Pharmacology Biochemistry & Behavior, Vol. 20, pp. 233–241, 1984. © Ankho International Inc. Printed in the U.S.A.

Alprazolam and Lorazepam Effects on Memory Acquisition and Retrieval Processes

ROBERT I. BLOCK[1]

Department of Psychiatry, Wayne State University School of Medicine and Lafayette Clinic Detroit, MI 48207

AND

RICHARD BERCHOU

Lafayette Clinic, Detroit, MI 48207

Received 18 July 1983

BLOCK, R. I. AND R. BERCHOU. *Alprazolam and lorazepam effects on memory acquisition and retrieval processes.* PHARMACOL BIOCHEM BEHAV 20(2) 233–241, 1984.—A double-blind study involving healthy young adult males examined acute effects of two benzodiazepines (alprazolam 1 mg and lorazepam 2 mg) on long-term memory acquisition and retrieval, using Buschke's "selective reminding" task and a free recall task. Subjects learned lists consisting of high and low imagery nouns. The assessments, done at baseline and hourly for 4 hours after drug ingestion, also included two psychomotor tests and subjective ratings by subjects. Both benzodiazepines produced marked memory impairment. Contrary to the prevailing view that benzodiazepines primarily impair long-term memory acquisition rather than retrieval, results from Buschke's task indicated impairment of retrieval as well. This finding may be related to the procedures and assumptions of Buschke's task. The benzodiazepine-induced impairments increased over the course of successive trials on the same list. Both drugs decreased the normal superiority in recall of high imagery words relative to low imagery words, impaired psychomotor performance, and increased subjective sedation. Alprazolam and lorazepam produced equally intense impairments. Alprazolam tended to produce earlier impairment and earlier recovery.

Benzodiazepines Alprazolam Lorazepam Memory Acquisition Retrieval Imagery Psychomotor performance

THE present study examined effects of two benzodiazepines, lorazepam (ATIVAN) and alprazolam (XANAX), on long-term memory acquisition and retrieval processes. Numerous studies have reported memory impairment from lorazepam (e.g., [3, 4, 14, 15, 25, 30]) and memory impairment from alprazolam is a possibility [2]. Diazepam has been used in most studies seeking more detailed information concerning the manner in which benzodiazepines impair memory. The prevailing view is that diazepam primarily impairs the acquisition of new information, rather than the retention or retrieval of information once it has been stored in long-term memory. Evidence for this view derives mainly from studies in which the subject is presented with a list of words and asked to immediately recall as many of the words as he can. A number of lists are presented in this way, some before drug administration, some afterward. At a later time following drug administration, delayed recall and/or recognition tests are given for all the lists. Studies using this or similar techniques [3, 4, 9, 10, 12, 18, 19, 20, 22] have shown that diazepam impairs memory for lists learned after drug administration, but does not impair recall or recognition for lists learned before drug administration. If diazepam impaired retrieval processes, it should impair memory for information learned before drug administration. The absence of such a deficit implies that diazepam affects acquisition rather than retrieval.

One study comparing memory for information learned before vs. after drug administration reported similar results with lorazepam [3,4]. However, for information presented after drug administration, delayed memory tests tended to show greater drug effects than initial memory tests [3]. This result, and other analogous but less convincing findings with diazepam [17] and lorazepam [25], suggest that benzodiazepine effects on post-acquisition memory processes merit further investigation.

Studies reporting effects on acquisition rather than retrieval have made the distinction by comparing performance on information learned before vs. after drug administration. Other factors (e.g., different retention intervals and differences in retroactive interference for lists learned predrug vs. postdrug, variability in test times relative to drug administration, possible state-dependent effects) complicate the interpretation of the drug effects. Buschke [5,7] has described a task simultaneously assessing acquisition and retrieval effects, which has recently become popular in psychopharmacology research. We used Buschke's "selective reminding"

[1]Requests for reprints should be addressed to Robert I. Block, Ph.D., Outpatient Department, Lafayette Clinic, 951 E. Lafayette, Detroit, MI 48207.

task to examine benzodiazepine effects on long-term memory acquisition and retrieval.

In this task, the subject hears a list of words and tries to recall as many as he can. Then he is presented with only the words he omitted, and again tries to recall the whole list of words. This procedure continues for a number of trials on the same list, with the subject trying to recall the whole list each time, although he is "reminded" each time only of the words he omitted on the immediately preceding trial.

Buschke's [5,7] scoring procedures provide measures of long-term storage, long-term and short-term retrieval, and consistent long-term retrieval. In essence, a word is assumed to enter long-term storage (acquisition) if it is recalled on two trials in a row. (The subject was not reminded of the word before the second trial of such a pair of trials, having recalled it on the first trial; therefore, he presumably stored that word in long-term memory on the first trial.) Once a word enters long-term storage, it is assumed to remain there on all subsequent trials. Every recall of a word is attributed to either short-term or long-term retrieval. Once a word enters long-term storage, its recall is always attributed to long-term retrieval; before this point, its recall is attributed to short-term retrieval. Long-term retrieval of a word is designated "consistent" starting on the trial after which it is never subsequently omitted. Consistent long-term retrieval is said to measure the extent to which words have been organized in memory in a manner which allows them to be reliably recalled. As an illustration, suppose a list of words is tested for 10 trials in a row, and a particular word, say "queen," is recalled on trials 1, 3, 5, 6, 8, 9, and 10. "Queen" would be counted as entering long-term storage on trial 5 and remaining there on trials 5 through 10 inclusive. Recall of "queen" would count as short-term retrieval on trials 1 and 3, long-term retrieval on trials 5, 6, 8, 9, and 10, and consistent long-term retrieval on trials 8, 9, and 10.

