel a bad drug effect; I feel dizzy; I have an upset stomach; I have blurred vision; I feel sleepy; I am having difficulty concentrating; I have muscle pain; I am yawning; I feel energetic; I have a runny nose; I feel jittery; I feel content; I have a headache; I have flu-like symptoms; I am sweating; I am having trouble sleeping; I feel unmotivated; I feel restless; I have the chills; I am dreaming more; I feel nauseous; I have been vomiting; I feel suicidal; I have gooseflesh; I have stomach pain; I feel forgetful; I feel mellow; my heart is pounding or beating faster than usual; I feel clumsy; I have numbness or tingling in my extremities; noises or sound seem louder than usual; I feel withdrawn; I feel heaviness in my limbs.

***Drug-Effect Questionnaire.*** During each assessment battery after dosing, participants rated "strength of the drug effect" on a 5-point scale from 0 ("no drug effect at all") to 4 ("very strong effect"). This questionnaire asked participants to rate "good effects" and "bad effects" from the drug on a 5-point scale from 0 ("no effect at all") to 4 ("very much"), as well as the degree they would be "willing to take the drug again" from 0 ("not at all") to 4 ("very much"). In addition, participants indicated what drug class they thought the drug effect was most like: placebo (no drug), stimulant, or sedative. Lastly, they rated how much they liked the drug effect on a 9-point scale: −4 indicated "dislike very much," 0 indicated "feel neutral, or feel no drug effect," and 4 indicated "like very much." Variations of this questionnaire have been shown to be sensitive to the effects of alprazolam in both sedative abusers (Evans et al. 1994) and normal volunteers (Evans et al. 1995).

## Performance Measures

All of the performance measures described below, with the exception of the Word Recall task, were conducted during the experimental sessions at baseline (before drug administration), 0.5, 1, 2, 3, and 4 h after drug administration (see Table 1).

***Balance Task.*** This task assessed the participant's ability to stand upright for a maximum of 30 s on each foot (Evans et al. 1994). The score was the total number of seconds the participant was able to balance (maximum of 60 s).

***Digit Symbol Substitution Test (DSST).*** This 3-min task consists of nine random 3-row by 3-column squares (one square blackened per row) displayed across the top of the computer screen(McLeod et al. 1982). Arrays are displayed from left to right across the screen and

each is associated with a number (1–9) centered directly below that array. In each trial, a randomly generated number (1–9), appears at the bottom of the screen, indicating which of the arrays displayed at the top of the screen should be reproduced. Participants were instructed to press the keys in a 3-row by 3-column keypad that corresponded to the pattern associated with the randomly generated number. Three responses were required per trial (one response in each row, corresponding to the blackened square in each row). A new randomly generated number was displayed in the center of the screen immediately after each trial. Participants were instructed to reproduce as many patterns as possible. The scores obtained were the number of attempted and the number of correct substitutions during a 3-min period.

***Divided-Attention Task.*** This 10-min task consists of concurrent pursuit-tracking and vigilance tasks (Miller et al. 1988). For the central tracking component, participants tracked a randomly moving circle on a computer screen with a cross-hair controlled by movement of the mouse, and were instructed to keep the cross-hair within the circle. The peripheral-vigilance task required a response (click on the mouse) when a small black square appeared at any of the four corners of the screen. Participants were not provided any information on the rate of central target movement or the frequency and probability of peripheral-target presentation. Participants were provided feedback on the vigilance component; if they correctly detected a peripheral stimulus "Hit" was presented on the bottom of the screen, if they failed to detect a peripheral stimulus "Miss" was presented on the bottom of the screen, and if they clicked on the mouse when no peripheral stimulus was presented "False Alarm" was presented on the bottom of the screen.

***Repeated Acquisition of Response Sequences.*** At the start of the 3-min learning task, four 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 one each time the entire 10-response sequence was correctly completed. The 10-response sequence remained the same throughout the 3-min 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.

***Word Recall/Recognition Task.*** Immediate free recall was assessed approximately 2 h after drug administration (time of peak effect); participants studied a list of 12 common nouns (four to eight characters each, drawn each day from a pool of 1000 nouns derived from Thorndike and Lorge, 1944) for 90 s, then they had to write, in any order, as many of the words as they could remember. Delayed free recall was tested 4 h after drug administration. For the recognition test, which immediately followed delayed recall, participants were presented with a list containing 48 words; they had to identify from this list the 12 words they had been shown 2 h earlier. Scores on each test were the number correct out of 12. Each session, participants were given a new list of nouns, and throughout the entire study, no word list (or word) was repeated.

## Other Measures

***Observer-Rated Questionnaires.*** Observer ratings were completed by a trained research assistant who was blind to the drugs being administered. The participant was rated on a 5-point scale, from 0, indicating normal, to 4, indicating extreme impairment or disruption, on the following dimensions: sedation/sleepiness, muscle relaxation/locomotor, posture, muscle relaxation/non-locomotor, speech, confusion/disorientation, and stimulation/arousal. The observer also rated the strength of the participant's drug effect from 0 ("no drug effect") to 4 ("very strong drug effect"). The observer was instructed to base his/her ratings on observation of the participant's gross behavior rather than on the participant's verbal reports or ratings. This rating scale has been shown to be sensitive to the effects of sedatives/hypnotics (Evans et al. 1994).

***Vital Signs.*** Heart rate and blood pressure were measured each session before drug administration (baseline), and 0.5, 1, 2, 3, and 4 h after drug administration using a Sentry II vital signs monitor (Model 6100; NBS Medical Services, Costa Mesa, CA). Respiration rate was measured before drug administration (baseline), and 4 h after drug administration.

## Drugs

Alprazolam (0.25, 0.50, 0.75 mg; Xanax®, The Upjohn Company, Kalamazoo, MI) tablets were prepared in blue colored gelatin capsules (size 0) with lactose powder as filler; placebo capsules contained only lactose powder. Each session (excluding the two practice sessions when no capsules were given), two identically-appearing blue capsules were ingested with 100 ml water under staff supervision. Both the staff and the participants were blind to study medication.

## Data Analysis

Analyses were based on the 20 women who completed the entire study. The results from the two practice days

were not included in the data analyses. One participant had a pronounced sedative effect when tested with 0.75 mg alprazolam in the luteal phase, therefore this dose was not administered to her in the follicular phase. For data analysis purposes, all of her data obtained from the 0.50 mg alprazolam condition were substituted for her 0.75 mg alprazolam condition in the follicular phase.

For all measures that were conducted more than once each session, separate three-factor repeated measures analyses of variance were conducted. The three factors were phase (late luteal vs. follicular), dose (0, 0.25, 0.50, 0.75), and time (time points depended on measure). Because significant phase effects may have been due to overall differences between the late luteal and follicular phases and/or differences in response to alprazolam, significant main effects were followed up with four comparisons on the three-way interaction term (phase $\times$ dose $\times$ time; $df = 1,285$). The first comparison, which was used to determine direct phase effects in the absence of drug, compared all the time points from the placebo session of the luteal phase to all the time points from the placebo session of the follicular phase. The remaining comparisons compared the effects of alprazolam, at the time points of maximal effect (0.5, 1, and 2 h), between the two phases for each dose separately (e.g., the effects of 0.50 mg alprazolam 0.5, 1, and 2 h after dosing in the luteal phase were compare to the effects of 0.50 mg alprazolam 0.5, 1, and 2 h after dosing in the follicular phase). Because of the numerous phase effects and dose effects, a secondary set of analyses was conducted using peak change from baseline (i.e., before drug administration) scores for the POMS subscales and the performance tasks which showed a phase effect, to determine if alprazolam produced differential effects as a function of menstrual cycle phase when these baseline differences were removed. For these analyses, a two-factor repeated measures ANOVA was conducted with phase and dose as the factors. The direction of peak effect relative to baseline was determined based on the time course analyses. The minimum change score from baseline was calculated for the performance tasks and the following POMS subscales: Anger-Hostility, Arousal, Depression-Dejection, Elation, Friendliness, Positive Mood, and Vigor. The maximum change score from baseline was calculated for Tension-Anxiety, Confusion, and Fatigue. Lastly, since 70% of the women started testing in the luteal phase, to determine if any of the performance tasks showed continued improvement over time, the mean scores for the last three time points on the second practice session were compared to the baseline (i.e., before drug administration) scores for each session sequentially.

