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SCIENTIFIC REPORT

The Efficacy and Memory Effects of Oral Triazolam Premedication in Highly Anxious Dental Patients

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Triazolam (0.375 or 0.50 mg) or placebo was administered orally to 31 highly anxious dental patients in a double-blind clinical trial 1 hr before treatment. The drug was safe and highly effective, in comparison to placebo, in reducing both anxious cognitions and disruptive movement during oral injections of local anesthetic and drilling. Episodic memory and implicit memory were both adversely affected by the active drug but not the placebo.

Severe anxiety and avoidance of dental care are well-demonstrated deterrents to oral health.[1] While it is unlikely that pharmacological agents alone will eliminate this problem, oral benzodiazepines have been shown to reduce the stress of dental treatment for many patients. Moreover, the cost and potential risk of intravenous agents make the search for effective short-acting oral agents of increased importance. Triazolam has a rapid uptake, minimal effects on respiration and the myocardium, and a short terminal half-life.[2] It has been suggested as a useful oral sedative in dentistry.[3] A recent report indicated that premedication of oral surgery patients with 0.25 mg of triazolam the morning of surgery attenuated anxiety in comparison to a placebo.[4] However, the differences appear small and are difficult to interpret because of the scales chosen to measure anxiety in the dental setting. A similar report examined the use of triazolam before placement of an intravenous line in a dental practice.[5] In neither case were the subjects demonstrated to have high levels of dental fear. In another report, this time with more anxious patients, oral triazolam with nitrous oxide appeared therapeutically similar to intravenous diazepam.[6]

Side effects associated with triazolam include ataxia and impairment in performance on mental tests and on the acquisition and recall of information.[7] The amnestic effects of triazolam and other benzodiazepines are sometimes seen as desirable when treatment is aversive. On the other hand, interference with the acquisition of coping skills or failure to retain postoperative instructions might be undesirable. Recent work with alprazolam suggests that benzodiazepines may affect the efficacy of exposure therapies for dental anxiety, perhaps differentially for high fear patients.[8] Previous tests of the amnestic effects of triazolam have been in nondental settings. These tests have used recall of pictures,[9] the Logical Memory test of the Wechsler memory scale,[10] and word recall.[7,11,12] When a dose of 0.25 mg was used, a word list was recalled well 3 hr later, but recall was significantly worse at 24 hr.[7] A 0.5-mg dose affected memory 1 and 8 hr later.[9,10]

The type of memory assessed by the direct tasks described above has been called episodic,[13] explicit,[14] or declarative memory.[15] Another type of task, which does not make explicit reference to any particular experience but which is nevertheless influenced by such experience, is used to assess memory classified as implicit[14] or procedural.[15] One example of a test for implicit memory is a word-completion test in which subjects are presented three-letter word stems and are instructed to complete them with the "first word that comes to mind." When subjects are required to complete stems with recently presented words or with words not presented, they more frequently complete the stems with words they have recently seen.[16,17] Although another benzodiazepine, diazepam, has been shown to impair episodic but not implicit

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memory,[18] tests of triazolam to date have not attempted to dissociate these types of memory.

The purpose of this randomized clinical trial was to examine the sedative effects of a single oral premedication dose of triazolam in a population of highly anxious dental patients undergoing restorative dentistry involving intraoral local anesthetic injections and drilling. In addition, we examined the effects of triazolam on episodic and implicit memory.

METHODS

Subjects

Thirty-one subjects were recruited through public service announcements in the Seattle community. Subjects were included if they were at least 18 yr of age and in need of at least one dental restoration. Subjects had to be healthy (ASAPS Class I or II). Exclusion criteria included allergy to benzodiazepines, pregnancy or lactation, history of psychiatric illness, chronic use of central nervous system (CNS) depressants or antidepressants, alcoholism, acute-angle glaucoma, excessive weight, or the use of medications that might interact with benzodiazepines. This study was approved by the institutional review board of the University of Washington, and the written informed consent of all subjects was obtained before enrollment in this study.