Using Buschke's technique, we presented lists for 10 succeeding trials, providing an opportunity to see if drug effects changed as learning progressed over successive trials. Memory impairments from diazepam reportedly tend to increase over successive trials [10,22]. Another factor, the image-evoking potential of the words, was also varied. For "high imagery words," people can easily bring to mind a visual image representing the word's meaning. This is harder for "low imagery words." Learning is better for high imagery words than for low imagery words in many tasks [27]. If benzodiazepines affect peoples' visual imagery ability, or their tendency to use "elaborative encoding" techniques such as imagery to facilitate learning, this might produce differential drug effects on the learning of high vs. low imagery words. Two studies with diazepam apparently did not find such differential effects [21,29].

Our subjects also rated subjective drug effects using visual analogue scales and participated in two short psychomotor tasks (critical flicker fusion and discriminant reaction time tasks) and a brief free recall task. These were included as part of an effort to develop a battery of brief tasks which are repeatable, reliable, and sensitive to psychotropic drug effects [1]. The free recall task was similar to the Buschke task except that the entire list of words was presented to the subject on each trial, and the task was only continued for two successive trials on the same list at each assessment. The purpose was to see if this brief task would be as sensitive as the longer Buschke task to benzodiazepine effects.

Subjects ingested lorazepam 2 mg and alprazolam 1 mg in separate sessions. Alprazolam (a triazolo-benzodiazepine) and lorazepam (a 3-hydroxy benzodiazepine) belong to different categories of benzodiazepines frequently used in clinical practice. Both drugs are well absorbed, lipid soluble, highly protein bound, and have similar rates of elimination. However, alprazolam may produce milder sedative effects than diazepam [11] or other benzodiazepines with doses equivalent in anxiolytic effects. The doses of alprazolam and lorazepam used in this experiment were intended to be equivalent in anxiolytic effects (based on their relationship in potency to diazepam), to see if alprazolam affected memory and psychomotor performance less than lorazepam.

METHOD

Subjects

Subjects were 9 paid young adult males (mean age 30.1, range 25–44), in good physical and mental health and not taking any psychotropic medications.

Tasks

The test battery consisted of five tasks, administered in the following order:

1. Visual analogue sedation ratings. Using a scale (a 100 mm line) labeled "ALERT" at one end and "DROWSY" at the other, subjects rated the current strength of their feeling of alertness or drowsiness by placing a mark at an appropriate point along the line. The position of this mark was measured. Ratings were recorded for TENSE/RELAXED and MENTALLY SLOW/QUICK-WITTED continua in the same way.

2. Free recall. The subject heard a recording of a list of 16 words read at a rate of 3 seconds per word. He immediately tried to orally recall as many of the words as possible during a 90 second period, with the experimenter recording his responses. The same list of words was then played again (in a different random order), and he again tried to recall as many words as he could in 90 seconds.

3. Critical flicker fusion. Critical flicker fusion threshold was measured using a two-alternative forced-choice double staircase method similar to one described previously [1]. On each of a series of trials, the subject viewed two light-emitting diodes through artificial pupils and decided which diode was flickering, pressing one of two switches to indicate his decision. The task took about 5 minutes to complete and was controlled by an IBM 1800 computer, which increased or decreased the frequency of the flickering light on successive trials depending on the correctness of the subject's responses.

4. Discriminant reaction time. Subjects viewed a small screen on which a series of single digits was flashed. They pressed a button as fast as possible each time the digit *4* was flashed. The flashing of the digits was controlled by the IBM 1800 computer, and became faster or slower depending on the correctness and speed of the subject's responses, following a procedure described previously [1]. Digits were presented for 50 seconds. The mean time between successive digits during this period provided a threshold-type measure of the subject's sustained response speed.

5. Buschke task. The experimenter read a list of 16 words. The subject immediately tried to recall as many of the words as he could and indicated when he could not recall any more. Then the experimenter read only those words from the list that the subject had omitted. The subject again tried to

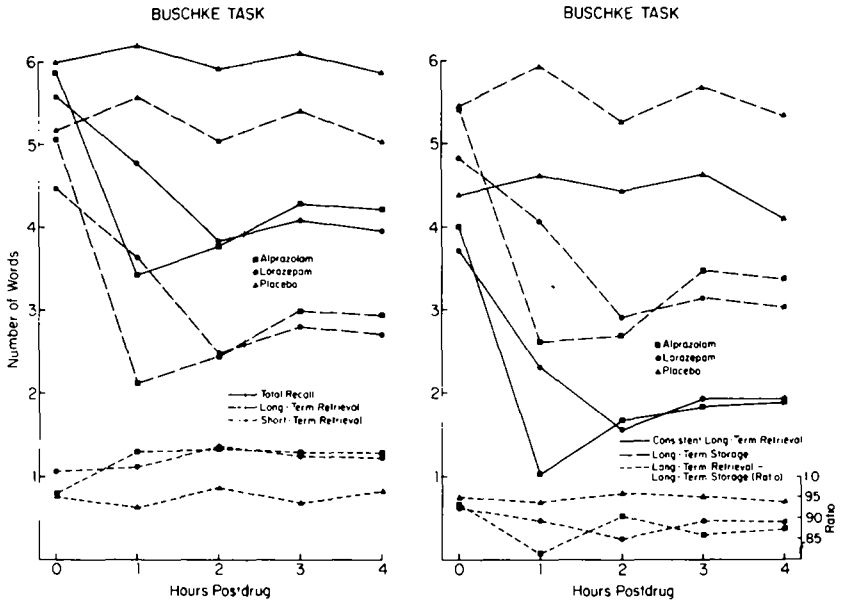

FIG. 1. Buschke task measures by drug and test time. For all measures except the ratio of long-term retrieval to long-term storage, values are expressed as the number of words out of the 8 words presented for each list and imagery condition (high imagery vs. low imagery words). Thus, a value of 4 in total recall represents 4/8=50% recall, etc. For the ratio of long-term retrieval to long-term storage, values are indicated by the scale in the lower right corner. This ratio could range between 0 and 1.

recall the entire list of words. This procedure continued for 10 trials on the same list. The subject tried to recall the whole list each time. The experimenter reminded the subject each time only of the words the subject had omitted on the immediately preceding trial. The experimenter read the words at a rate of 3 seconds per word. As the subject responded orally, the experimenter recorded his responses.

