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Clinical Use of Benzodiazepines and Decreased Memory Activation in Anxious Problem Drinkers

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Clinical use of benzodiazepines (BZDs) may improve treatment outcome in anxious problem drinkers. Decreased activation of alcohol-related memories by negative affective cues may partly explain the beneficial effects of BZDs. To explore this possibility, the present study assessed semantic priming of alcohol words by negative affective words in anxious problem drinkers who received their standard dose of BZD and in unmedicated controls. Two groups of nine subjects each were matched on levels of anxiety, alcohol use, and alcohol dependence before performing a lexical decision task. Medicated subjects displayed significantly less activation than did unmedicated subjects on trials containing negative affective primes and alcohol-related targets, but displayed equivalent activation on control trials with neutral, categorized words. Degree of activation also correlated with a drug's affinity for the BZD receptor. These preliminary results suggest that BZD-induced amnesia may contribute to the therapeutic effects of these drugs in anxious problem drinkers.

Key Words: Benzodiazepines, Problem Drinkers, Anxiety, Activation, Priming.

PROBLEM DRINKERS often experience anxiety as part of their disorder,[1] and are very likely to suffer acute anxiety during attempts to stop drinking.[2] Benzodiazepines (BZDs) have been used to treat both kinds of anxiety,[3] as well as to reduce chronic anxiety in problem drinkers with concurrent anxiety disorders.[4] When used in this controlled manner, some research suggests that BZDs may improve treatment outcome in anxious problem drinkers without leading to abuse or dependence.[5,6] However, their abuse liability and their synergistic effects with alcohol make BZDs a controversial treatment for anxiety in problem drinkers.[7]

Anxious problem drinkers are most likely to drink when their anxiety symptoms are pronounced.[8] Therefore, one way BZDs may improve treatment outcome in this population is by reducing the need to "self-medicate" anxiety symptoms with alcohol. However, BZDs also have a range of effects in addition to anxiolysis that may contribute to their clinical utility. One such effect is impairment of memory. Specifically, BZDs impair encoding of information into memory more than retrieval of information from memory.[9] They impair explicit (conscious, deliberate) memory more than implicit (unconscious, involuntary) memory;[10,11] they also impair episodic memory (personal experiences) more than semantic memory (general knowledge).[12] Although all BZDs appear to produce these amnesic effects, they do so with varying intensity.[13] Pharmacological factors, such as lipid solubility[14] and affinity for the BZD binding site,[15] have been cited as factors mediating the amnesic effects of BZDs.

Some researchers have argued that amnesia is causally related to the clinical utility of BZDs.[16] These investigators suggest that BZDs may augment a naturally occurring stress response whereby anxiogenic stimuli disrupt encoding and consolidation of memory by reducing the activity of the amygdala and the hippocampus. As a result, representations of anxiogenic stimuli in memory may be impoverished. Impaired encoding or consolidation of anxiogenic stimuli (e.g., negative affective cues) may also reduce or negate the effects that these stimuli exert on drinking by way of memory.

Reactivity to conditioned cues for alcohol, including interoceptive cues like anxiety or negative affect,[17] can undermine abstinence in problem drinkers.[18,19] Recent research has focused on the speed of access to concepts in memory as a way of measuring cue reactivity in problem drinkers. Unlike healthy controls, alcohol-dependent subjects take longer to name the print colors of alcohol-related words (e.g., BEER) than of neutral words (e.g., TABLE) on a modified Stroop task.[20] Similarly, compared with neutral words, brief exposure to alcohol words leads to faster lexical decisions (word/nonword) to subsequent alcohol word targets in alcohol-dependent subjects, but not in controls.[21] Such facilitation is called "semantic priming," and has been attributed to spreading activation among concepts in memory.[22,23]

Recently, Zack et al.[24] found that negative affect words prime lexical decisions to alcohol-related target words in problem drinkers with high levels of anxiety on the Symptom Checklist-90.[25] Thus, negative affective and alcohol concepts were associated in memory in this population. No such activation was observed in nonanxious problem drinkers, suggesting that this effect may be restricted to problem drinkers with high levels of psychiatric distress. The degree of priming displayed also correlated with the relative frequency of drinking in negative affective states, suggesting

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that conditioned associations between negative affect and alcohol use may contribute to the linkage of these concepts in memory.

Activation of memory networks can bias decision-making,[26] as well as overt behavior.[27] Activation of alcohol memories by cues denoting affective correlates of alcohol use can also promote drinking behavior in social drinkers.[28] Although such a direct causal effect has not been demonstrated in problem drinkers, activation of alcohol memories by negative affective cues did predict self-reported risk of relapse in negative affective states in these individuals.[24] Together, these findings suggest that treatments that reduce primed activation of alcohol memories may reduce the likelihood of drinking in problem drinkers. Therefore, decreased activation by BZDs in anxious problem drinkers would be consistent with the notion that BZD-induced amnesia contributes to the therapeutic effects of these drugs in this population.