Subjects were eight males and 23 females with a mean age of 39 yr (range, 21 to 58 yr) and a mean weight of 75.7 kg (SD = 18.4 kg). Subjects completed the Dental Fear Survey (DFS)[19] before treatment. The mean DFS score of 78.6 (SD = 13.9) indicated a high level of fear of dentists.[20] Subjects also completed the Medical Outcome Study (MOS) short form health history questionnaire[21] assessing six aspects of general health. Mean scores (±SD) were physical health, 92.5 (±14.8); role functioning, 96.7 (±9.2); social functioning, 93.3 (±19.4); mental functioning (mood), 70.0 (±4.5); overall health perception, 58.1 (±8.9); and bodily pain in the last 4 wk, 43.3 (±22.3). Few, if any, of the subjects in this study had significant health limitations. There were no differences in either DFS scores or MOS scores between treatment groups.

Subjects were questioned preoperatively regarding their preferences for a drug to help them feel more comfortable during dental treatment. Sixty-eight percent indicated a strong preference for a drug, the remainder preferring a drug over treatment without a drug to increase their comfort. Fifty-seven percent preferred a drug "that would totally put me to sleep." The remainder preferred a drug that "would make me not care what was going on" (33%), or a drug that "helped me relax but definitely did not 'take over' " (10%). One subject did not respond to this question.

Medications

Subjects were randomly assigned to one of two groups where one group (n = 15) received triazolam (Halcion) based on body weight and the other a lactose placebo (n = 16), both in pharmacy-coded capsules. Dosing with triazolam was based on body weight as follows: ≤81 kg, 0.375 mg; >81 kg, 0.5 mg. The purpose of using two dosages was to narrow the mg/kg dose used in the study. The medication dose ranged from 0.0046 to 0.0071 mg/kg for the active drug group. The medication was administered under supervision 1 hr before the start of the dental procedure. No other sedative medications were used during the study.

Measures

Safety. Throughout the visit, the physiological status of the subject was monitored. Oxygen saturation (Ohmeda Biox 3740, Englewood, CO), heart rate, and intermittent blood pressure were assessed.

Efficacy. Anxiety was assessed along two dimensions. A cognitive self-report of anxiety[22] was obtained preoperatively and just before the injection of local anesthetic. The scale, which is like a thermometer, runs from 0 to 42, where 42 indicates terrified. The subject indicates his/her level of anxiety by pointing at the word that best describes how he/she feels right now. The behavioral aspect of anxiety was rated by the dental assistant on a 1 to 4 scale where 4 indicates movement that prevents proceeding with the procedure. After the procedure, drug preferences were again obtained.

Memory. Items used to test episodic memory effects were of two kinds: simple line drawings and word pairs. The drawings of common objects, such as a shoe or chair, were presented singly at each of three presentation times. In the first test of episodic memory, subjects were presented with an array of 12 pictures, which included nine pictures not previously shown, and were asked to mark the drawings seen previously. Word pairs were formed of words of intermediate frequency (70 to 220 of 50,400 sampled American English words)[23] to produce pairs of moderate association (eg, tradition–club). Thirty-six word pairs were presented, both aurally and visually, as three sets of 12 at each of three presentation times. A second test of episodic memory for all 36 pairs was conducted by giving subjects the first word of each pair, in mixed order, and assessing recognition of the second word of the pair among four other words.

A test of implicit memory was also administered between the test of picture and word-pair recognition. Subjects were asked to complete three-letter word stems (eg,

tra _____) with the "first word that comes to mind." These word stems could be completed with the first words of the word pairs presented previously or with at least six other common words. About one-half of the subjects (n = 15) were given one set of word pairs, and the remaining 16 subjects were given a different set, the first words of which began with the same three initial letters (eg, train–student). Word stems completed with words from the nonpresented list were used to establish a baseline response rate.

Procedures

Procedures are summarized in Figure 1. Each subject was seated in the dental operatory and given the study medication. Monitors were placed, and the subject was observed. At 60 min, the dental procedure commenced. Subjects were able to stop the procedure at any time with the understanding that the procedure could be rescheduled using the unblinded drug. The dental procedures lasted from 20 to 80 min.