Word Lists

Thirty lists, each consisting of 8 high imagery nouns and 8 low imagery nouns, were constructed. No word occurred in more than one list. The 30 sets of high imagery words were balanced on normative imagery ratings [28], normative free recall [8], and word frequency [24], as were the 30 sets of low imagery words. The high and low imagery words were balanced on word frequency.

Procedure

Under double-blind conditions, each subject received doses of alprazolam 1 mg, lorazepam 2 mg, and placebo in three different sessions, separated by at least 3 days. Drugs were given orally in capsules identical in appearance. Drugs were counterbalanced over test sessions by assigning subjects to three different orders of drug administration, using a Latin Square design.

Each session began between 8:00 and 8:45 a.m. to avoid diurnal variations in performance. Subjects were told to get at least 6 hours sleep on the night before the session, to eat a light breakfast, and to abstain from caffeine and nicotine on the morning of the session and during the testing itself.

Following a baseline administration of the test battery, subjects ingested the medication. The test battery was then repeated beginning 1, 2, 3, and 4 hours post drug ingestion, taking about 30 minutes to complete at each administration.

Each subject received 30 memory tests (15 free recall and 15 Buschke tests) during his three sessions. The 30 word lists were randomly assigned to these 30 memory tests for each subject, with the constraint that, as nearly as possible, the different word lists occurred equally often in the free recall task and the Buschke task over all subjects combined.

RESULTS

Buschke Task

Buschke's [5] scoring procedures provided measures of total recall, long-term storage, long-term and short-term retrieval, and consistent long-term retrieval. For each of these, analyses of variance were done including the factors time (the predrug and four hourly postdrug tests), trial (the 10 successive trials given on each list at each test time), and imagery (high vs. low imagery words). In each case, the main analysis compared alprazolam, lorazepam, and placebo, and a subanalysis compared alprazolam and lorazepam directly (omitting placebo). Numerous significant effects occurred. The significant effects involving drug are listed in Table 1 and described here.

1. Drug effects. Figure 1 shows mean total recall, long-term storage, long-term and short-term retrieval, and consistent long-term retrieval for each drug and test time. Both benzodiazepines impaired recall relative to placebo, as indicated by significant differences among alprazolam, lorazepam, and placebo in total recall (drug effect) and in changes in total recall over time (drug × time effect). This impairment in total recall was accompanied by drug-induced decreases in long-term storage, long-term retrieval, and consistent long-term retrieval as well, and by a compensa-

TABLE 1
SIGNIFICANT DRUG EFFECTS IN BUSCHKE TASK ANALYSES*

Measure	Alprazolam vs. Lorazepam vs. Placebo		Alprazolam vs. Lorazepam	
	Effect	p†	Effect	p‡
Total Recall	Drug	0.001	Drug × Time	0.05
	Drug × Time	0.001	Drug × Trial	0.05
	Drug × Imagery	0.05	Drug × Time × Trial × Imagery	0.05
	Drug × Trial	0.001		
	Drug × Time × Trial × Imagery	0.05		
Long-Term Storage	Drug	0.001	Drug × Trial	0.001
	Drug × Time	0.001	Drug × Time × Trial × Imagery	0.01
	Drug × Trial	0.001		
	Drug × Trial × Imagery	0.001		
	Drug × Time × Trial × Imagery	0.05		
Long-Term Retrieval	Drug	0.001	Drug × Trial	0.001
	Drug × Time	0.001	Drug × Time × Trial × Imagery	0.05
	Drug × Trial	0.001		
	Drug × Trial × Imagery	0.001		
Short-Term Retrieval	Drug	0.01	—	
	Drug × Trial	0.05		
	Drug × Trial × Imagery	0.05		
Consistent Long-Term Retrieval	Drug	0.001	Drug × Trial	0.05
	Drug × Time	0.01		
	Drug × Imagery	0.01		
	Drug × Trial	0.001		
	Drug × Trial × Imagery	0.01		

*Significance levels are indicated for the significant drug effects in the Buschke task analyses of variance described in the text.

†Degrees of freedom are 2 and 16 for drug, 2 and 16 for drug × imagery, 8 and 64 for drug × time, 18 and 144 for drug × trial, 18 and 144 for drug × trial × imagery, and 72 and 576 for drug × time × trial × imagery.

‡Degrees of freedom are 4 and 32 for drug × time, 9 and 72 for drug × trial, and 36 and 288 for drug × time × trial × imagery.

tory increase in short-term retrieval, reflecting greater reliance on short-term memory processes (drug and drug × time effects). The benzodiazepine effects also varied over the course of the successive trials on each list and depended on word imagery.

2. Drug interactions over trials. At each test period, subjects received 10 trials on the same list. Total recall naturally increased from one trial to the next, as indicated in Fig. 2. However, as the figure shows, the impairment in total recall from the benzodiazepines, relative to placebo, also became greater over successive trials (drug × trial effect). This same pattern occurred not only for total recall, but for long-term storage and retrieval and consistent long-term retrieval. These also increased over successive trials, and the impairment from the benzodiazepines relative to placebo increased over trials. Short-term retrieval, in contrast, decreased over successive trials (since progressively more information was entered into long-term storage). However, this decrease in short-term retrieval over the successive trials given at each test time was smaller for the benzodiazepines than for placebo, consistent with greater reliance on short-term memory under the active drug conditions.

3. Drug interactions with imagery. As expected, recall was better for high imagery words than for low imagery words, as Fig. 2 shows. This superiority of high imagery words over low imagery words also occurred for long-term storage and retrieval and for consistent long-term retrieval. For each of these, the size of the imagery effect can be calculated as the mean for high imagery words minus the mean for low imagery words. For total recall, the size of the imagery effect varied depending on which drug the subjects received. Both benzodiazepines decreased the size of the imagery effect in comparison to placebo (drug × imagery effect). Each drug also decreased the size of the imagery effect in consistent long-term retrieval.