To date, only one published study appears to have tested the effects of BZDs on memory activation by negative affective cues in a clinical population. This study[29] found that, relative to placebo, an acute dose of diazepam slowed color-naming responses to both threat words and neutral words on a modified Stroop task,[30] but did not reduce the difference in response time to these two types of words in anxious subjects with no drinking problem. However, because the relative latencies to color-name threat words and neutral words did not differ between anxious subjects and controls prior to diazepam, the null effect of the drug may have partly reflected a measurement limitation (i.e., a ceiling effect). In addition, BZDs may have different effects in drug-naive subjects, like those in the diazepam study, than in subjects treated chronically with a BZD.[31]

The present study explored the effects of acute BZD administration on activation of alcohol concepts by negative affective cues in anxious problem drinkers who had been taking a prescribed BZD on a continuing basis. A matched sample of unmedicated anxious problem drinkers served as a control. A lexical decision task, previously validated in anxious[24] and in nonanxious[21] problem drinkers, measured memory activation. Subjects saw every combination of negative affective and alcohol-related prime and target words, along with neutral, categorized control words. It was predicted that subjects who received their standard dose of BZD would display significantly less activation of memory-based alcohol concepts by negative affective cues than would subjects who received no BZD.

Published high-performance liquid chromatograph (HPLC) retention index scores[32] and equilibrium dissociation constants (K_ds)[32,33] measured the lipid solubility and binding affinity, respectively, of each BZD. High HPLC scores (relative to a drug standard) indicate high availability of the drug to target brain receptors. Low K_ds indicate high stimulation of the cells activated by that receptor. Thus, an inverse correlation between memory activation under a BZD, and the lipid solubility and binding affinity of that BZD would provide tentative support for a pharmacological interpretation of group differences in activation.

Table 1. DSM-IV Axis I Diagnoses for Anxious Problem Drinkers Taking a BZD (Group Med, n = 9) and for Unmedicated Anxious Problem Drinkers (Group No-Med, n = 9)

Diagnosis	n	%
Group Med		
Panic with agoraphobia	3	33
Substance-induced anxiety	2	22
Social phobia	2	22
Generalized anxiety disorder	1	11
Agoraphobia	1	11
Group No-Med		
Panic with agoraphobia	3	33
Substance-induced anxiety	3	33
Social phobia	1	11
Generalized anxiety disorder	1	11
Adjustment disorder with anxiety	1	11

METHODS

Subjects

Subjects (Ss) were 18 anxious alcohol-dependent[34] outpatients (age 21 to 55 years) seeking treatment for problem drinking. Nine medicated Ss (Group Med) were taking a BZD prescribed by a referring physician. Nine unmedicated Ss (Group No-Med), matched on gender (6 males, 3 females), self-reported anxiety, and alcohol use, served as controls. Diagnoses were made by a clinical psychologist or psychiatrist, based on DSM-IV criteria,[34] during an initial interview after intake. The diagnoses for each group are shown in Table 1. The table shows that Panic with Agoraphobia was the most common diagnosis in each group, followed by Substance-induced Anxiety, Social Phobia, and Generalized Anxiety Disorder; one S in each group met none of these diagnoses. A two-way χ^2 test of the frequency of these diagnoses in each group (with Yates correction) was nonsignificant, χ^2 (4, n = 18) = 0.53, p>0.90. Therefore, the diagnostic composition of the groups did not differ. All Ss had normal or corrected-to-normal vision. Ss knew that the study was not a part of their treatment and that they would be paid $10 for their participation.

Lorazepam was the most commonly used BZD (n = 3; mean dose = 2.5 mg), followed by alprazolam (n = 2; mean dose = 0.25 mg). Chlordiazepoxide (2.5 mg), clonazepam (1.0 mg), oxazepam (0.5 mg), and diazepam (10.0 mg) were each taken by one S. All dosage levels were in the range of therapeutic efficacy.[35] The duration of use of BZDs ranged from 2 weeks to 7 years (mean = 2.03 years).

The Obsessive-Compulsive, Interpersonal Sensitivity, Anxiety, and Phobic Anxiety subscales of the Symptom-Checklist-90-Revised (SCL-90)[25] measured anxiety. The 90-day Timeline Followback (TLFB)[36] measured levels of alcohol use, and the Alcohol Dependence Scale (ADS)[37] measured severity of alcohol dependence. The Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS-R)[38] measured Ss' word knowledge. These and other descriptive characteristics of Ss are reported in the "Results" section.