For pre-study Daily Ratings Form scores, mean scores for the 5 days before the onset of menstruation were compared to mean scores on days 6–10 after the onset of menstruation using a one-factor analysis of variance with phase as the factor. During the study, Beck Depression Inventory scores and Trait Anxiety scores for the four luteal phase sessions were compared to the four follicular phase sessions using a repeated measures analysis of variance with phase as the factor. Similarly, mean scores on the Daily Ratings Form for the four luteal phase sessions were compared to the four follicular phase sessions using a two-factor analysis of variance with phase and dose condition as the factors. Due to some uncompleted Daily Ratings Forms for two women, only 18 women were used for this analysis. For all analyses, results were considered statistically significant if $p < 0.05$, using Huynh-Feldt corrections.

## RESULTS

### Mood Questionnaires

Participants experienced moderate to severe premenstrual symptoms for a minimum of 5 days before the onset of menstruation. This was documented by significantly higher Daily Ratings Form scores in the luteal phase ($4.2 \pm 0.2$) compared to the follicular phase ($1.7 \pm 0.1$) for the two menstrual cycles before the study ($p < .0001$). The Daily Ratings Form scores from the two months prior to the first session were highly correlated with one another (luteal phase, $r = 0.73$; follicular phase, $r = 0.80$) indicating the consistency of the severity of premenstrual symptoms between the two cycles. Correspondingly, the Daily Ratings Form scores during the study were also significantly higher in the luteal phase ($3.8 \pm 0.1$) compared to the follicular phase ($1.7 \pm 0.1$) and there was no effect on these evening scores as a function of the alprazolam dose received during the day.

Table 2 documents the mood changes as a function of menstrual cycle phase based on the baseline scores (i.e., before drug administration) obtained on the mornings of experimental sessions. Beck Depression scores, Trait Anxiety scores, State Anxiety scores, and several POMS subscales (Anger-Hostility, Confusion, Depression-Dejection, Fatigue, and Tension-Anxiety) were significantly increased before drug administration in the luteal phase compared to the follicular phase. For instance, Beck Depression scores increased from 4.25 in the follicular phase to 11.76 in the luteal phase, which was an increase of 174%. The remaining five subscales of the POMS (Arousal, Elation, Friendliness, Positive Mood, and Vigor) were significantly decreased before drug administration in the luteal phase compared to the follicular phase.

Table 3 summarizes all significant main phase and dose effects for the State Anxiety Inventory, the POMS, and the VAS based on the time course analyses. State Anxiety scores, every POMS subscale, and 21 of the 50 VAS showed a significant difference as a function of

**Table 2.** Summary of Selected Mood Changes as a Function of Menstrual Cycle Phase Before Drug Administration

| Measure | Follicular Phase[a] | Luteal Phase | Significance ($df$ = 1,19) | Mean % Change Luteal/Follicular[b] |
|---|---|---|---|---|
| Beck Depression | 4.25 (0.49) | 11.76 (1.18) | 0.004 | 174% ↑ |
| Trait Anxiety | 35.86 (0.89) | 39.54 (1.24) | 0.040 | 10% ↑ |
| State Anxiety | 32.99 (0.91) | 44.55 (1.68) | 0.001 | 35% ↑ |
| POMS | | | | |
| Anger-Hostility | 1.21 (0.04) | 1.80 (0.09) | 0.001 | 49% ↑ |
| Confusion | 0.59 (0.03) | 1.28 (0.08) | 0.002 | 117% ↑ |
| Depression-Dejection | 1.19 (0.03) | 1.75 (0.10) | 0.006 | 47% ↑ |
| Fatigue | 1.46 (0.07) | 2.11 (0.12) | 0.004 | 45% ↑ |
| Tension-Anxiety | 0.78 (0.03) | 1.45 (0.09) | 0.009 | 86% ↑ |
| Arousal | 1.24 (0.14) | −0.03 (0.19) | 0.002 | 102% ↓ |
| Elation | 2.33 (0.10) | 1.73 (0.08) | 0.001 | 26% ↓ |
| Friendliness | 3.00 (0.10) | 2.28 (0.10) | 0.001 | 24% ↓ |
| Positive Mood | 1.24 (0.10) | −0.02 (0.16) | 0.002 | 102% ↓ |
| Vigor | 2.50 (0.10) | 1.82 (0.09) | 0.001 | 27% ↓ |

[a]Values represent the mean and the standard error.
[b]Percentages indicate the amount of change at baseline in the luteal phase relative to baseline in the follicular phase; arrows indicate the direction of the change.

menstrual cycle phase. Furthermore, as can be seen in Table 3, many of the measures that varied as a function of menstrual cycle phase, were not affected by any dose of alprazolam. This included Anger-Hostility, Depression-Dejection, and Tension-Anxiety scores on the POMS subscales and items such as irritable and unmotivated on the VAS. In contrast, alprazolam produced dose-related increases in other measures (e.g., bad drug effect, dizzy, heaviness in limbs) and these effects were similar between the two phases. Although several mood measures showed both a phase effect and a dose effect (e.g., Confusion and Fatigue on the POMS, difficulty concentrating), only three items showed a phase × dose interaction: Friendliness (POMS; $p < .01$) content ($p < .0367$), and friendly ($p < .0367$). In all three cases, alprazolam increased negative mood in the follicular phase but did not alter these scores in the luteal phase.

Figure 1 illustrates the magnitude and time course of selected subjective responses as a function of menstrual cycle phase, dose of alprazolam, and time for three POMS subscales. In all cases, Tension-Anxiety, Depression-Dejection, and Fatigue scores were significantly increased in the luteal phase compared to the follicular phase, regardless of alprazolam dose. There was no evidence that alprazolam decreased the already elevated Tension-Anxiety scores in the luteal phase. In contrast, alprazolam tended to increase Tension-Anxiety scores during the follicular phase (phase × dose; $p < .06$). Similar effects were observed for Vigor (POMS), Friendliness (POMS) scores and ratings of content, energetic, friendly, and self-confidence (i.e., alprazolam decreased these ratings in the follicular phase, but not in the luteal phase [based on the alprazolam comparisons]). Alprazolam did not alter Depression-Dejection scores, regardless of menstrual cycle phase. In contrast, alprazolam significantly increased Fatigue scores (which were already elevated in the luteal phase) in a dose-related manner in both phases, although the overall scores were always higher in the luteal phase. Similar effects to Fatigue were observed for Confusion (POMS), Arousal (POMS), Elation (POMS), Positive Mood (POMS), and ratings of alert, difficulty concentrating, confused, forgetful, and sedated.

Figure 2 shows the peak effects of four POMS subscales presented as a change from predrug baseline. When presented in this format, Tension-Anxiety scores and Depression-Dejection scores still showed significant phase effects ($p < .0155$ and .0044, respectively), but no dose effects. That is, Tension-Anxiety scores were increased relative to baseline in the follicular phase whereas Depression-Dejection scores were decreased relative to baseline in the luteal phase. Similar results were observed for Anger-Hostility and Friendliness. In contrast, when baseline phase differences were taken into account, only significant dose effects remained for Fatigue ($p < .0001$) and Confusion scores ($p < .0044$) (i.e., alprazolam increased Fatigue and Confusion scores similarly in both phases). Similar results were observed for Arousal and Vigor.