The size of the imagery effects, in addition to being influenced by the drugs, varied over the course of the 10 trials on each list. This interaction (drug × trial × imagery effect) was significant for long-term storage and retrieval (see Fig. 2) and for consistent long-term retrieval. For placebo, the size of the imagery effects generally decreased over successive trials. With lorazepam, in contrast, the size of the imagery effects generally increased over successive trials. With alprazolam, the size of the imagery effects showed little

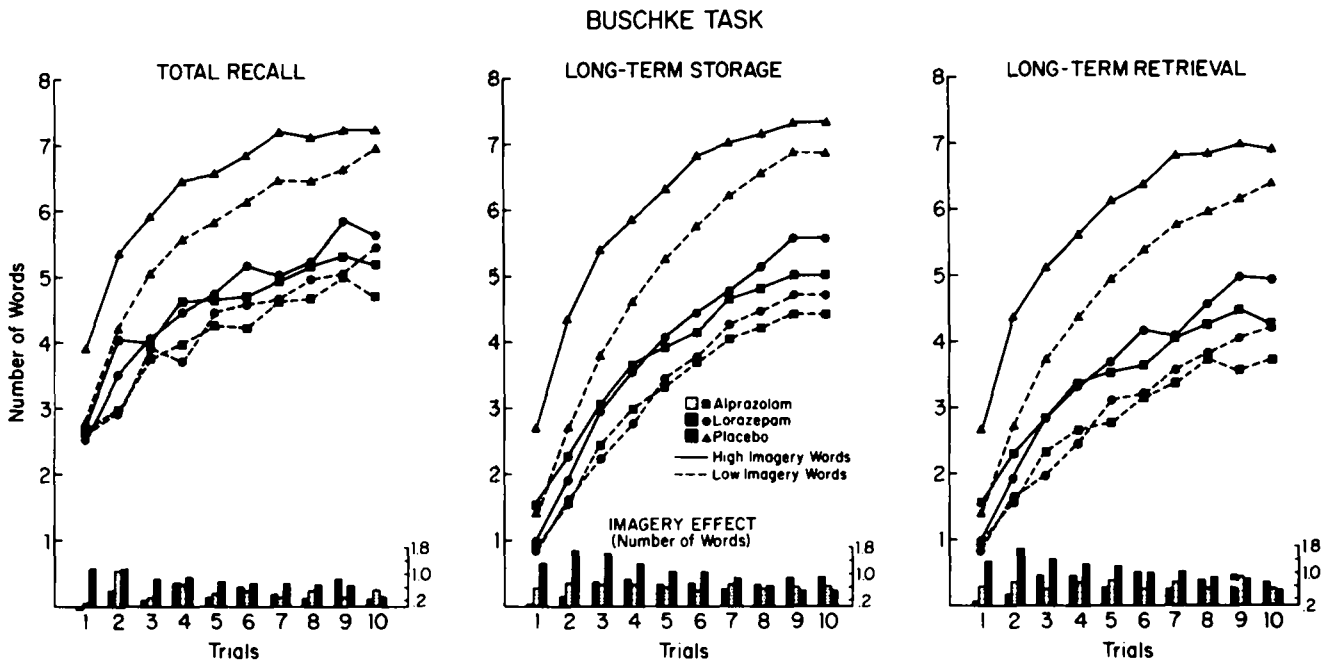

FIG. 2. Buschke task measures by drug, word imagery, and trial. For all measures, values are expressed as in Fig. 1. Values are shown separately for high imagery and low imagery words, and for each of the 10 successive trials given on the same list at each test time. The histograms at the bottom show the size of the imagery effect, defined as the mean for high imagery words minus the mean for low imagery words. These values, also expressed as the number of words, are indicated by the scales at lower right, and are shown separately for each trial. All values shown are means averaged over the baseline and 4 hourly postdrug tests.

change over successive trials. This interaction was also significant for short-term retrieval, but the data for short-term retrieval were less systematic in this respect and not easily interpretable.

4. Ratio measures of retrieval. Buschke's retrieval measures correlate strongly with his measure of long-term storage. To help determine if the benzodiazepines affected retrieval processes per se, we also analyzed the ratio of long-term retrieval to long-term storage, and the ratio of consistent long-term retrieval to long-term storage. The former ratio is shown in Fig. 1. Both benzodiazepines, in comparison to placebo, significantly decreased both of these ratio measures of retrieval, implying that they affected retrieval processes as well as storage. (For the long-term retrieval ratio, $F(2,16)=11.18$, $p<0.001$ for drug and $F(8,64)=3.95$, $p<0.001$ for drug × time; for the consistent long-term retrieval ratio, $F(2,16)=27.52$, $p<0.001$ for drug and $F(8,64)=2.60$, $p<0.05$ for drug × time.)

5. Differences between alprazolam and lorazepam. The subanalysis contrasting alprazolam and lorazepam directly (excluding placebo) indicated that the two drugs differed significantly in the time course of their effects on total recall (see Fig. 1). Compared to lorazepam, alprazolam produced a faster onset of impairment, but subjects also showed earlier recovery (drug × time effect).

Alprazolam and lorazepam also differed in the way they affected total recall over the 10 successive trials given at each test time (drug × trial effect) (see Fig. 2). On early trials, lorazepam produced slightly more impairment than alprazolam. But the improvements in recall over successive trials were slightly greater for lorazepam than alprazolam. This pattern occurred not only for total recall, but for long-term storage and retrieval (see Fig. 2) and for consistent long-term retrieval.

Free Recall

Total recall in the free recall task was submitted to analyses of variance similar to those done on the Buschke task data, including the factors time, trial, and imagery. Subjects received 2 free recall trials on each list, rather than the 10 trials given in the Buschke task. The main analysis compared alprazolam, lorazepam, and placebo. Subanalyses compared the different pairs of drug conditions.