Apparatus and Materials

An IBM-compatible 386 microcomputer with a 14-inch VGA monitor administered the lexical decision task and recorded the data with millisecond accuracy. Ss sat facing the screen at a distance of 60 cm. Responses to target letter strings were made by pressing the "z" key (Nonword) or the "?" key (Word) with the index finger of the left hand or right hand, respectively. To control for confusion or memory lapse, plastic stickers identified the keys that corresponded to Word and Nonword responses.

A J-4-X ALERT model breathalyzer[39] assessed breath samples before testing to ensure that every S's blood alcohol concentration was 0.

Table 2. Mean (SD) Levels of Self-Reported Anxiety (0–4), Alcohol Dependence (0–51), and Alcohol Use in Unmedicated Subjects (Group No-Med) and Subjects Treated with a BZD (Group Med)

	Symptom Checklist-90 Subscale*				
	OC	INT	ANX	PHOB	ADS
Group No-Med	2.69 (0.61)	2.05 (1.24)	2.73 (1.04)	2.66 (0.92)	29.33 (11.72)
Group Med	2.07 (1.22)	1.81 (1.19)	2.07 (1.16)	2.26 (0.94)	24.33 (11.73)

	TLFB (preceding 90 days)*			
	Years problem drinking	Drinks/drinking day	Heavy days†,‡	Abstinent days‡
Group No-Med	13.75 (8.12)	14.37 (8.14)	4.45 (1.70)	1.77 (1.14)
Group Med	19.25 (7.65)	11.19 (5.98)	4.53 (2.27)	2.32 (1.96)

* Symptom Checklist-90 (SCL-90) Subscale: OC, Obsessive-Compulsive; INT, Interpersonal Sensitivity; ANX, General Anxiety; PHOB, Phobic Anxiety; TLFB: Timeline Followback; ADS: Alcohol dependence scale.

† Heavy days (>4 standard drinks).

‡ Occasions/week.

Procedure

The testing procedure has been detailed elsewhere,[24] so only an overview is presented herein. Briefly, each S performed the lexical decision task alone in a quiet well-lit room between the hours of 10 AM and 12 noon. Ss in Group Med took their standard dose of BZD at the usual time and reported to the laboratory 2 hr later. This interval ensured that drug blood levels of each BZD should be near peak concentration.

Before testing, Ss signed a consent form and provided a breath sample. Ss then did 335 (15 practice, 320 test) lexical decision trials, administered in five blocks of 60 and one block of 20, with 1-min rests between blocks. Event sequence on each trial was identical: /fixation stimulus (++++; 250 msec)/blank screen (250 msec)/prime stimulus (750 msec)/target stimulus (until response)/blank screen (1000 msec). Stimuli were white upper case letter strings (1 cm in height) against a black background. Prime stimuli appeared at the center of the screen; target stimuli appeared 1 cm below the center of the screen. These stimulus parameters have been shown to yield semantic priming in anxious nonproblem drinkers,[40] in nonanxious problem drinkers,[21] and in anxious problem drinkers.[24] Time to complete the task was ~25 min.

Ss received instructions from the experimenter both orally and on the computer screen prior to the task. They were told that they would see a series of letter strings, some of which were real English words and some of which were nonsense. They were told that the strings would appear in pairs, one following the other. They were instructed to read the first string of each pair silently, and then to respond to the second string as quickly and carefully as possible by pressing the appropriate key. On completion of the lexical decision task, Ss performed the Vocabulary subtest of the WAIS-R and filled out the questionnaires, after which they were debriefed and paid $10.

Stimulus Conditions for the Lexical Decision Task

There were five prime-target test conditions [Negative Affective-Alcohol (NEG-ALC), ALC-NEG, ALC-ALC, NEG-NEG, Categorical-Categorical (CAT-CAT-matched)] and three baseline conditions [Neutral-Alcohol (NEU-ALC), NEU-NEG, CAT-CAT-unmatched], with 20 trials per condition. Each test condition assessed activation of target concepts by putatively related prime cues. Each corresponding baseline condition assessed response time (RT) to the targets when they were preceded by neutral, unrelated primes. The difference in RT to a class of targets after putatively related test primes as opposed to neutral, unrelated baseline primes (e.g., ΔRT = [NEU-ALC − NEG-ALC]) measured priming. Faster mean RT to targets following test rather than baseline primes indicated activation of the target concepts in memory by the test prime stimuli

The complete set of stimuli for the lexical decision task is available from the first author upon request. NEG stimuli consisted of symptoms endorsed by anxious drug and alcohol abusers on the SCL-90 (e.g., WORRY, TENSE).[41] ALC stimuli were drawn from previous studies on activation of alcohol concepts (e.g., BEER, SMASHED). NEU stimuli were the names of parts of a building (e.g., CHIMNEY, PLANK). CAT stimuli were words from two neutral categories: four-legged mammals (e.g., DOG) and articles of clothing (e.g., SHIRT). Half of the target stimuli were pronounceable nonwords (NON) (e.g., FIBBAGE, SLORE). There were 40 prime-target pairs in each of the NON conditions, so that word and nonword targets were equally probable. Prime-target condition varied randomly over trials. To prevent confounding of categories and exemplars, stimuli from each word category were randomly paired with stimuli from the other categories, including nonwords, to form nine unique stimulus sets. Each set was seen by only one subject in each group.