### Psychomotor Performance and Memory

There were no significant practice effects (i.e., a continued learning curve across sequential sessions), for balance, the Divided Attention task, or the Word Recall/Recognition tasks. In contrast, there was a significant improvement ($p < .05$) in performance prior to drug ad-

Table 3. Summary of All Significant Main Mood Effects[a]

| Measure | Phase ($df$ = 1,19) | Dose ($df$ = 3,57) | Phase × Dose ($df$ = 3,57) |
|---|---|---|---|
| State Anxiety (↑)[b] | 0.0034 | ns[c] | ns |
| POMS | | | |
| Anger-Hostility (↑) | 0.0107 | ns | ns |
| Depression-Dejection (↑) | 0.0325 | ns | ns |
| Tension-Anxiety (↑) | 0.0078 | ns | ns |
| Friendliness (↓) | 0.0031 | ns | 0.0111 |
| Arousal (↓) | 0.0014 | 0.0001 | ns |
| Confusion (↑) | 0.0062 | 0.0001 | ns |
| Elation (↓) | 0.0032 | 0.0257 | ns |
| Fatigue (↑) | 0.0030 | 0.0001 | ns |
| Positive Mood (↓) | 0.0098 | 0.0665 | ns |
| Vigor (↓) | 0.0012 | 0.0005 | ns |
| VAS | | | |
| Anxious (↑) | 0.0039 | ns | ns |
| Depressed (↑) | 0.0065 | ns | ns |
| Irritable (↑) | 0.0003 | ns | ns |
| Miserable (↑) | 0.0234 | ns | ns |
| On Edge (↑) | 0.0072 | ns | ns |
| Social (↓) | 0.0078 | ns | ns |
| Talkative (↓) | 0.0312 | ns | ns |
| Unmotivated (↑) | 0.0049 | ns | ns |
| Withdrawn (↑) | 0.0082 | ns | ns |
| Alert (↓) | 0.0013 | 0.0001 | ns |
| Difficulty Concentrating (↑) | 0.0057 | 0.0001 | ns |
| Clumsy (↑) | 0.0288 | 0.0178 | ns |
| Confused (↑) | 0.0524 | 0.0014 | ns |
| Forgetful (↑) | 0.0091 | 0.0004 | ns |
| Bad Drug Effect (↑) | ns | 0.0001 | ns |
| Blurred Vision (↑) | ns | 0.0002 | ns |
| Dizzy (↑) | ns | 0.0003 | ns |
| Heaviness in Limbs (↑) | ns | 0.0011 | ns |
| Mellow (↓) | ns | 0.0001 | ns |
| Stimulated (↓) | ns | 0.0209 | ns |
| Yawning (↑) | ns | 0.0001 | ns |
| Sedated (↑) | 0.0130 | 0.0001 | ns |
| Sleepy (↑) | 0.0277 | 0.0001 | ns |
| Tired (↑) | 0.0134 | 0.0001 | ns |
| Content (↓) | 0.0285 | ns | 0.0367 |
| Friendly (↓) | 0.0038 | ns | 0.0367 |
| Energetic (↓) | 0.0029 | 0.0149 | ns |
| Self-confident (↓) | 0.0287 | 0.0086 | ns |

[a]Analyses were based on the time course data; measures not listed were not significantly different based on either phase or dose.
[b]Arrows indicate the direction of any phase or dose effects; in all cases when there was both a phase effect and a dose effect, the direction was the same.
[c]ns indicates not significant.

ministration across successive sessions for the DSST and the Repeated Acquisition task.

Table 4 summarizes all significant main phase and dose effects for the various performance tasks based on the time course analyses. Several tasks, including the Repeated Acquisition task and the DSST, showed a main phase effect in that women were significantly more impaired in the luteal phase compared to the follicular phase. In contrast, there were no phase differences on any of the Divided Attention task measures. In addition, Table 4 shows that alprazolam produced significant dose-related decreases in performance on all tasks regardless of menstrual cycle phase.

Figure 3 illustrates the magnitude and time course of performance as a function of menstrual cycle phase, dose of alprazolam and time for two tasks. Based on the phase comparison which compared the two placebo conditions, performance was significantly more impaired in the luteal phase compared to the follicular phase on balance ($p < .0307$) and DSST ($p < .0001$). Further, based on the alprazolam comparisons, balance was significantly more impaired in the luteal phase com-

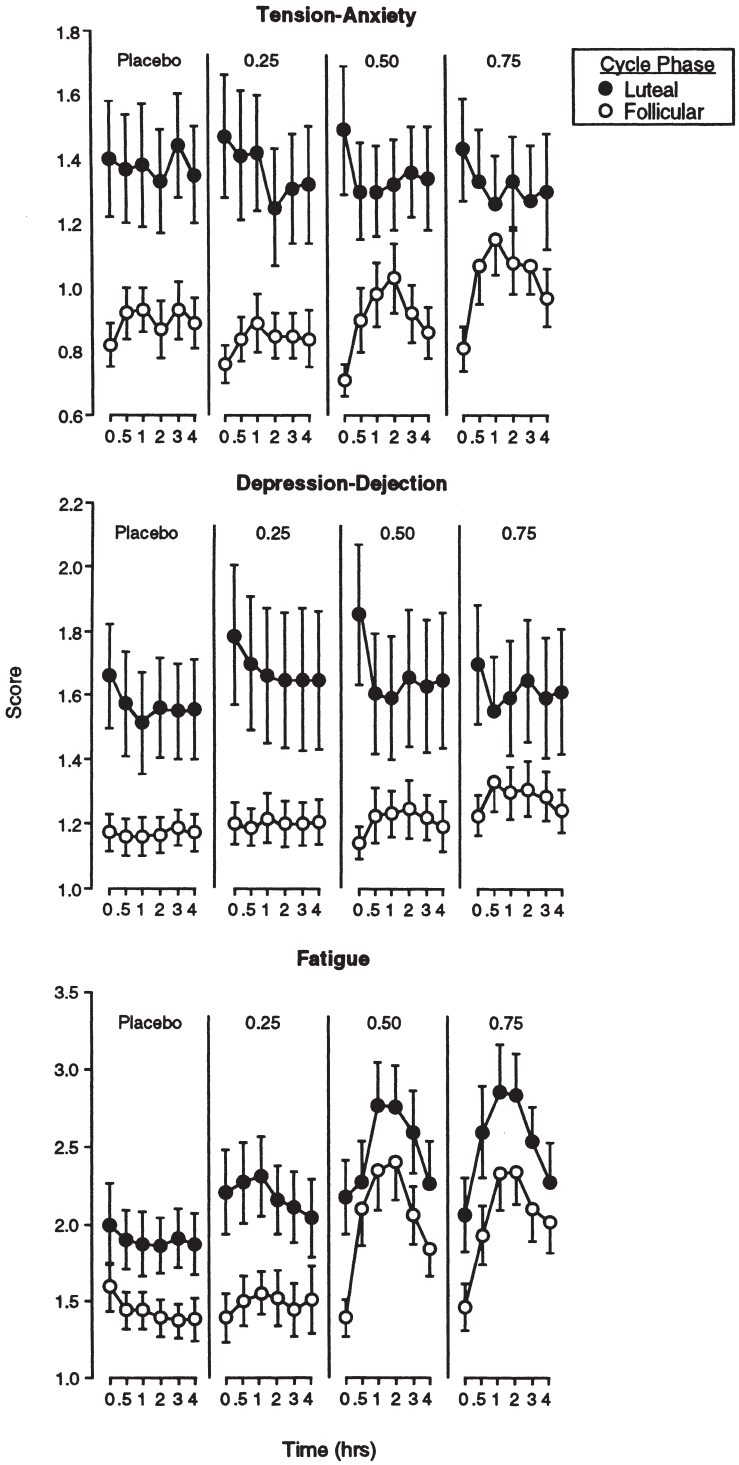


**Figure 1.** Time course functions of selected subjective-effects measures from the POMS as a function of menstrual cycle phase (luteal vs. follicular) and alprazolam dose. X-axes: 0 indicates predrug baseline; time points are equidistant for clarity. Data points show means of 20 individuals; vertical bars show ± 1 SEM. Some error bars have been omitted for clarity and the absence of any bars indicates 1 SEM fell within the area of the data symbol. At each of the time points used for the placebo condition comparisons (all six time points for the luteal phase compared to the follicular phase) and the alprazolam comparisons (the time points of peak drug effect; 0.5, 1, and 2 h), there were significant differences between the two phases.

pared to the follicular phase following 0.50 mg ($p < .0012$) and 0.75 mg alprazolam ($p < .0314$). Similarly, DSST scores were significantly lower in the luteal phase compared to the follicular phase following 0.25 mg ($p < .0137$) and 0.75 mg alprazolam ($p < .0077$).