1. Drug effects. Figure 3 shows mean total recall for each drug and test time. Both benzodiazepines impaired memory relative to placebo, as indicated by significant differences among alprazolam, lorazepam, and placebo in recall, $F(2,16)=30.60$, $p<0.001$, and in changes in recall over time, $F(8,64)=3.92$, $p<0.001$ for drug × time. Drug effects also depended on word imagery and varied over the course of the successive trials given on each list at each test time, though these effects were not as consistent as with the Buschke task.

2. Drug interactions over trials. Recall naturally increased from the first to the second trial given on each list, as shown in Fig. 4. However, the impairment in recall with the benzodiazepines, relative to placebo, also tended to increase from the first to the second trial given on each list (drug × trial effect). This interaction was marginally significant in the main analysis, $F(2,16)=3.45$, $p=0.06$, and was significant in comparing alprazolam directly against placebo, $F(1,8)=9.09$, $p<0.05$.

3. Drug interactions with imagery. Recall was better for

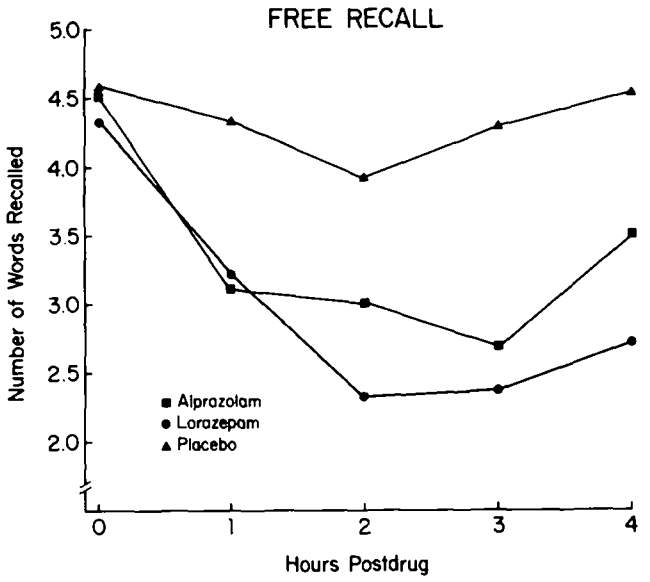

FIG. 3. Free recall by drug and test time. The number of words recalled out of the 8 words presented for each list and imagery condition (high imagery vs. low imagery words) is shown.

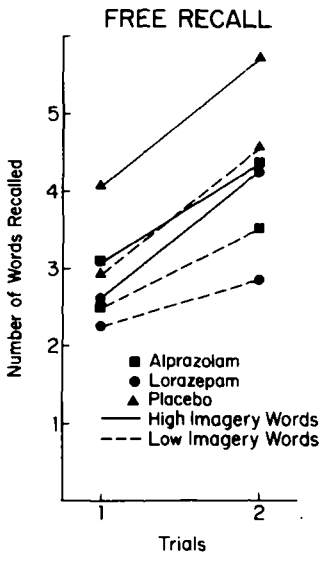

FIG. 4. Free recall by drug, word imagery, and trial. The number of words recalled is shown separately for high imagery and low imagery words, and for each of the 2 successive trials given on the same list at each test time. All values shown are means averaged over the baseline and 4 hourly postdrug tests, and are expressed as in Fig. 3.

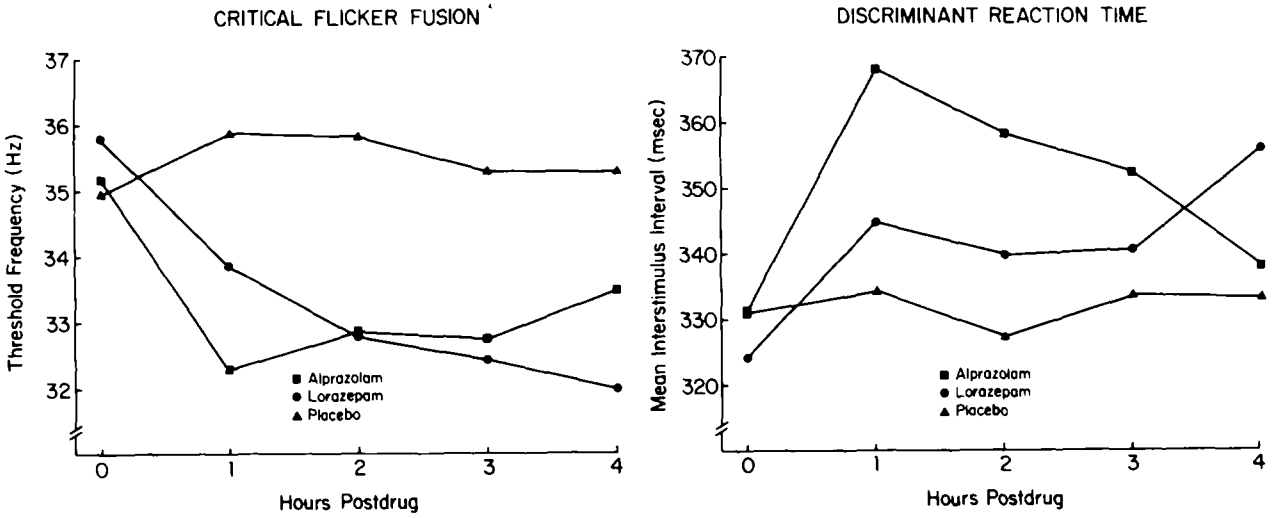

FIG. 5. Psychomotor task performance by drug and test time. Left: critical flicker fusion threshold (Hz). Right: discriminant reaction time (msec). The values for discriminant reaction time represent the mean time between successive digits during the 50 second period of digit presentation. Higher times indicate slower performance.

high imagery words than for low imagery words (see Fig. 4). Both benzodiazepines tended to reduce the size of the imagery effect, as in the Buschke task, but this change was not significant ($p>0.10$). The reduction in the size of the imagery effect was notable for alprazolam during its period of peak effects, at 2–3 hours postdrug. This contributed to a drug × time × imagery interaction ($F(8,64)=1.80$, $p=0.09$ in main analysis; $F(4,32)=2.70$, $p<0.05$ in comparing alprazolam vs. placebo).