RESULTS

Procedural Checks

All Ss displayed a blood alcohol concentration of 0 on their pretest breath measure. No S reported drinking alcohol or using recreational drugs in the 24 hr before testing.

Both word frequency[42] and word length[43] influence semantic priming. A one-way analysis of variance (ANOVA) comparing mean frequency of occurrence in print of the NEG, ALC, NEU, CAT-mammal, and CAT-clothing stimuli showed no significant effect ($p > 0.10$). Thus, word frequency cannot account for any between- or within-group differences in RT on the lexical decision task. However, a one-way ANOVA comparing mean length of the stimuli in each of these conditions obtained a significant effect [$F(4,475) = 13.69$, $p < 0.001$]. Post-hoc comparisons (Tukey's HSD) found that NEG stimuli contained more letters (mean = 7.76) than all other types of stimuli (mean = 6.47), $p < 0.05$], and that CAT-clothing stimuli were longer (mean = 6.93) than CAT-mammal stimuli (mean = 5.82), $p < 0.05$]. Because longer words tend to reduce semantic priming,[43] facilitation of RT on trials containing NEG words is likely to be a conservative estimate.

Subject Characteristics

Table 2 reports the mean scores for Groups Med and No-Med on the measures of anxiety (SCL-90), alcohol use (TLFB), and alcohol dependence (ADS). The anxiety scores were considerably higher (99% on average) than published norms for psychiatric outpatients.[44] Mean drink-

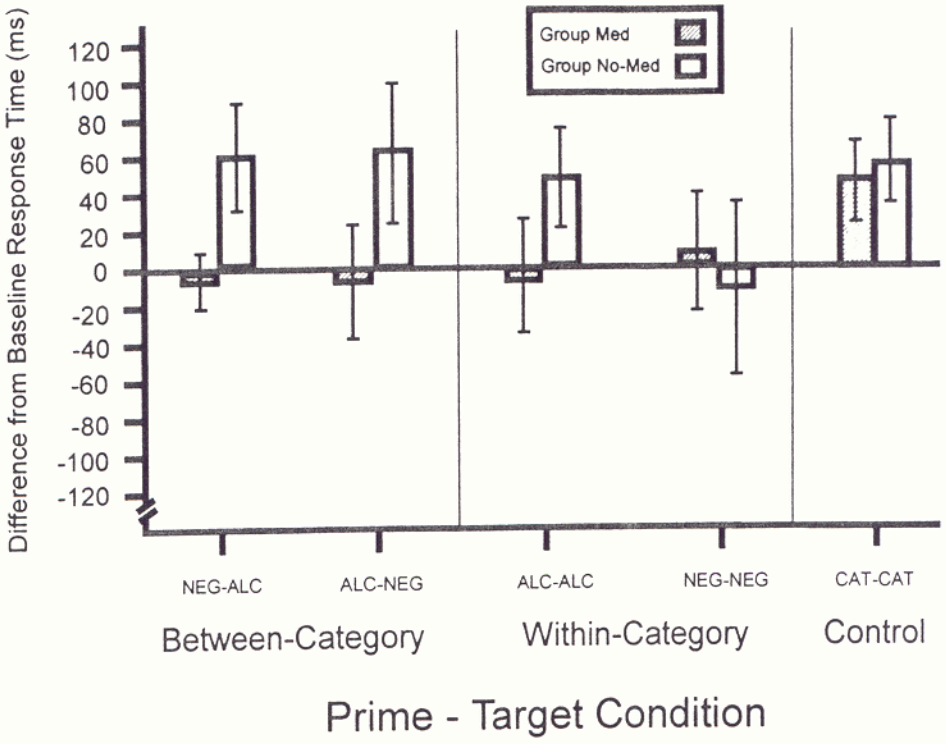

Fig. 1. Mean difference from baseline response time (msec) in five prime-target conditions on the lexical decision task in unmedicated anxious problem drinkers (Group No-Med; $n = 9$) and in anxious problem drinkers treated with BZDs (Group Med; $n = 9$). Stimuli were negative affective (NEG), alcohol-related (ALC), and neutral, categorized (CAT) words. Positive scores indicate facilitation; negative scores indicate interference. Vertical lines show standard errors of the difference.

ing levels were in the "heavy" range,[45] and degree of dependence was "substantial,"[46] based on norms for problem drinkers. As indicated, the anxiety and alcohol dependence scores were somewhat higher in Group No-Med, whereas the duration of problem drinking was somewhat longer in Group Med.