Figure 4 shows the peak effects for DSST and the Repeated Acquisition task presented as a change from baseline. Once the baseline effects of phase were accounted for, only significant dose effects remained. Alprazolam decreased the number correct on the DSST ($p < .0001$) and decreased the total number of sequences on the Repeated Acquisition task ($p < .0121$) similarly in both phases. Similar results were obtained for balance ($p < .0001$).

Figure 4 also shows the results for the Word Recall/Recognition task (each component was only done at

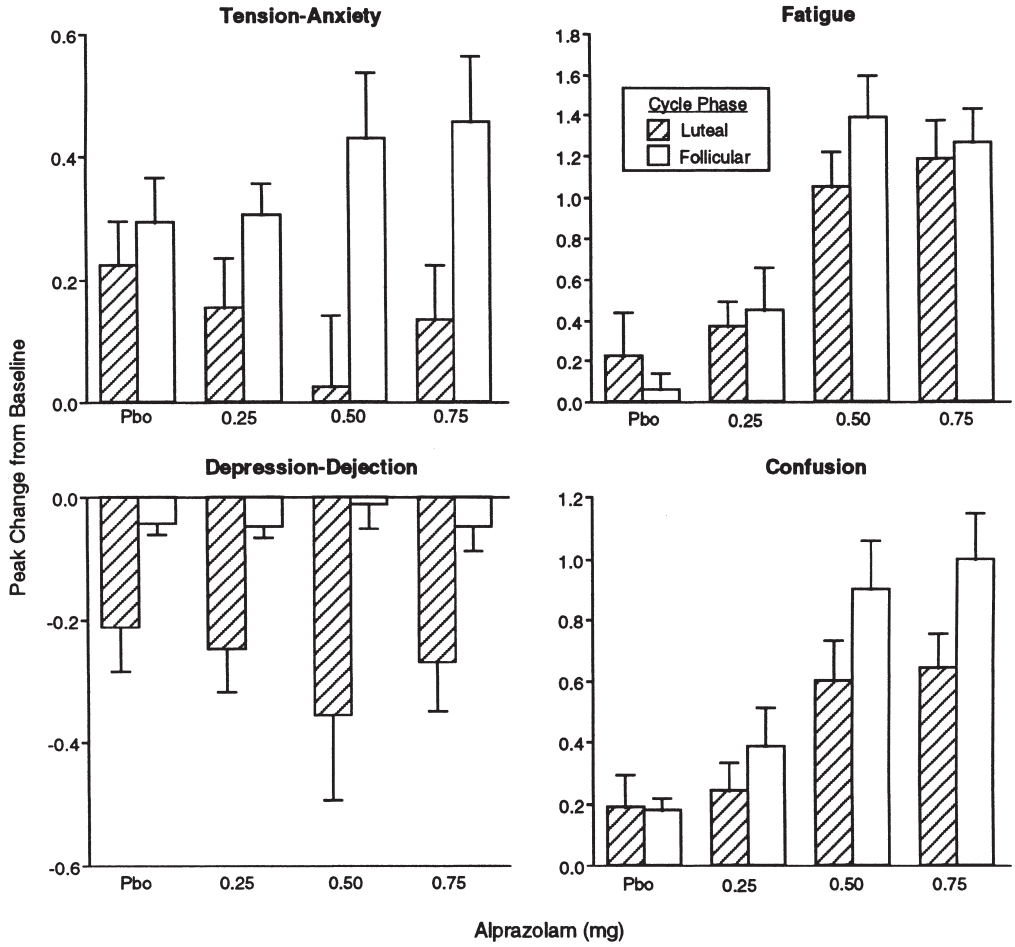


**Figure 2.** Dose-response functions of the peak scores for four POMS subscales calculated as a change from baseline (highest score for Tension-Anxiety, Fatigue and Confusion; lowest score for Depression-Dejection) as a function of menstrual cycle phase. Pbo indicates placebo and data points show means of 20 individuals; vertical bars show 1 SEM.

one time each day) as a function of menstrual cycle phase and dose. Alprazolam produced significant dose-related decreases on immediate and delayed word recall, and delayed word recognition (Table 4). Further, based on the alprazolam comparisons, delayed word recall was impaired significantly more in the luteal phase compared to the follicular phase following 0.25 mg ($p < .05$) and 0.50 mg alprazolam ($p < .0231$), but not following the highest dose.

### Drug-Effect Questionnaire

There were no changes on the Drug-Effect Questionnaire as a function of menstrual cycle phase. However, alprazolam produced dose-related increases in ratings for a number of measures (data not shown). Alprazolam increased ratings of "strength of drug effect" ($p < .0001$) in both phases. Similar results were observed for "bad effects" ($p < .0001$). In addition, alprazolam significantly decreased ratings of "willingness to take the drug again" ($p < .04$) and "drug liking" ($p < .009$) to the same extent in both phases. Correspondingly, alprazolam did not increase ratings of "good effects." For "willingness to take the drug again," ratings following 0.25 mg alprazolam were significantly higher premenstrually than postmenstrually ($p < .0004$), but otherwise there were not differences as a function of menstrual cycle phase on any Drug-Effect Questionnaire items.

With respect to the drug identification question, responses did not vary as a function of menstrual cycle phase. When placebo was administered, it was correctly identified on 66% of the occasions. At the time of peak drug effect (2 h), alprazolam was identified as a sedative in a dose-related manner; 38%, 83%, and 88% of the participants identified 0.25, 0.50, and 0.75 mg alprazolam, respectively, as a sedative.

### Observer-Rated Questionnaire

There were no changes on the Observer-Rated Questionnaire as a function of menstrual cycle phase when

**Table 4.** Summary of All Significant Main Performance and Memory Effects[a]

| Measure | Phase ($df$ = 1,19) | Dose ($df$ = 3,57) | Phase × Dose ($df$ = 3,57) |
|---|---|---|---|
| Balance (↓)[b] | ns[c] | 0.0051 | ns |
| DSST, number attempted (↓) | 0.0133 | 0.0001 | ns |
| DSST, number correct (↓) | 0.0310 | 0.0001 | ns |
| Repeated Acquisition, total sequences (↓) | 0.0016 | 0.0001 | ns |
| Divided Attention Task | | | |
| Number of false alarms (↑) | ns | 0.0027 | ns |
| Number of hits (↓) | ns | 0.0050 | ns |
| Number of misses (↑) | ns | 0.0003 | ns |
| Word Recall/Recognition | | | |
| Immediate recall (↓) | ns | 0.0001 | ns |
| Delayed recall (↓) | ns | 0.0001 | ns |
| Delayed recognition (↓) | ns | 0.0001 | ns |

[a]Analyses were based on the time course data; measures not listed were not significantly different based on either phase or dose.
[b]Arrows indicate the direction of any phase or dose effects; in all cases when there was both a phase effect and a dose effect, the direction was the same.
[c]ns indicates not significant.

placebo was administered, based on the comparison. However, alprazolam produced significant dose-related increases on several blind observer-rated measures including strength of drug effect ($p < .0001$), sedation/sleepiness ($p < .0001$), muscle relaxation/locomotor ($p < .0007$), muscle relaxation/non-locomotor ($p < .0211$), posture ($p < .01$), and speech ($p < .0048$). For all of the above measures there was also a significant phase × dose interaction such that the staff rated women as being more impaired in the follicular phase following alprazolam compared to the luteal phase, and this was most evident following the highest dose of alprazolam. For example, observer-rated sedation/sleepiness was significantly greater in the follicular phase compared to the luteal phase following 0.50 mg ($p < .0001$) and 0.75 mg alprazolam ($p < .0201$). Similar interactions following 0.75 mg alprazolam were obtained for observer-rated strength of drug effect ($p < .0001$), confusion ($p < .0012$), muscle relaxation/locomotor ($p < .0001$), muscle relaxation/non-locomotor ($p < .0001$), posture ($p < .024$), and speech ($p < .0001$).