The influence of the drugs on the size of the imagery effect also varied over the course of the 2 trials on each list. For lorazepam, the size of the imagery effect increased sharply from the first to the second trial. This contrasted with a slight increase for alprazolam and a slight decrease for placebo (for drug × trial × imagery, $F(2,16)=3.05$, $p=0.08$ in the main analysis; $F(1,8)=6.09$, $p<0.05$ in comparing lorazepam vs. placebo).

4. Differences between alprazolam and lorazepam. Although alprazolam seemed to produce slightly less memory impairment than lorazepam, with subjects showing earlier

recovery, the subanalysis comparing recall under alprazolam and lorazepam directly (excluding placebo) showed no significant differences between the drugs.

5. Serial position. Additional analyses were done including the serial positions of words in the word lists as a factor; i.e., recall was evaluated for words in the 1st vs. 2nd vs. . . . 16th positions of the 16-word lists. As is usually the case, recall was best for words in the last few positions of the lists, presumably because these words were more likely than others to remain available in short-term memory. Lorazepam altered the serial position effect occurring under placebo, $F(15,120)=1.88$, $p<0.05$. The impairment produced by lorazepam was fairly constant over all serial positions except toward the end of the list, where it was markedly smaller, suggesting greater reliance on short-term memory under lorazepam.

Psychomotor Tests and Subjective Ratings

Analyses of variance were done on critical flicker fusion and discriminant reaction time performance at the various test times, and on subjective ratings made with the visual analogue scales. The main analysis compared alprazolam, lorazepam, and placebo. A subanalysis compared alprazolam and lorazepam directly (omitting placebo). Figure 5 shows performance on the psychomotor tasks.

The benzodiazepines slowed response speed, as indicated by significant differences among alprazolam, lorazepam, and placebo in discriminant reaction time performance, $F(2,16)=4.47$, $p<0.05$, and in changes in this measure over time, $F(8,64)=2.55$, $p<0.05$. Alprazolam, lorazepam, and placebo also differed in the change of critical flicker fusion thresholds over time, $F(8,64)=2.77$, $p<0.05$, with both benzodiazepines producing impairments. Subjects rated themselves as drowsier, more relaxed, and mentally slower under the benzodiazepines relative to placebo, $F(2,16)=17.23$, 4.72, and 13.65, respectively; p's<0.05. The change in MENTALLY SLOW ratings over time also differed among the drug conditions, $F(8,64)=4.67$, $p<0.001$.

The subanalyses contrasting alprazolam and lorazepam directly (excluding placebo) showed no significant differences between them, except on ratings of drowsiness and mental slowness, $F(1,8)=8.13$ and 5.76, respectively; p's<0.05, where differences already present at baseline precluded an interpretation in terms of differential drug effects. On the discriminant reaction time task, there was a marginally significant tendency for alprazolam to have stronger initial effects, with subjects showing more rapid recovery than with lorazepam, $F(4,32)=2.31$, $p=0.08$. On the critical flicker fusion task, there was a nonsignificant trend in the same direction ($p>0.10$).

DISCUSSION

Buschke Task

The most important finding was the benzodiazepine-induced impairment of retrieval measures in the Buschke task. In contrast, prior studies comparing recall of information learned before vs. after drug administration (the "predrug/postdrug technique") have suggested that benzodiazepines primarily impair acquisition rather than retrieval. A very similar discrepancy between conclusions based on the predrug/postdrug technique (e.g., [13]) and on Buschke's methods [26] has occurred in research on a very different drug, marijuana. What accounts for the discrepancy between our results indicating benzodiazepine-induced retrieval impairments and the results of past benzodiazepine studies employing the predrug/postdrug technique? Several possible explanations may be considered.

1. Most previous studies used diazepam. Perhaps lorazepam and alprazolam differ from diazepam in their effects on memory. However, one study using the predrug/postdrug technique obtained similar results with lorazepam and diazepam [3,4]. In addition, the effects of lorazepam and alprazolam in our study showed more similarities than differences.

2. Buschke's technique, which assesses acquisition and retrieval processes simultaneously, may be a more sensitive method for distinguishing drug effects on acquisition vs. retrieval than the predrug/postdrug technique, which requires impaired memory for predrug learning as evidence for drug effects on retrieval.

3. The logic of the predrug/postdrug technique may be flawed. For example, in some studies, drug effects on retrieval might be hidden by differences between drug conditions in retroactive interference. Subsequent learning can interfere with memory for information learned previously. Thus, postdrug learning may interfere with memory for predrug learning. If benzodiazepines impair acquisition and therefore reduce postdrug learning, they might consequently reduce retroactive interference with memory for predrug learning. This paradoxically "beneficial" benzodiazepine effect on memory for predrug learning might then "hide" a negative benzodiazepine effect on memory for predrug learning arising from impaired retrieval processes. This argument helps explain some details of observed results [3,4].

4. The logic of Buschke's technique, or its subsequent interpretation by others, may be flawed. Buschke's retrieval measures are closely related to his measure of long-term storage. A drug which reduced long-term storage would almost inevitably reduce his retrieval measures. To infer that the drug impairs retrieval is unreasonable unless one can show (as we did above) that the drug reduces the ratio of long-term retrieval or consistent long-term retrieval to long-term storage. Another consideration is that Buschke's technique seems to demand relatively high motivation and earnest effort by the subject. Unenthusiastic subjects sometimes seem to favor short-term retrieval of the words they have just heard. Nonspecific drug effects (sedation, confusion, decreased motivation or attention) might influence patterns of performance on the various storage and retrieval measures. In one previous study [16], lorazepam-induced memory impairment was associated with non-specific sedative drug effects but not with changes in motivation.