A 2 (Group) × 4 (Subscale) multivariate ANOVA (MANOVA) comparing the groups' ratings on the anxiety-related subscales of the SCL-90 showed no significant multivariate ($p > 0.60$) or univariate effects (Bonferonni $ps > 0.70$) This confirmed that the groups did not reliably differ with respect to anxiety. A 2 (Group) × 4 (Measure) MANOVA comparing the groups on drinks/drinking day, heavy drinking days (>4 standard drinks), abstinent days, and duration (years) of problem drinking, also showed no significant multivariate ($p > 0.30$) or univariate group differences (Bonferonni $ps > 0.70$). Therefore, the intensity and longevity of problem drinking did not differ in the two groups. An independent samples t test comparing the groups ADS scores was also nonsignificant ($p > 0.30$), indicating equivalent levels of dependence in each group. These results show that the groups were well matched with respect to anxiety, alcohol use, and alcohol dependence. Therefore, group differences in task performance cannot be attributed to these variables.

Independent samples t tests also found no differences in the groups' mean age or mean score on the WAIS-R Vocabulary subtest ($ps > 0.40$). Therefore, differences in the groups' lexical decision performance did not reflect differences in age-related functioning (e.g., psychomotor speed), or in word knowledge. The mean (SD) age of Ss was 41.1 (9.3) years for Group Med and 36.1 (7.3) years for Group No-Med. Their mean (SD) Vocabulary scores were 41.1 (10.8) and 45.7 (13.0) for Groups Med and No-Med, respectively.

Task Performance

Response Time. NON stimuli are semantically meaningless, so that only trials containing word targets were used to assess semantic priming. In line with conventional procedure in semantic priming studies,[47,48] outlier responses (RT <100 msec | RT > 3000 msec) were analyzed separately. Mean RT to the 20 prime-target pairs in each word-word condition on the lexical decision task was the dependent measure.

Figure 1 displays the mean change from baseline RT for Groups Med and No-Med in the five test conditions. The figure shows large positive change scores for Group No-Med, indicating substantial facilitation in each condition, except NEG-NEG. In contrast, Group Med displayed negligible change scores in all but the control condition, CAT-CAT.

Test RT and baseline RT were significantly correlated in each condition, $0.94 < r < 0.98$, $ps < 0.001$. Such intercorrelations can reduce the reliability of change scores derived by subtracting test RT from baseline RT.[49] Accordingly, RT scores from each test condition were directly compared with RTs from the corresponding baseline condition in the statistical analyses.[50] Because primes and targets were not fully crossed, separate ANOVAs assessed between-category (ALC-NEG, NEG-ALC) priming, within-category

(ALC-ALC, NEG-NEG) priming, and priming of control stimuli (CAT-CAT).

A preliminary 2 (Group) × 3 (Condition) ANOVA assessing RT in the three baseline conditions (NEU-ALC, NEU-NEG, CAT-CAT-unmatched) showed a significant effect of condition [$F(2,32) = 103.26$, $p < 0.001$], but no main effect of group and no interaction ((ps >0.50). RT was faster in the control condition, CAT-CAT-unmatched (844 msec) than in the NEU-ALC (904 msec) and NEU-NEG (911 msec) conditions. The lack of a main effect of group or of an interaction ensured that group differences in change from baseline on test trials (i.e., priming) did not derive from group differences in baseline RT.

To assess between-category priming, a 2 (Group) × 2 (Target) × 2 (Relation) ANOVA compared RT to ALC and NEG targets preceded by putatively related primes (NEG and ALC, respectively) and by unrelated (NEU) primes. There was a significant group × relation interaction [$F(1,16) = 5.01$, p <0.05], but no other significant effects (ps >09). Simple effects analyses showed that Group No-Med displayed significantly faster RT on test than on baseline trials involving both ALC and NEG targets [$F1,16) = 8.08$, (p <0.05], whereas Group Med showed no corresponding difference (ps >0.70).

To assess within-category priming, a 2 (Group) × 2 (Target) × 2 (Relation) ANOVA compared RT to ALC and NEG targets preceded by putatively related primes (ALC and NEG, respectively), or by unrelated (NEU) primes. The analysis obtained no significant effects (ps >0.30). Figure 1 shows that the mean difference from baseline RT in the ALC-ALC condition was sizeable and positive in Group No-Med (+44 msec), but small and negative in Group Med (−8 ms), consistent with the hypothesis. However, inspection of the error bars in the figure suggests that high within-group variability obscured between-group differences in change from baseline in the ALC-ALC condition. In addition, there was very little change from baseline RT in the NEG-NEG condition in Group No-Med (−11 msec) and in Group Med (+ 4 msec). Therefore, NEG prime cues did not reliably alter RT to NEG targets in either group.