The to-be-remembered items were presented to subjects at each of three different times during the appointment. The first was in the waiting room just before the subject received the study medication. The second presentation was about 50 min later, just before the dentist entered the operatory to begin treatment. The third presentation was at the completion of the dental work, 80 to 140 min after the first presentation. The memory tests were given at two times: 10 to 20 min after time 3 above, and 24 hr later. The test of picture recognition was administered first, then word-stem completion, followed by word-pair recognition. At the end of the appointment, each subject was given a stamped envelope containing materials for self-administration of the memory tests 24 hr later.

RESULTS

Safety

No subject experienced any drop in oxygen saturation below 91% and only 6 of 31 subjects had saturations below 95% at 1 hr. Three subjects with drops in saturation below 95% were in the active drug group; two were in the placebo group. The only side effects reported in the active drug group were sleepiness (3) and a slight headache (1). No side effects were reported in the placebo condition.

Efficacy

Table 1 gives the results of the self-reported anxiety just before injection of local anesthetic for the drug and placebo groups. A rank sum test yielded a significant difference in anxiety between the two conditions, with the drug group self-reporting less anxiety (Mann-Whitney U test = 170.0, $P = 0.04$). A multivariable analysis was also done using logistic regression where the dependent measure was the self-reported anxiety (dichotomized at score <42 vs 42) and the drug group was entered as a dummy variable (drug, placebo) controlling for the preoperative, predrug self-report. The results confirm the relationship

Figure 1. Timeline of memory test procedures.

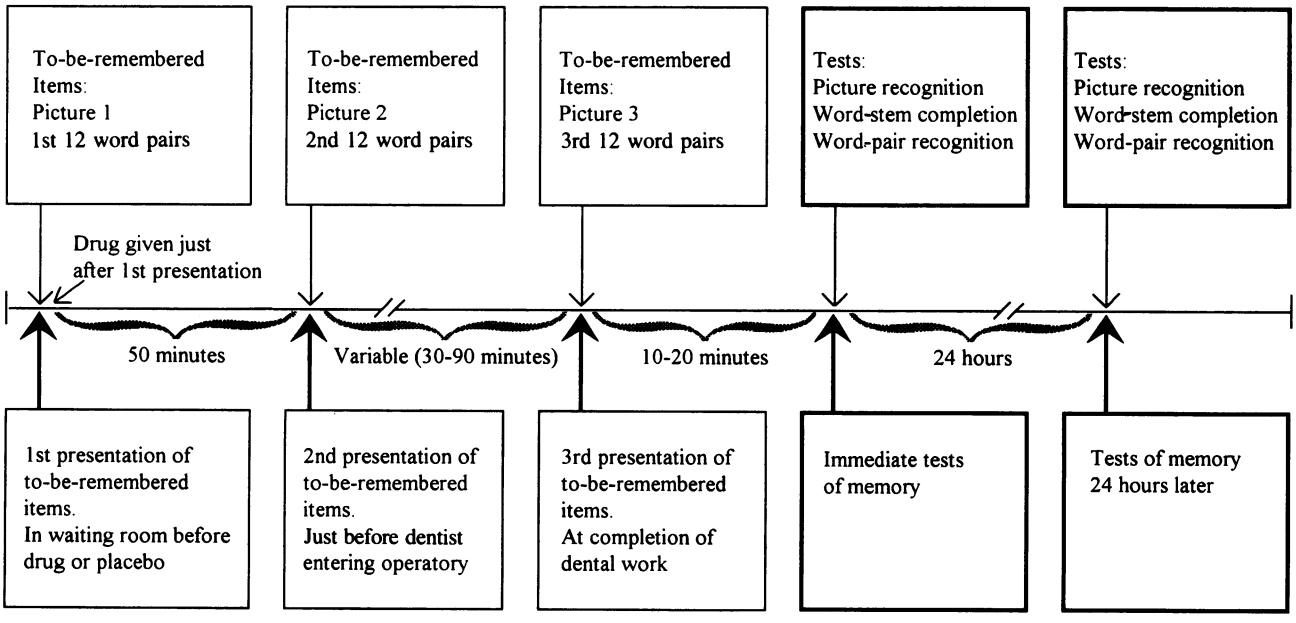


Table 1. Frequency of Self-Reported Anxiety at Injection

	Self-Report Score[a]					
Group	*2*	*8*	*13*	*18*	*26*	*42*
Placebo	2	2	1	0	2	9
Drug[b]	3	2	6	1	1	2

n = 31.
[a] Score range 0 to 42 where 0 = calm, relaxed and 42 = terrified.
[b] Significantly lower than placebo group ($P = 0.04$, Mann-Whitney U test).

between drug and outcome. Other analyses controlling for the DFS score had a similar outcome.