### Vital Signs

There were no significant phase or dose-related effects on systolic blood pressure, diastolic blood pressure, heart rate, or respiration rate.

## DISCUSSION

The results of the present study indicate that (1) women with confirmed PMS experienced substantial changes in mood as a function of menstrual cycle phase; (2) acute doses of alprazolam did not improve negative premenstrual mood, including anxiety, under controlled laboratory conditions, but did increase negative mood in the follicular phase (e.g., decreased Friendliness scores); (3) alprazolam impaired performance on all tasks, although this impairment was generally similar in both phases when baseline phase differences were taken into consideration; and (4) there was little evidence that alprazolam has abuse liability in women with PMS.

### Mood Effects

The women who participated met the DSM-IV criteria for PMS, that is, they experienced substantial mood changes during the luteal phase, which resolved during the follicular phase. This was documented by 2 months of prospective Daily Ratings Form scores. Further, during the study, Daily Ratings Form scores and measures related to anxiety (e.g., the State-Trait Anxiety Inventory, Tension-Anxiety scores on the POMS) and depression (Beck Depression Inventory scores, Depression-Dejection scores on the POMS) were significantly increased in the luteal phase compared to the follicular phase, even before drug administration. In fact, every subscale on the POMS questionnaire, and numerous items on the VAS, showed differential effects as a function of menstrual cycle phase. One limitation of the present study was the fact that ovulation was not confirmed, although premenstrual symptoms are often absent during anovulatory cycles (Barr et al. 1995). Another limitation was that cycle phase was not confirmed by plasma levels of progesterone; we were primarily interested in monitoring mood and performance in the luteal phase when women were maximally symptomatic (Redei and Freeman 1995) and this was confirmed by the Daily Ratings

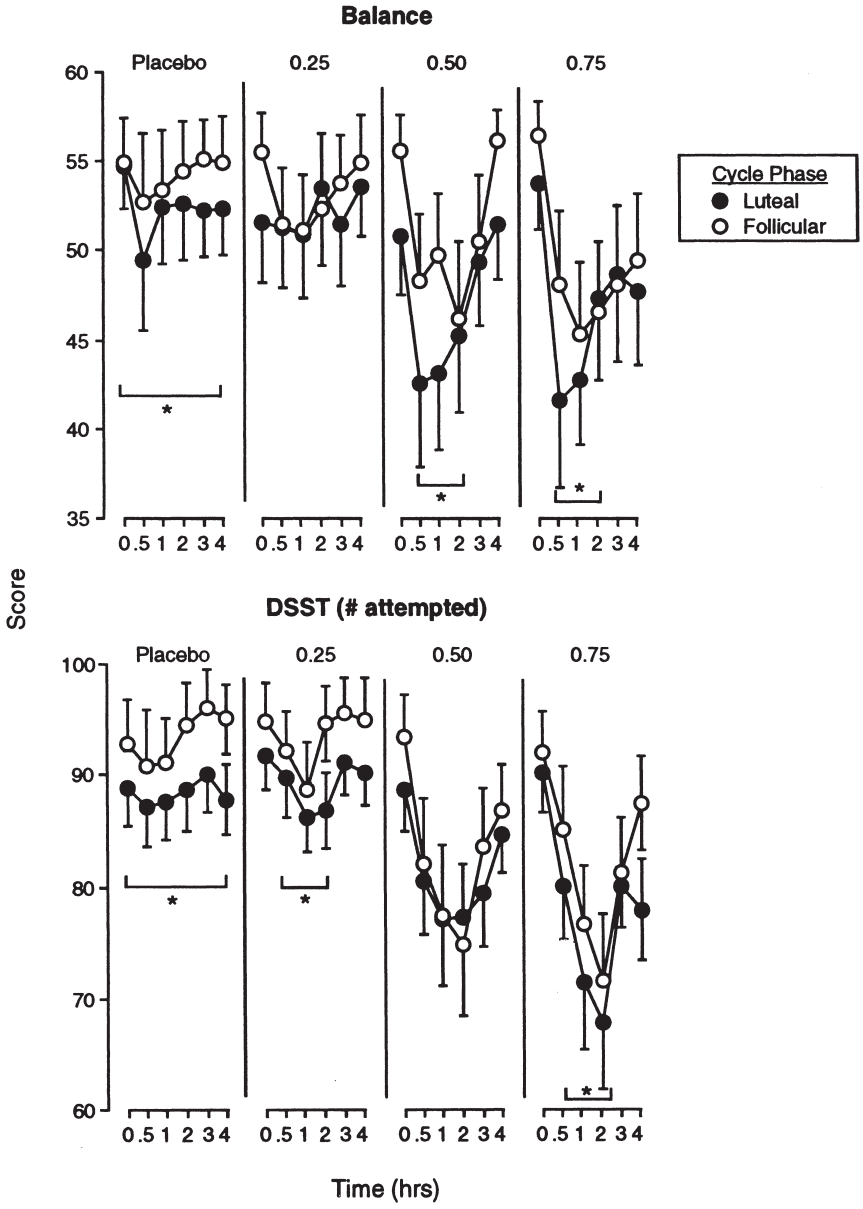


**Figure 3.** Time course functions of selected psychomotor performance tasks as a function of menstrual cycle phase (luteal vs. follicular) and alprazolam dose. Asterisks indicate significant phase effects based on the comparisons and corresponding brackets indicate the time points used; for the comparison between the luteal and follicular placebo conditions, all six luteal time points were compared to all six follicular time points and for the comparisons for alprazolam, the time points of peak effect (0.5, 1, and 2 h) were compared for each dose condition separately between the two phases. For details, see description for Figure 1.

Forms and the baseline mood changes obtained during the experimental sessions before drug was administered. Despite these limitations, we were successful in scheduling sessions during the correct phase of the cycle, in large part because these women mailed in their Daily Ratings Forms each day and they had consistent and severe premenstrual symptoms for a sufficient length of time before the onset of menstruation. These cyclical changes in mood are consistent with previous studies (e.g., Halbreich et al. 1982; Freeman et al. 1985; Rapkin et al. 1989; Bancroft et al. 1993).