To assess priming of control stimuli, a 2 (Group) × 2 (Relation) ANOVA compared RT scores to CAT targets when primes came from a related (CAT-matched) or an unrelated (CAT-unmatched) category. There was a significant main effect of relation [$F(1,16) = 10.03, p$ <0.01], and no significant group effect or interaction (ps >0.70), confirming that the task was capable of detecting facilitation of categorized, neutral targets. Therefore, absence of priming in Group No-Med on trials containing clinically relevant (i.e., ALC, NEG) stimuli cannot be attributed to inadequacies in the testing procedure or in the parameters of the lexical decision task. The lack of a group effect or interaction for control stimuli indicated that medicated and unmedicated Ss did not differ in memory activation caused by nonclinically relevant stimuli. Together, these results imply that group differences in RT to clinically relevant stimuli did not reflect a nonspecific deficit in Group Med's performance, such as sedation or impaired decision making.

Pharmacological Factors in Priming. To assess the relation between the lipid solubility and binding affinity of each BZD and the degree of facilitation displayed on the lexical decision task by a S taking that BZD, a unitary measure of facilitation was required. Although the mean change from baseline RT provides such a measure, intercorrelated test and baseline scores can lead to spurious results when change scores are correlated with a third variable.[51] The regression residual, obtained by regressing the change in RT (baseline − test) onto the baseline RT, removes shared variance between test and baseline, and so provides an unambiguous measure of change.[52]

Retention indices, based on HPLC, reflected the lipid solubility of each BZD relative to diazepam, with higher values indicating greater lipid solubility. Dissociation constants (K_ds), based on the displacement of each BZD from its receptor by tritiated flunitrazepam, reflected the binding affinity of the BZDs, with lower scores indicating greater affinity of the BZD for its receptor.

Previous research had shown that NEG-ALC priming was the best index of the specific pattern of activation in problem drinkers with high anxiety on the SCL-90.[24] Accordingly, scores from the NEG-ALC condition were used to assess the relation between priming and the pharmacological properties of the BZDs. The Pearson correlation between HPLC scores and residualized change in RT on NEG-ALC trials was nonsignificant (Bonferonni p >0.10). However, the correlation between K_d values and change in RT was significant ($r = 0.73$, Bonferonni p <0.05). Figure 2A depicts this correlation in eight of the nine Ss. The figure indicates that BZDs with low K_d values (high binding affinity) were associated with negative change scores (interference with RT), whereas BZDs with moderate to high K_d values (lower binding affinity) coincided with low-to-moderate positive change scores (facilitation of RT).

Figure 2A excludes the one case who was taking chlordiazepoxide: the dissociation constant of this BZD (K_d = 684) is 59 times greater than the next highest one (oxazepam, $K_d = 11.53$),[32,33] so that inclusion of this case would have grossly distorted the scale of the predictor. To compensate for this distortion, K_d scores for all nine cases were subjected to a logarithmic transformation.[53] Figure 2B shows the relation between the residualized NEG-ALC change scores and the log-transformed dissociation constants for the entire sample. Although attenuated, the correlation remained statistically significant $r = 0.59$, p <0.05, one-tailed). Negative change scores indicate slower RT on test trials relative to neutral baseline. Therefore, Figures 2A and 2B suggest that BZDs with high binding affinity are associated not only with reduced facilitation of RT, but also with interference in the activation of alcohol concepts by negative affective cues relative to neutral cues. The correlations