Table 2 gives the outcome of the behavioral analysis. Subjects in the placebo group were more likely to show disruptive movement or stop the procedure than subjects in the active drug condition ($\chi^2 = 7.98$, $P = 0.02$). A logistic regression analysis where the dependent measure was the behavioral measure (dichotomized score <4 vs 4) and the drug group was entered as a dummy variable, controlling for preoperative self-reported anxiety, confirmed the contingency table analysis result. Similarly, analyses controlling for the DFS score did not change the result.

When questioned after the procedure, subject, assistant, and dentist all were able to detect which was the active drug. The results of the analysis for patients are provided in Table 3. The posttreatment preferences for having a drug to feel more comfortable during dental treatment are shown in Table 4. Paired comparisons between preferences before and after treatment showed no change in the subjects' preferences for drug (McNemar symmetry $\chi^2 = 1.0$, $P = 0.32$).

Memory

Episodic Memory for Pictures. Recognition of the first picture shown was perfect for both drug and placebo groups (Figure 2), indicating that this memory was unaffected when the drug was not present at the time of presentation but present at the time of testing. That is, when the drug was not in the bloodstream at the time the picture was learned, there was no effect on later recognition, even when the drug was present during recall. In contrast to the placebo group, where recognition was perfect, only 72% of the drug group recognized the pictures presented at time 2, and only 58% of the group recognized the pictures presented at time 3 (Fisher's exact test, $P < 0.05$). Twenty-four hours later, despite near-perfect recognition of the first picture presented, 64% of subjects given the active drug did not recognize the pictures presented at time 2, and 36% did not recognize the pictures presented at time 3 (Fisher's exact test, $P < 0.05$). That is, when the drug was "active" at the time the picture was learned, it was recognized less often in the drug than in the placebo group, regardless of whether the drug was active at the time of testing.

Table 2. *Frequency of Assistant-Rated Behavior at Injection*

	Behavior[a]			
Group	*1*	*2*	*3*	*4*
Placebo	2	3	0	9
Drug[b]	5	8	0	2

n = 29 (in two cases the assistant failed to rate behavior).
[a] Behavior rating 1 to 4, where 1 = no movement and 4 = patient's movement or behavior prevents dental treatment.
[b] Significantly improved compared to placebo ($P = 0.02$, χ^2 analysis).

Table 3. Subject Surmise of Drug Administered

	Subject Surmise	
Group	*Placebo*	*Drug*
Placebo	11	3
Drug[a]	3	11

n = 28 (three subjects did not complete the evaluation).
[a] Significantly better than chance ($P = 0.007$, Fisher's exact test).

Episodic Memory for Word Pairs. For word-pair recognition (Figure 3) recognition was significantly impaired in the drug condition when the drug was present at the time of presentation compared to the placebo group. In other words, having the drug present at the time of learning the word pairs significantly decreased the subject's ability to recognize the second word of the pair when given the first word, both when the drug was present at the time of the immediate test and when it was not (24 hr later). The difference seen in the control group time 1 versus time 3 performance 24 hr later may indicate an upper limit in the number of word pairs that can be recognized in the long term (paired t-test, $P < 0.05$). But, in all cases, the decrement in performance of the drug group was greater.

Table 4. Posttreatment Drug Preference

Preference	*n*	*(%)*
Strong preference for drug	21	75
Prefer drug	7	25
Prefer no drug	0	—
Strong preference for no drug	0	—

n = 28 (three subjects did not complete the evaluation).