Since several placebo-controlled studies (Smith et al. 1987; Harrison et al. 1990; Berger and Presser 1994; Freeman et al. 1995) have shown that alprazolam is an effective treatment for women with PMS, we expected that alprazolam would improve many of the negative mood symptoms women experienced in the luteal phase. Interestingly, alprazolam did not improve mood premenstrually and when there was an interaction between menstrual cycle phase and alprazolam dose (based on the alprazolam comparisons), it was due to an increase in negative mood in the follicular phase rather than an improvement in mood in the luteal phase (e.g., decreased Friendliness, increased Tension-Anxiety; cf. Figure 1 and Table 3). The observer ratings corresponded well with these findings in that research assistants, blinded to drug and dosing schedule, noted that the women were more affected by the study medication in the follicular phase. Taken together, these data could be interpreted as indicating that women are less responsive to alprazolam in the luteal phase. In fact, Sundström et al. (1997a,b) concluded that women with PMS were less sensitive to the effects of benzodiazepines because they had lower increases in sedation ratings fol-

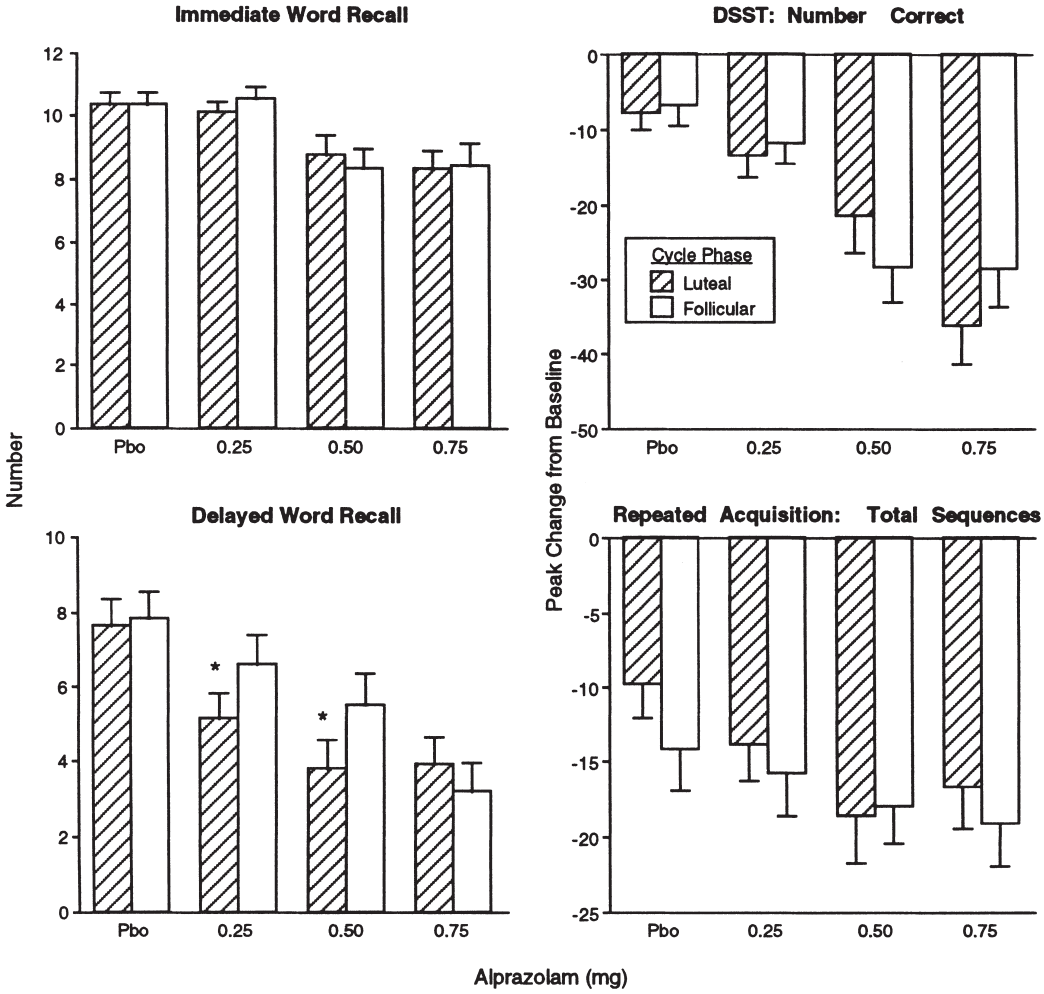


**Figure 4.** Left panels: Dose-response functions of immediate and delayed word recall as a function of menstrual cycle phase (luteal vs. follicular) and alprazolam dose. Immediate and delayed recall were only assessed once each session. Asterisks indicate significant phase effects based on the comparisons. Right panels: Dose-response functions of the lowest scores for the DSST (number correct) and the Repeated Acquisition tasks (total number of sequences) calculated as change from baseline as a function of menstrual cycle phase. For all panels, Pbo indicates placebo and data points show means of 20 individuals; vertical bars show 1 SEM.

lowing intravenous challenges of either diazepam or midazolam in the luteal phase compared to women without PMS. However, as shown in the present study, several scores, including Fatigue and Confusion scores were increased by alprazolam in both phases, and although the scores were highest in the luteal phase, this was accounted for by higher baseline scores in the luteal phase since change scores were not different (see Figure 3). Thus, when there was a response to alprazolam, it was not modulated by the negative mood in the luteal phase.

The failure of alprazolam to improve mood in women prospectively diagnosed with PMS in this study could be attributed to a variety of factors, including the dose range tested, the method of dosing, the time frame of testing, the instruments used to measure changes in mood, and finally the testing environment. Across the treatment studies with alprazolam, the mean dose of alprazolam ranged from 0.75 mg/day (Smith et al. 1987) to 2.25 mg/day (Harrison et al. 1990). The acute doses used in this study were within this range since we tested 0.25–0.75 mg, which if given three times a day would be 0.75 to 2.25 mg/day. Thus, it is unlikely that the failure of alprazolam to improve mood in the luteal phase is due to testing an inadequate dose range.

This study and other studies have demonstrated that acute doses of alprazolam produce significant changes in mood (e.g., sedation) and performance (e.g., Evans et al. 1994, 1995), with peak effects occurring 1 to 2 h after drug administration. Even though the acute doses of alprazolam tested produced significant increases in various measures of sedation and decreases in measures of performance, it is possible that repeated dosing over several days to a week is needed to observe a therapeu-

tic effect (e.g., a reduction in anxiety or depression). This is supported by the clinical literature indicating that anxious patients improved after 1 week of alprazolam treatment (e.g., Rickels et al. 1983). Unfortunately, most clinical studies generally measure treatment response weekly, making it unclear how soon an anxiolytic effect could be detected. Studies treating women with PMS administered alprazolam three to four times a day and most started alprazolam treatment during the luteal phase, before the premenstrual symptoms were maximal (e.g., Smith et al. 1987; Harrison et al. 1990; Freeman et al. 1995), again making it impossible to determine how many doses or days were needed before a reduction in symptoms was observed. Moreover, when the treatment studies are examined more closely, the effects of alprazolam are quite variable, which could be due to the fact that the dose range varied substantially within a study. For example, in the study by Freeman et al. (1995), the daily dose ranged from 0.75 to 2.25 mg/day and in the study by Harrison et al. (1990) the daily dose ranged from 0.25 to 5 mg/day. Although Harrison et al. (1990) showed that alprazolam was superior to placebo, only the "best" cycle for each condition was used in the analysis. In another study conducted in 138 women (Freeman et al. 1995), a 50% improvement in daily symptom reports was obtained in 37% of the alprazolam group compared to 30% of the placebo group. Taken together, the effectiveness of alprazolam in treating women with PMS is modest at best.

The primary dependent measures used in treatment studies of PMS have been scores on daily ratings questionnaires which are filled out once a day (Smith et al. 1987; Harrison et al. 1990; Freeman et al. 1995), although Rapkin et al. (1989) showed similar changes in mood in women prospectively diagnosed with PMS using many of the same instruments used in the present study (i.e., the POMS, the Beck Depression Inventory, and the State-Trait Anxiety Inventory). In the present study, scores on the Daily Ratings Form, which women completed approximately 12 h after drug administration, were not altered by alprazolam. However, in contrast to the treatment studies, our primary measures were the POMS subscales, the State Anxiety Inventory, and the VAS, which were administered repeatedly for 4 h after drug administration during both phases of the cycle. Although these well-validated instruments were sensitive to changes in baseline mood between the luteal phase and the follicular phase and the direct effects of alprazolam (e.g., increased Fatigue scores), they were unable to detect any potential therapeutic effects of alprazolam on premenstrual mood. However, acute doses of benzodiazepines do not routinely reduce anxiety as measured by the Tension-Anxiety subscale of the POMS and VAS ratings of anxiety (e.g., Chutuape and de Wit 1995). In addition, the fact that we measured responses to these items under controlled laboratory conditions, rather than in the natural environment, may have also prevented our ability to detect a reduction in premenstrual symptoms following alprazolam. Further, although these women clearly met the diagnosis for PMS, they were not actively seeking treatment for the disorder.