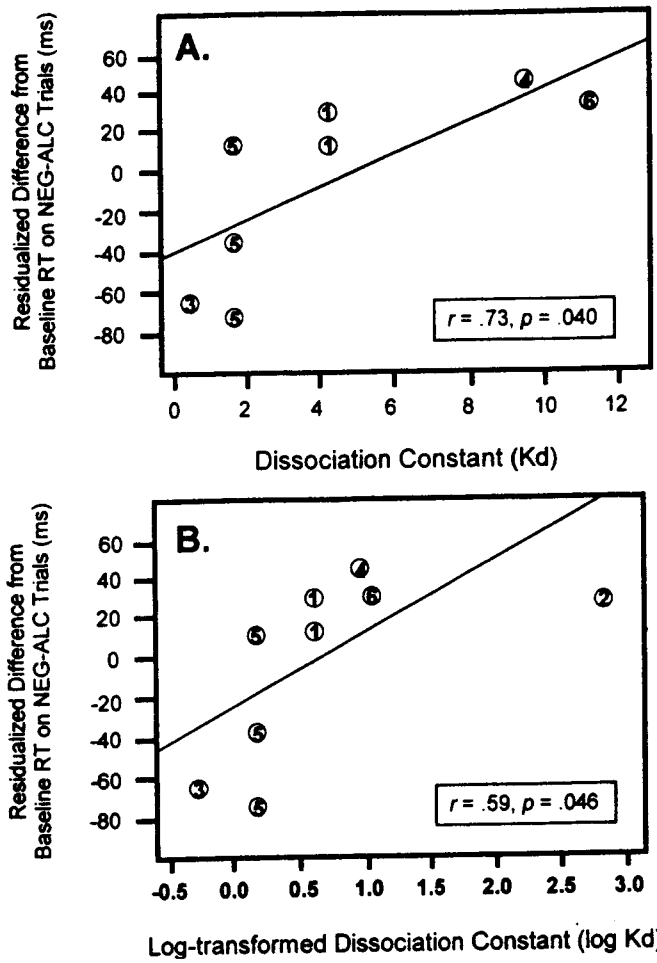

Fig. 2. Mean difference from baseline response time (msec) to alcohol-related (ALC) targets preceded by negative affective (NEG) primes in anxious problem drinkers treated with BZDs (Group Med) as a function of drug affinity for the BZD receptor. (A) Relation between the dissociation constant (K_d) and the difference from baseline on NEG-ALC trials (n = 8; chlordiazepoxide excluded). (B) Relation between the log-transformed dissociation constant and difference from baseline on NEG-ALC trials (n = 9). Lower K_d values denote higher binding affinity. Numbers in the data points represent the particular BZD: 1 = alprazolam, 2 = chlordiazepoxide, 3 = clonazepam, 4 = diazepam, 5 = lorazepam, and 6 = oxazepam.

between the change in RT on NEG-ALC trials and the half-life of the BZDs, as well as the period of chronic use of the BZDs, were nonsignificant (Bonferonni *ps* >0.20). Therefore, neither the acute nor the chronic blood levels of the BZDs were related to NEG-ALC priming.

Supplemental Performance Measures. There were no significant group differences or interactions involving Group in the frequency of errors (reporting a word when the target was a nonword or vice versa) or outliers (RT <100 msec | RT > 3000 msec) (*ps* >0.10). Therefore, the analyses of RT scores were not biased by differences in the number of scores that comprised the groups' mean RT in each prime-target condition.

Exploratory Analyses. Exploratory ANOVAs obtained no significant effects of gender on priming in any of the test conditions (Bonferonni *ps* >0.20). Correlational analyses between scores on the psychiatric and alcohol use indexes (SCL-90, TLFB, ADS) and the residualized change from baseline RT on NEG-ALC trials were likewise nonsignificant (Bonferonni *ps* >0.20). Therefore, priming was not associated with the severity of psychopathology or with alcohol use in this sample.

DISCUSSION

Previous research had shown that BZDs impair encoding of environmental information to memory.[9] This suggested that encoding of negative affective stimuli may be impaired by BZDs in anxious problem drinkers. As a result, the ability of such cues to activate associated alcohol concepts in memory would be diminished. Consistent with this reasoning, the present study found that unmedicated anxious problem drinkers displayed significant facilitation of alcohol targets by negative affective primes, whereas anxious problem drinkers who took their standard dose of BZD before testing displayed no facilitation. A parallel group difference was observed in RT to negative affective targets preceded by alcohol primes.

Priming of lexical decisions is considered to reflect activation in memory of target concepts linked to the primes via an associative network.[22,23] Therefore, the present results suggest that clinical use of BZDs by anxious problem drinkers coincides with decreased activation of alcohol-related concepts by negative affective cues. The parallel deficit in ALC-NEG priming indicates that alcohol cues also failed to activate negative affective concepts in subjects taking BZDs. Previous research suggests that activation of alcohol concepts by affective cues may bias decisions and overt behavior toward alcohol use.[26-28] Thus, the present results suggest that negative affective cues may be less able to bias alcohol-related behavior in anxious problem drinkers chronically treated with BZDs. However, the causal effects of BZDs on activation, and the relation between these effects and treatment outcome, remain to be established.

Although the medicated and unmedicated groups displayed different levels of between-category priming, no group differences were observed in priming of alcohol targets or negative affective targets by primes from the same category. Absence of NEG-NEG priming is consistent with previous research;[24] absence of ALC-ALC priming is not.[21,24] Inspection of the descriptive statistics revealed that, relative to baseline, the mean facilitation in RT on ALC-ALC trials in Group No-Med (+44 msec) was similar to the priming effects observed in previous samples.[21,24] The pronounced standard error scores (Fig. 1) further implied that within-group variability prevented detection of priming in the ANOVA. The descriptive statistics also indicated that Group Med displayed no priming (−8 msec) on alcohol-alcohol trials, a finding that is consistent with the hypothesis. Thus, although the inferential statistics did not demonstrate a group difference in ALC-ALC priming,

the mean change scores of the groups differed in the predicted direction.