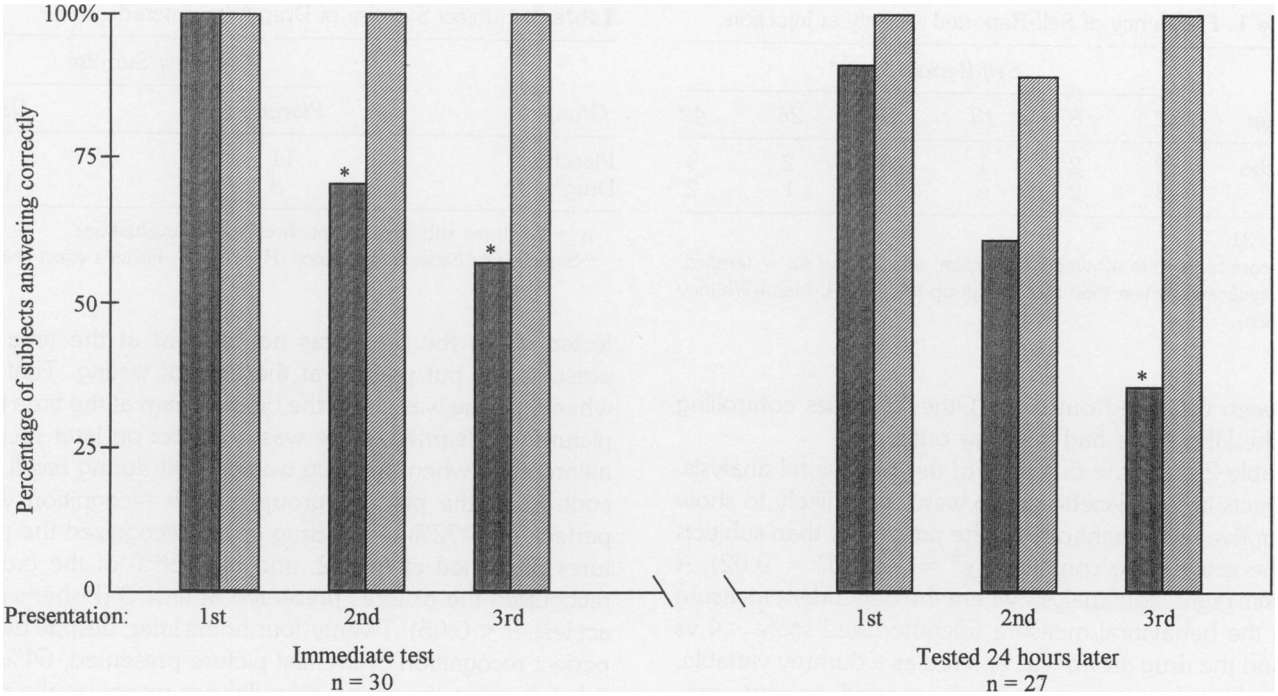