5. The concepts of "retrieval" implicit in the predrug/postdrug technique and in Buschke's technique may differ. The predrug/postdrug technique views retrieval as an "event" occurring solely while the subject is trying to remember the words. Buschke's retrieval measures are apparently not intended to assess retrieval processes in this strict sense, but to reflect as well the nature of the information stored in memory [6]. Recall of a word without an immediately preceding presentation, Buschke's criterion for long-term storage, indicates storage of some minimal representation of the word in long-term memory. But further enhancement of this representation occurs subsequently. Consistent long-term retrieval is intended to measure the extent to which words have been organized for regular, reliable recall. This may involve storage in memory of an organized, integrated, elaborated semantic structure interrelating

the list words. A drug-induced deficit in forming and storing such elaborated semantic structures, while fundamentally a deficit in acquisition, would reduce consistent long-term retrieval, as would a drug effect truly localized in the "act" of retrieval itself.

This might explain the discrepancy between our results and the lack of benzodiazepine-induced deficits in recall of information learned predrug. Drug and placebo subjects naturally store equally elaborated representations for information learned predrug. If the drug interferes with forming and storing integrated, elaborated representations—not the "act" of retrieval itself—it would reduce Buschke's retrieval measures but not memory for predrug learning, as observed.

While our results do not rule out any of these explanations, the last one seems especially compatible with the changes we found in drug effects over successive trials and the differences in drug effects for high vs. low imagery words.

The benzodiazepine-induced impairment in total recall and in the long-term storage and retrieval measures increased over the 10 successive trials on each list. This slowed learning agrees with previous findings [10,22] and is consistent with (though not proof of) a benzodiazepine-induced deficit in forming and storing organized, elaborated semantic representations.

Now consider the imagery effects. Learning is improved by elaborative encoding of words using visual images; i.e., by forming images expressing interrelations among the words [27]. The superior performance with high imagery words compared to low imagery words is apparently related to the richer representations available for high imagery words. The benzodiazepines decreased the size of this imagery effect in total recall and in consistent long-term retrieval. More impoverished—hence more uniform—representations for high and low imagery words in drugged subjects might explain this. Thus the decreased imagery effects could reflect a benzodiazepine-induced deficit in forming and storing elaborated representations.

With placebo, the imagery effects in the long-term storage and retrieval measures were initially large and generally decreased over successive trials on the list. Under placebo, one might suggest, the richer representations available for high imagery words produced substantial imagery effects on early trials; but as performance improved markedly on later trials, reflecting the development of elaborated representations for low as well as high imagery words, the size of the imagery effects decreased. With lorazepam, in contrast, the poor performance on early trials was accompanied by minimal imagery effects. But on later trials, as performance gradually improved to a level attained much earlier under placebo, the size of the imagery effects showed a corresponding increase. Alprazolam fell between lorazepam and placebo in this respect. The size of the imagery effects changed little over successive trials. There is no obvious explanation for this difference between alprazolam and lorazepam. But it corresponds to another difference between alprazolam and lorazepam, the tendency for lorazepam to produce slightly poorer performance on early trials but slightly greater improvements over successive trials.

Alprazolam vs. Lorazepam

Apart from the differences just discussed, alprazolam and lorazepam effects differed little, except in the time course of the drug effects. Compared to lorazepam, alprazolam produced a faster onset of impairment, but subjects also showed earlier recovery. This difference was significant for Buschke task total recall. Similar but nonsignificant trends occurred in the other three tasks. The rate of onset of activity after a single oral benzodiazepine dose depends mainly on the rate of absorption. The faster onset of impairment with alprazolam is consistent with pharmacologic data indicating a more rapid attainment of peak serum levels with alprazolam than lorazepam. Our findings with lorazepam are comparable to prior reports of longer-lasting memory impairment with lorazepam than diazepam [3, 4, 14].

Does alprazolam produce less performance impairment than other benzodiazepines with doses equivalent in anxiolytic effects? With respect to this clinically important question, our findings are negative. The overall impairments from alprazolam and lorazepam did not differ significantly in any task.

Free Recall and Psychomotor Tasks

The critical flicker fusion and discriminant reaction time tasks proved highly sensitive to alprazolam and lorazepam effects, confirming their utility as part of a battery of brief tests which are repeatable, reliable, and sensitive to psychotropic drug effects [1]. The free recall task also showed marked impairments from both benzodiazepines, and its brevity makes it suitable for inclusion in this test battery.

The free recall task was as sensitive as the Buschke task in detecting overall impairment, but the variation in drug effects over successive trials and their relationship to word imagery emerged more clearly in the lengthier Buschke task. Standard free recall procedures obviously preclude analyses of Buschke's storage and retrieval measures. However, serial position effects in the free recall task showed some consistency with Buschke's short-term retrieval measure. The relative resistance of words toward the end of the list to lorazepam-induced impairment, which was otherwise fairly constant over all serial positions, suggested a sparing of short-term memory under lorazepam. Changes in Buschke's short-term retrieval measure suggested greater reliance on short-term memory under both lorazepam and alprazolam. Others have reported changes in serial position effects consistent with greater reliance on short-term memory under the influence of benzodiazepines [22,23].

CONCLUSION

The discrepancy between our findings of benzodiazepine-induced retrieval impairments using Buschke's task, and the absence of such retrieval impairments implied by past studies using the predrug/postdrug technique, requires clarification. Of the possible explanations for this discrepancy discussed above, the one we favored—that Buschke's retrieval measures may not measure "retrieval" in a strict sense—seems to undercut the novelty of our findings. But determining the locus of drug effects on memory is important—not only for theoretical reasons, but to allow clinicians to anticipate and manage adverse side effects on memory when prescribing these drugs—and Buschke's technique has become increasingly popular for this purpose. Critical examination of methods used for studying drug effects on human memory seems overdue. Clarification of the discrepancy between results with Buschke's task and the predrug/postdrug technique might emerge from a more direct comparison of the two techniques in conjunction with variations in orienting tasks or instructions (e.g., imagery instruc-

tions) that provide some experimental control over the subject's acquisition processes and the nature of the representations stored in memory.