The correlation between the dissociation constants of the BZDs and the mean change in RT on the NEG-ALC trials indicated that drugs with a higher affinity for the benzodiazepine receptor coincided with less priming. This is consistent with a pharmacological explanation for decreased priming in the present study, and with previous research showing that BZDs with high binding affinities (e.g., triazolam) produce the most profound amnesic effects.[54] However, given the range in drug type, dose, and duration of use of the BZDs, this one correlation cannot by itself confirm a pharmacological basis for decreased activation.

Equivalent change scores in each group on CAT-CAT trials indicated that both medicated and unmedicated subjects displayed significant priming of categorized control stimuli. This result is consistent with previous research showing that BZDs do not impair semantic memory (e.g., vocabulary),[9] or implicit memory of neutral (i.e., nonclinically relevant) information.[10,12] Significant activation of neutral concepts but not of clinically relevant concepts in Group Med is important for two reasons. First, it ensures that Group Med's lack of activation in the other conditions did not derive from a nonspecific effect of BZDs on task performance (e.g., motor slowing, sedation). Second, it suggests that some feature of the clinically relevant cues, other than semantic relation to the targets, was not fully processed by subjects taking BZDs.

A parsimonious explanation for the present results comes from psychophysiological research showing that lorazepam reduces the P300 component of the event-related electrical potential to visual cues in nonanxious subjects.[55] P300 is an index of cue salience or novelty, and is acutely sensitive to the conceptual features of a stimulus.[56] P300 deficits under lorazepam were thus taken as evidence of "a reduced capacity to process information or allocate neural resources required for encoding specific events" (p. 270).[55] Sober alcoholics display a significantly greater P300 response than sober nonalcoholics after brief presentation of the word VODKA.[57] This suggests that biased responses to clinically relevant cues by problem drinkers may reflect increased allocation of neural resources to those cues. Brain imaging research with drug abusers showing heightened activity in the amygdala during exposure to drug-related cues, but not neutral cues, supports this interpretation.[58] Increased allocation of neural resources to cues associated with drinking may partly explain NEG-ALC priming in unmedicated anxious problem drinkers in the present study. Conversely, lack of NEG-ALC priming in drinkers taking BZDs may have reflected decreased allocation of resources to negative affective cues, and a corresponding decrease in the ability of those cues to activate their alcohol-related associates in memory.

Interpretation of the present results must be tempered by their preliminary nature. First, the small sample size restricts the reliability of the findings. The heterogeneity of the subjects means that the effects of treatment (BZDs, cues) are confounded with dispositional factors so that the relative contribution of these variables cannot be determined. The fact that the BZDs were taken chronically makes it impossible to distinguish their acute effects from their chronic effects. Similarly, heterogeneity in the type of BZDs received precludes general conclusions about the effects of this class of drugs on memory activation. Given these limitations, group differences in activation in this study essentially reflect a covariation between chronic BZD use and activation of alcohol-specific memories in anxious problem drinkers.

The results of this study also must be reconciled with previous research that observed no effect of diazepam on anxious subjects' response to negative affective cues on a modified Stroop task.[29] This finding is at variance with the present finding of decreased between-category activation in Group Med. The discrepancy may reflect differences in how activation of clinically relevant concepts was measured in the two studies. The modified Stroop task measures memory activation in terms of *slower* color-naming RT to clinically relevant stimuli. Because a general effect of BZDs is to slow RT,[59] decreased activation under BZDs on a Stroop task entailed a drug-opposite effect (i.e., facilitation of RT). In contrast, the lexical decision task measures activation in terms of *faster* RT. Therefore, decreased activation on the lexical decision task entailed a drug-congruent effect (i.e., interference with RT). Thus, a differential handicapping effect of BZDs on task performance may explain the apparent discrepancy. Together, the results of the two studies illustrate how task-specific variables can influence the observed effects of psychotropic drugs.

The results of this study may have implications for understanding the therapeutic effects of BZDs in anxious problem drinkers. Cue reactivity has long been implicated in craving and in relapse to alcohol use.[60] NEG-ALC priming has been found to predict self-reported risk of relapse in negative affective states in unmedicated problem drinkers.[24] Together with these findings, the present results raise the possibility that improved treatment outcome in anxious problem drinkers treated with BZDs partly reflects decreased activation of alcohol memories by negative affective cues. Future research that controls factors such as dose, type, and duration of use of BZD can verify the reliability of the present results, and explore the predictive relation between memory activation under BZDs and treatment outcome in anxious problem drinkers.

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ERRATUM

The article by H. Wayne Sampson, Ph.D., which was published in the December 1998 issue of *Alcoholism: Clinical and Experimental Research,* titled Effect of Alcohol Consumption on Adult and Aged Bone: A Histomorphometric Study of the Rat Animal Model, was incorrectly placed in the Clinical section. It should have been placed in the Preclinical section. We regret the error.