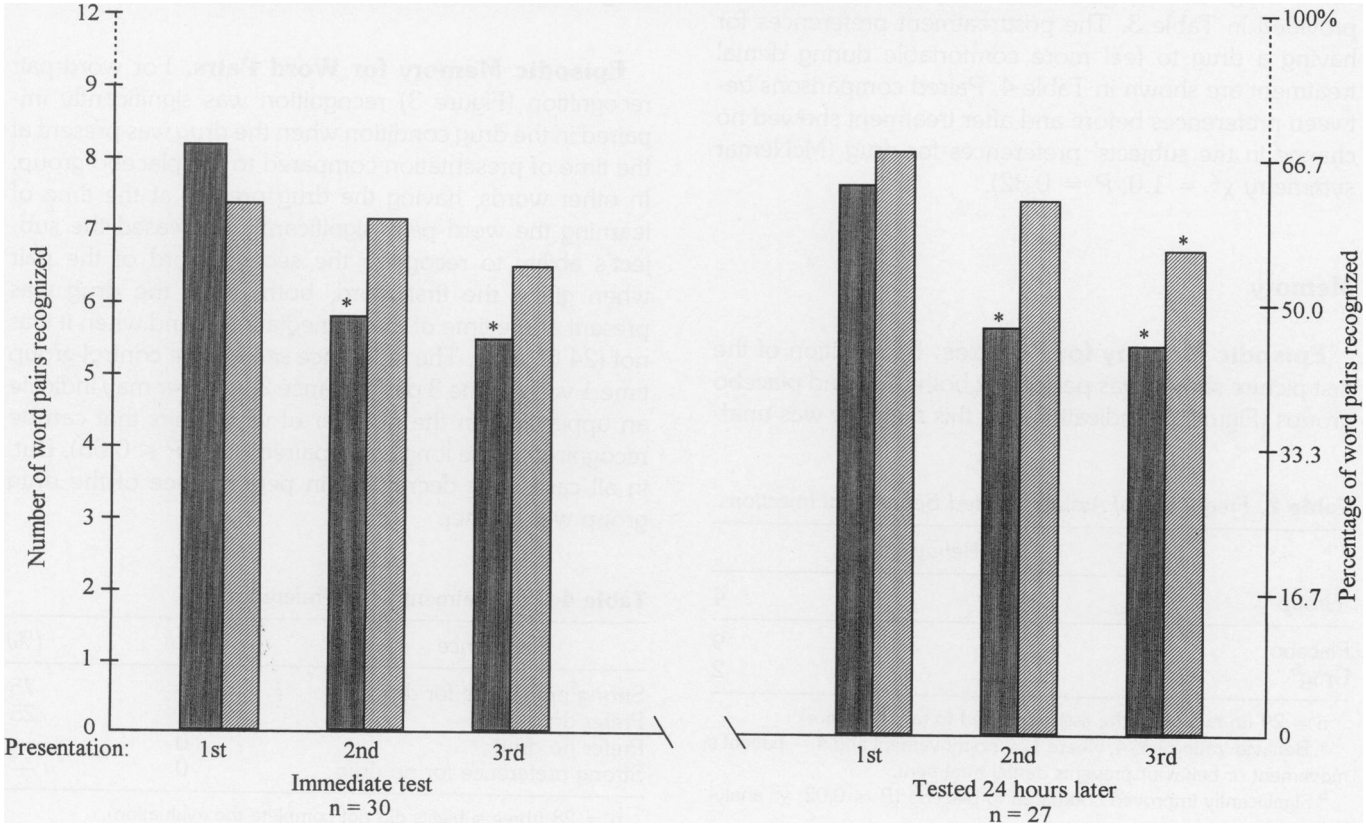