### Performance Effects

In addition to cyclical alterations in mood, there was evidence that performance on certain tasks (e.g., Balance, DSST, Repeated Acquisition) was more impaired in the luteal phase compared to the follicular phase under placebo conditions. However, 70% of women were tested in the luteal phase before the follicular phase and even though all women had two intensive practice sessions, there was an improvement over time on the DSST and the Repeated Acquisition task. Thus, these phase differences in performance could be attributed to practice effects. In fact, previous studies have routinely failed to show substantial, if any, performance impairment during the luteal phase in women with PMS. For instance, Keenan et al. (1992, 1995) showed that verbal recall, but not performance on other tasks, was impaired in women with PMS compared to women without PMS, irrespective of menstrual cycle phase. Another study (Posthuma et al. 1987) reported that only fine motor dexterity was significantly impaired during the late luteal phase in women with PMS compared to a control group. In a recent study, the only reported performance impairment was that women with PMS showed more psychomotor slowing during the luteal phase compared to the follicular phase (Resnick et al. 1998). Lastly, other studies (Jensen 1982; Rapkin et al. 1989; Morgan et al. 1996) have not shown any differences in performance between women with PMS compared to control women.

To our knowledge, this is the first study to evaluate the effects of alprazolam on performance in women with PMS. Alprazolam impaired performance in a dose-related manner on every task, including the Word Memory task, which is consistent with earlier studies conducted primarily in men (e.g., Aranko et al. 1985; Linnoila et al. 1990; Evans et al. 1994, 1995). In addition, based on the time course analyses, there was some evidence that alprazolam decreased performance to a greater extent for some tasks (e.g., Balance, Word Recall) in the luteal phase compared to the follicular phase. There was no effect of menstrual cycle phase on the World Recall task when placebo was administered, but the two lowest doses of alprazolam decreased delayed word recall more in the luteal phase. However, when data from the other performance tasks (which were conducted multiple times over the day) were analyzed as peak change scores from baseline, alprazolam produced a similar degree of impairment in both the luteal and the follicular phases indicating that premen-

strual fluctuations in mood do not enhance the effects of alprazolam. Other important factors to consider when assessing performance is the issue of prior training on the tasks and the duration of testing. In previous studies testing women with PMS, little or no practice was provided on the tasks (Jensen 1982; Posthuma et al. 1987; Rapkin et al. 1989; Keenan et al. 1995; Morgan et al. 1996; Resnick et al. 1998). Further, in all of these studies women were tested within each phase for a single session and each task was measured once, whereas in the present study, performance on a range of tasks was repeatedly tested over the day. Despite the extensive testing in the present study, the overall findings support and extend previous studies indicating that performance changes in women with PMS are subtle even in the presence of marked alterations in mood.

### Abuse Liability

We originally hypothesized that women with PMS may be at increased risk to misuse or abuse benzodiazepines, such as alprazolam, because alprazolam had been shown to clinically improve PMS symptoms (e.g., Harrison et al. 1990) and other studies indicated that women with PMS tended to drink alcohol (e.g., Christensen et al. 1989; Mello et al. 1990; McLeod et al. 1994) and use other drugs more often premenstrually (Mello and Mendelson 1985; Mello et al. 1987). Even though alprazolam has increased abuse potential among various populations (DuPont 1988), and women were tested using a laboratory procedure shown to be sensitive to detecting the abuse liability of acute doses of various anxiolytics in humans (de Wit and Griffiths 1991; Evans et al. 1991, 1995), the present study found no evidence that women with PMS are at increased risk to abuse alprazolam. Contrary to what we expected, acute administration of alprazolam did not improve mood in the luteal phase and correspondingly, alprazolam did not increase the various subjective measures suggestive of abuse liability, such as ratings of "drug liking" or "good effects." The only measure that showed a significant increase in the luteal phase was ratings of "willingness to take the drug again" following 0.25 mg alprazolam. In contrast, alprazolam only exacerbated the premenstrual negative mood symptoms and produced a typical profile of adverse subjective effects, including increased ratings of measures related to sedation and "bad drug effects" during both phases. It is unclear whether repeated administration of alprazolam, similar to the dosing regimen used for treatment of PMS, would engender increased positive mood and abuse liability.

### Summary

In summary, this is, to our knowledge, the first study to evaluate systematically the mood and performance effects of alprazolam in women with confirmed PMS. The results do not support the majority of treatment studies showing that alprazolam is an effective medication for PMS. Rather, the present study shows that acute alprazolam doses do not improve mood during the luteal phase and actually produce negative mood changes in the follicular phase when women are nonsymptomatic. In fact, the overall magnitude of the effects produced by alprazolam were often greater in the luteal phase due to the underlying mood disturbance (e.g., Fatigue). Although alprazolam did not produce any greater impairment in the luteal phase on most tasks, alprazolam did impair delayed word recall more in the luteal phase compared to the follicular phase. Thus, caution should be used in prescribing alprazolam to women diagnosed with PMS. Alprazolam may not improve symptoms and can impair some aspects of performance. This is particularly important since women with PMS usually take alprazolam for 10 days before menstruation and taper over one to two days after the onset of menstruation. Thus, alprazolam could have profound effects on sedation and on memory during the first few days of use each menstrual cycle. Lastly, a positive finding of the current study was that there was little evidence that these women are at increased risk to abuse or misuse alprazolam as a result of their premenstrual symptoms.

## ACKNOWLEDGMENTS

This research was supported by DA-03476 and DA-09114 from the National Institute on Drug Abuse, and approved by the New York State Psychiatric Institute-Columbia University Department of Psychiatry Institutional Review Board. The assistance of Dr. Jean Endicott, Eunice Dong, Christie Ieronimo, Shannon Miller, Jacqueline Schatz, and Grace Shiao is gratefully acknowledged. Portions of these data were presented to the Collegium Internationale Neuropsychopharmacologicumm in July 1996.

## REFERENCES

American College of Obstetricians and Gynecologists (ACOG) (1989): Premenstrual syndrome. Committee Opinion, No. 66. Washington, DC: American College of Obstetricians and Gynecologists

American Psychiatric Association (1994): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, U.S. Department of Health and Human Services

Aranko K, Matilla MJ, Bordignon D (1985): Psychomotor effects of alprazolam and diazepam during acute and subacute treatment, and during the follow-up phase. Acta Pharmacol et Toxicol 56:364–372

Bancroft J, Williamson L, Warner P, Rennie D, Smith SK (1993): Perimenstrual complaints in women complaining of PMS, menorrhagia, and dysmenorrhea: Toward a

dismantling of the premenstrual syndrome. Psychosom Med 55:133–145

Barr S, Janelle KC, Prior JC (1995): Energy intakes are higher during the luteal phase of ovulatory menstrual cycles. Am J Clin Nutr 61:39–43

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961): An inventory form measuring depression. Arch Gen Psychiatry 4:561–571

Berger CP, Presser B (1994): Alprazolam in the treatment of two subsamples of patients with late luteal phase dysphoric disorder: A double-blind, placebo-controlled crossover study. Obstet Gynecol 84:379–385

Block RI, Berchou R (1984): Alprazolam and lorazepam effects on memory acquisition and retrieval processes. Pharmacol Biochem Behav 20:233–241

Christensen AP, Oei TP, Callan VJ (1989): The relationship between premenstrual dysphoria and daily ratings dimensions. J Affect Disord 16:127–132

Chutuape MD, de Wit H (1995): Preferences for ethanol and diazepam in anxious individuals: An evaluation of the self-medication hypothesis. Psychopharmacology 121:91–103

Ciraulo DA, Sands BF, Shader RI (1988): Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psychiatry 145:1501–1506