ACKNOWLEDGEMENTS

The authors express their appreciation to Mrs. Debra Sheppard for her assistance.

REFERENCES

1. Berchou, R. and R. I. Block. Use of computerized psychomotor testing in determining CNS effects of drugs. *Percept Mot Skills* **57**: 691–700, 1983.
2. Boyd, E. L., R. B. Knapp and W. H. Hess. The cardiopulmonary effects of alprazolam—A new benzodiazepine derivative. *W Va Med J* **74**: 270, 1978.
3. Brown, J., V. Lewis, M. Brown, G. Horn and J. B. Bowes. A comparison between transient amnesias induced by two drugs (diazepam or lorazepam) and amnesia of organic origin. *Neuropsychologia* **20**: 55–70, 1982.
4. Brown, J., V. Lewis, M. W. Brown, G. Horn and J. B. Bowes. Amnesic effects of intravenous diazepam and lorazepam. *Experientia* **34**: 501–502, 1978.
5. Buschke, H. Selective reminding for analysis of memory and learning. *J Verb Learn Verb Behav* **12**: 543–550, 1973.
6. Buschke, H. Retrieval in human learning. *Trans NY Acad Sci* **36**: 721–729, 1974.
7. Buschke, H. and P. A. Fuld. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology (NY)* **24**: 1019–1025, 1974.
8. Christian, J., W. Bickley, M. Tarka and K. Clayton. Measures of free recall of 900 English nouns: Correlations with imagery, concreteness, meaningfulness, and frequency. *Memory & Cognition* **6**: 379–390, 1978.
9. Clark, E. O., M. Glanzer and H. Turndorf. The pattern of memory loss resulting from intravenously administered diazepam. *Arch Neurol* **36**: 296–300, 1979.
10. Clark, P. R. F., P. S. Eccersley, J. P. Frisby and J. A. Thornton. The amnesic effect of diazepam (Valium). *Br J Anaesth* **42**: 690–697, 1970.
11. Cohn, J. B. Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* **42**: 347–351, 1981.
12. Cooper, S. A., J. E. Anthony, E. Mopsik, M. S. Moore, D. C. Sullivan and G. O. Kruger. A technique for investigating the intensity and duration of human psychomotor impairment after intravenous diazepam. *Oral Surg* **45**: 493–502, 1978.
13. Darley, C. F., J. R. Tinklenberg, W. T. Roth, L. E. Hollister and R. C. Atkinson. Influence of marihuana on storage and retrieval processes in memory. *Memory & Cognition* **1**: 196–200, 1973.
14. Dundee, J. W. and K. H. George. The amnesic action of diazepam, flunitrazepam and lorazepam in man. *Acta Anaesthiol Belg* **27**: 3–11, 1976.
15. File, S. E., A. J. Bond and R. G. Lister. Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* **2**: 102–106, 1982.
16. File, S. E. and R. G. Lister. Do lorazepam-induced deficits in learning result from impaired rehearsal, reduced motivation or increased sedation? *Br J Clin Pharmacol* **14**: 545–550, 1982.
17. Frumin, M. J., U. R. Herekar and M. E. Jarvik. Amnesic actions of diazepam and scopolamine in man. *Anesthesiology* **45**: 406–412, 1976.
18. Ghoneim, M. M. and S. P. Mewaldt. Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. *Psychopharmacologia* **44**: 257–262, 1975.
19. Ghoneim, M. M. and S. P. Mewaldt. Studies on human memory: The interactions of diazepam, scopolamine, and physostigmine. *Psychopharmacology (Berlin)* **52**: 1–6, 1977.
20. Ghoneim, M. M., S. P. Mewaldt, J. L. Berie and J. V. Hinrichs. Memory and performance effects of single and 3-week administration of diazepam. *Psychopharmacology (Berlin)* **73**: 147–151, 1981.
21. Hartley, L. Diazepam: Human learning of different materials. *Prog Neuro-Psychopharmacol* **4**: 193–197, 1980.
22. Hinrichs, J. V., S. P. Mewaldt, M. M. Ghoneim and J. L. Berie. Diazepam and learning: Assessment of acquisition deficits. *Pharmacol Biochem Behav* **17**: 165–170, 1982.
23. Jones, D. M., M. E. L. Jones, M. J. Lewis and T. L. B. Spriggs. Drugs and human memory: Effects of low doses of nitrazepam and hyoscine on retention. *Br J Clin Pharmacol* **7**: 479–483, 1979.
24. Kučera, N. and W. N. Francis. *Computational Analysis of Present-day American English*. Providence, RI: Brown University Press, 1967.
25. Lister, R. G. and S. E. File. Performance impairment and increased anxiety resulting from the combination of alcohol and lorazepam. *J Clin Psychopharmacol* **3**: 66–71, 1983.
26. Miller, L., T. Cornett and D. Mcfarland. Marijuana: An analysis of storage and retrieval deficits in memory with the technique of restricted reminding. *Pharmacol Biochem Behav* **8**: 327–332, 1978.
27. Paivio, A. *Imagery and Verbal Processes*. New York: Holt, Rinehart, and Winston, 1971.
28. Paivio, A., J. C. Yuille and S. A. Madigan. Concreteness, imagery, and meaningfulness values for 925 nouns. *J Exp Psychol* **76**: 1–25, 1968.
29. Peterson, R. C. and M. M. Ghoneim. Diazepam and human memory. Influence on acquisition, retrieval, and state-dependent learning. *Prog Neuro-Psychopharmacol* **4**: 81–89, 1980.
30. Roth, T., K. M. Hartse, P. G. Saab, P. M. Piccione and M. Kramer. The effects of flurazepam, lorazepam, and triazolam on sleep and memory. *Psychopharmacology (Berlin)* **70**: 231–237, 1980.