Figure 2. Effect of triazolam on picture recognition. Dark columns = triazolam; light columns = placebo. Significant differences between groups ($P < 0.05$, Fisher's exact test) are indicated by asterisks (*).

Figure 3. Effect of triazolam on word-pair recognition. Dark columns = triazolam; light columns = placebo. Significant differences between first presentation and later presentations (paired samples, $P < 0.05$) are indicated by asterisks (*).



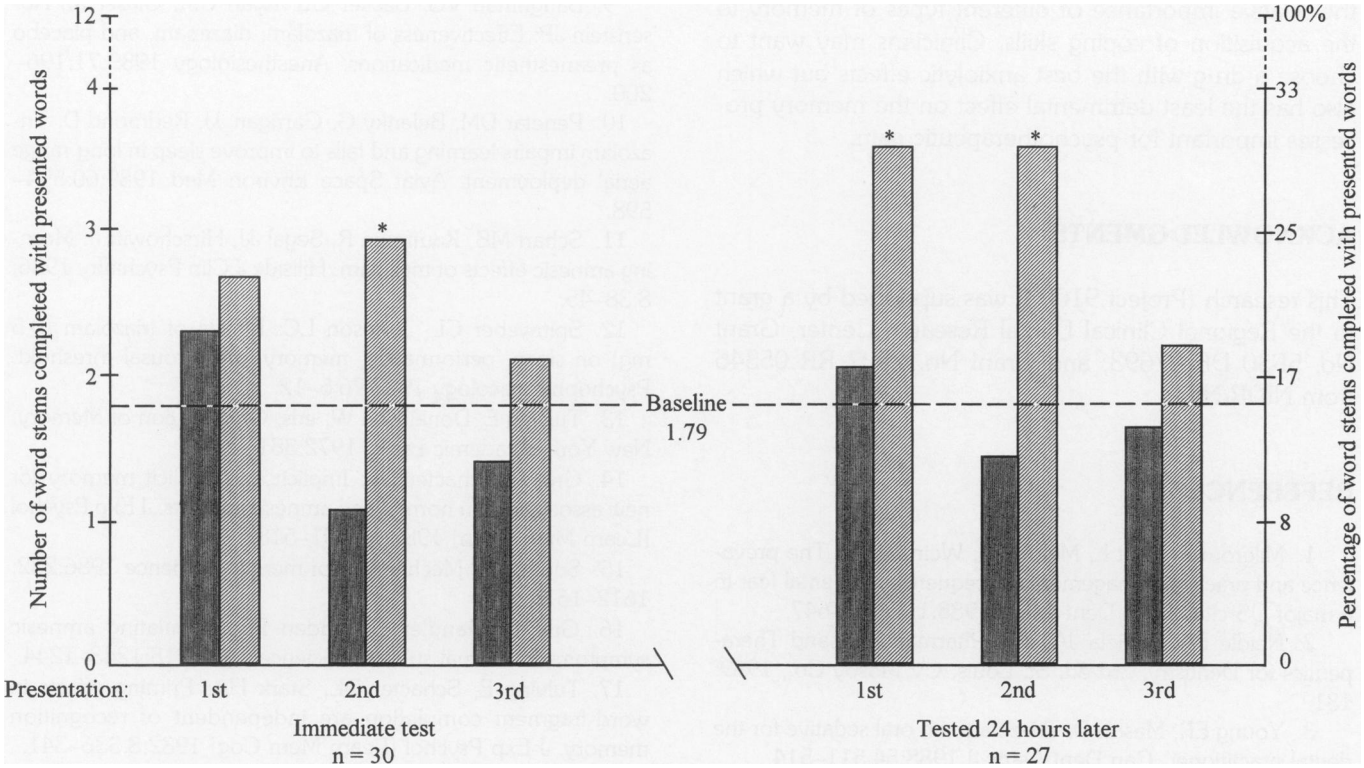


Figure 4. Effect of triazolam on word-stem completion. Dark columns = triazolam; light columns = placebo. Scores significantly different than baseline ($P < 0.05$) are indicated by asterisks (*).

Implicit Memory Tested with Word-Stem Completion. Completion of word stems with presented words (Figure 4) was above baseline in the placebo drug group for all the words that had been shown previously, significantly so for the time 2 immediate test and times 1 and 2 test 24 hr later, but in the group receiving triazolam, performance was above baseline for words shown at time 1 only ($P < 0.05$). That is, triazolam adversely affects the word-stem completion with words that are presented when the drug is active, and this appears true whether or not the drug was present at the time of the test.

DISCUSSION

We conducted a randomized, placebo-controlled clinical trial investigating the safety and efficacy of triazolam as an oral premedication in highly anxious dental patients about to receive oral injections and drilling. The results of pulse oximetry confirm that triazolam given in modest dosages has little if any respiratory depressant effect. Oxygen saturations were all within normal limits. In addition, the drug appears efficacious in relation to a placebo in controlling self-reported anxiety and disruptive movement. This remained true when preoperative anxiety levels were controlled in the statistical procedures. Following drug treatment, subjects had either very strong or strong preferences for treatment employing the drug. Side effects were clinically insignificant.

This study also demonstrated significant effects of triazolam on episodic memory as measured by both picture and word-pair recognition. Implicit memory, as measured by word-stem completion, was also affected when the drug was present at the time the words were shown. However, this apparent drug effect on implicit memory should be interpreted with caution since, when word-stem completion tasks are given in the context of two tests of episodic memory, subjects may (contrary to instructions) attempt to actively recall previously presented words with which to complete the stems. The persistence of implicit memory 24 hr later in the placebo group also suggests that episodic learning may have affected these results.

These results suggest that triazolam may be useful in reducing recall of discomfort during dental procedures in outpatient settings. However, if the therapeutic goal includes teaching patients new ways of responding to anxiety-provoking situations (eg, coping), then pharmacologically induced memory deficits may not be advantageous. The current data indicate that episodic memory is impaired by triazolam. The memory impairment may also include implicit memory. Future work should determine

the relative importance of different types of memory to the acquisition of coping skills. Clinicians may want to choose a drug with the best anxiolytic effects but which also has the least detrimental effect on the memory processes important for psychotherapeutic gain.

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