Dennerstein L, Morse C, Burrows G, Brown J, Smith M (1986): Alprazolam in the treatment of premenstrual syndrome. In Dennerstein L, Fraser I (eds), Hormones and Behaviour. Elsevier, pp 175–182

de Wit H, Griffiths RR (1991): Testing the abuse liability of anxiolytic and hypnotic drugs in humans. Drug Alcohol Depend 28:83–111

de Wit H, Pierri J, Johanson CE (1989): Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharmacol Biochem Behav 33:205–213

DuPont EL (1988): Abuse of benzodiazepines: The problems and the solutions. Am J Drug Alcohol Abuse 14(Suppl. 1):1–69

Endicott J, Nee J, Cohen J, Halbreich U (1986): Premenstrual changes: Patterns and correlates of daily ratings. J Affect Disord 10:127–135

Evans SM, Critchfield TS, Griffiths RR (1991): Abuse liability assessment of sedative/anxiolytics: Rationale and laboratory lore. Br J Addiction 86:1625–1632

Evans SM, Troisi JR II, Griffiths RR (1994): Tandospirone and alprazolam: Comparison of behavioral effects and abuse liability in humans. J Pharmacol Exp Ther 271:683–694

Evans SM, Foltin RW, Levin FR, Fischman MW (1995): Behavioral and subjective effects of DN-2327 (Pazinaclone) and alprazolam in normal volunteers. Behav Pharmacol 6:176–186

Evans SM, Griffiths RR, de Wit H (1996): Preference for diazepam, but not buspirone, in moderate drinkers. Psychopharmacology 123:154–163

First MB, Spitzer RL, Gibbon M, Williams JBW (1995): Structured clinical interview for DSM-IV Axis I disorders-Patient Edition (SCID-I/P, version 2.0) Biometrics Research Department, New York, NY, New York State Psychiatric Institute

Freeman EW, Sondheimer SJ, Rickels K, Weinbaum P (1985): PMS treatment approaches and progesterone therapy. Psychosomatics 26:811–816

Freeman EW, Rickels K, Sondheimer SJ, Polansky M (1995): A double-blind trial of oral progesterone, alprazolam, and placebo in the treatment of severe premenstrual syndrome. JAMA 274:51–57

Halbreich U, Endicott J, Schacht S (1982): Premenstrual syndromes: A new instrument for their assessment. J Psychiatr Treat Eval 4:161–164

Harrison WM, Endicott J, Nee J (1990): Treatment of premenstrual dysphoria with alprazolam: A controlled study. Arch Gen Psychiatry 47:270–275

Iguchi MY, Handelsman L, Bickel WB, Griffiths RR (1993): Benzodiazepine and sedative use/abuse by methadone maintenance clients. Drug Alcohol Depend 32:257–266

Jensen BK (1982): Menstrual cycle effects on task performance examined in the context of stress research. Acta Psychologica 50:159–178

Kelly TH, Foltin RW, Emurian CS, Fischman MW (1993): Performance-based testing for drugs of abuse: Dose and time profiles of marijuana, amphetamine, alcohol, and diazepam. J Anal Toxicol 17:264–272

Keenan PA, Stern RA, Janowsky DS, Pedersen CA (1992): Psychological aspects of premenstrual syndrome I: Cognition and memory. Psychoneuroendocrinology 17:179–187

Keenan PA, Lindamer LA, Jong SK (1995): Menstrual phase-independent retrieval deficit in women with PMS. Biol Psychiatry 38:369–377

Linnoila M, Stapelton J, Lister R, Moss H, Lane E, Granger A, Eckardt MJ (1990): Effects of single doses of alprazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers. Eur J Clin Pharmacol 39:21–28

Logue AM, Moos RH (1986): Perimenstrual symptoms: Prevalence and risk factors. Psychosom Med 48:388–414

McLeod D, Griffiths RR, Bigelow GE, Yingling J (1982): An automated version of the digit symbol substitution test (DSST). Behav Res Methods Instrum 14:463–466

McLeod DR, Foster GV, Hoehn-Saric R, Svikis DS, Hipsley PA (1994): Family history of alcoholism in women with both generalized anxiety disorder and premenstrual syndrome: Patient reports of premenstrual alcohol consumption and premenstrual symptoms of anxiety. Alcohol Clin Exp Res 18:664–670

McNair D, Lorr M, Droppleman LF (1971): Profile of Mood States. San Diego, Educational and Industrial Testing Services

Mello NK, Mendelson JH (1985): Operant acquisition of marihuana by women. J Pharmacol Exp Ther 235:162–171

Mello NK, Mendelson JH, Palmieri SL (1987): Cigarette smoking by women: Interactions with alcohol use and menstrual cycle phase. Psychopharmacology 93:8–15

Mello NK, Mendelson JH, Lex BW (1990): Alcohol use and premenstrual symptoms in social drinkers. Psychopharmacology 101:448–455

Metropolitan Life Insurance Company (1983): Metropolitan

height and weight tables. Statistical Bulletin Metropolitan Insurance Companies 64:2–9

Miller TP, Taylor JL, Tinklenberg JR (1988): A comparison of assessment techniques measuring the effects of methylphenidate, secobarbital, diazepam and diphenhydramine in abstinent alcoholics. Neuropsychobiology 19:90–96

Morgan M, Rapkin AJ, D'Elia L, Reading A, Goldman L (1996): Cognitive functioning in premenstrual syndrome. Obstet Gynecol 88:961–966

Podolsky E (1963): Women alcoholics and premenstrual tension. J Am Med Women Assoc 18:816–818

Price WA, DiMarzio LR, Eckert JL (1987): Correlation between PMS and alcoholism among women. Ohio State Med J 3:201–202

Posthuma BW, Bass MH, Shelley BB, Nisker JA (1987): Detecting changes in functional ability in women with premenstrual syndrome. Am J Obstet Gynecol 156:275–278

Rapkin AJ, Chang LC, Reading AE (1989): Mood and cognitive style in premenstrual syndrome. Obstet Gynecol 74:644–649

Redei E, Freeman EW (1995): Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. Psychoneuroendocrinology 20:259–267

Resnick A, Perry W, Parry B, Mostofi N, Udell C (1998): Neuropsychological performance across the menstrual cycle in women with and without premenstrual dysphoric disorder. Psychiatry Research 77:147–158

Rickels K, Csanalosi I, Greisman P, Cohen D, Werblowsky J, Ross HA, Harris H (1983): A controlled clinical trial of alprazolam for the treatment of anxiety. Am J Psychiatry 140:82–85

Rivera-Tovar AD, Frank E (1990): Late luteal phase dysphoric disorder in young women. Am J Psychiatry 147:1634–1636

Schmidt PJ, Grover GN, Rubinow DR (1993): Alprazolam in the treatment of premenstrual syndrome. Arch Gen Psych 50:467–473

Smith S, Rinehart JS, Ruddock VE, Schiff I (1987): Treatment of premenstrual syndrome with alprazolam: Results of a double-blind, placebo controlled, randomized cross over clinical trial. Obstet Gynecol 70:37–42

Spielberger CD, Gorsuch RL, Lushene RE (1970): STAI Manual for the State-Trait Anxiety Inventory ("Self-Evaluation Questionnaire"), Palo Alto, CA, Consulting Psychologists Press, Inc.

Sundström I, Ashbrook D, Bäckström T (1997a): Reduced benzodiazepine sensitivity in patients with premenstrual syndrome: A pilot study. Psychoneuroendocrinology 22:25–38

Sundström I, Nyberg S, Bäckström T (1997b): Patients with premenstrual syndrome have reduced sensitivity to midazolam compared to control subjects. Neuropsychopharmacology 17:370–381

Thorndike EL, Lorge I (1944): The Teacher's Word Book of 30,000 Words. Columbia University, NY, Teachers College

Weddington WW, Carney AC (1987): Alprazolam abuse during methadone maintenance therapy. JAMA 257:3363

Woods JH, Katz JL, Winger G (1992): Benzodiazepines: Use, abuse, and consequences. Pharmacol Rev 44:151–347