# **CME** ACTIVITY

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#### **CME** Objectives

- After completing this CME activity, physicians practicing clinical psychiatry should be able to:
- Describe the potential cognitive effects of benzodiazepines in patients admitted to the hospital after a suicide attempt with benzodiazepines.
- Develop a strategy for an initial psychiatric interview in a patient who has attempted suicide with benzodiazepines.

#### Statement of Need and Purpose

Benzodiazepines, which are still used extensively, are now recognized as major drugs of abuse and addiction. Physicians responding to questionnaires in the *Journal* and its related CME activities have requested updated information on the risks and benefits of benzodiazepines. This CME activity was created to address that need. There are no prerequisites for participation in this CME activity.

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#### Date of Original Release/Review

This article was published in June 2000 and is eligible for CME credit through November 30, 2000. The latest review of this material was May 2000.

#### **Faculty Disclosure**

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None of the authors of this article has significant commercial relationships to disclose relative to the presentation.

#### **Discussion of Investigational Information**

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### Memory Impairment in Those Who Attempted Suicide by Benzodiazepine Overdose

Bas Verwey, M.D.; Paul Eling, Ph.D.; Henk Wientjes, M.Sc.; and Frans G. Zitman, M.D., Ph.D. I thas been demonstrated in man diazepines can induce memory in Coding is anterograde amnes presented af

**Background:** A prospective study was conducted to investigate the presence of anterograde amnesia in those who attempted suicide by benzodiazepine overdose and to study the correlation with sedation.

*Method:* In 43 patients who attempted suicide by taking benzodiazepines, memory was tested with a 15-word memory recall task. The immediate and delayed recall on the first day after admission (day 1) and 24 hours later (day 2) were rated. Each patient and the interviewer scored the patient's degree of sedation on a visual analogue scale. Patients also had to try to recognize, from photographs, the psychiatrist with whom they had spoken the day before.

**Results:** The ratings of immediate and delayed recall were significantly lower on day 1 than on day 2. Subjective ratings of sedation of the patients were not significantly higher than the ratings of the observer. Less than half of the patients recognized the psychiatrists and knew that they were the ones they had spoken to the day before.

*Conclusion:* Anterograde amnesia is present in suicide attempters who take over-doses of benzodiazepines. The implications of this finding for the assessment of suicide attempters during admission are discussed.

(J Clin Psychiatry 2000;61:456–459)

t has been demonstrated in many studies that benzodiazepines can induce memory impairment.<sup>1,2</sup> A common finding is anterograde amnesia, the phenomenon whereby information presented after benzodiazepines have been taken is poorly remembered.<sup>3,4</sup> Severity and duration of the amnesia are dependent on the particular benzodiazepine used, the dosage, the route of administration, the time (postdrug) at which information is presented and retrieval is required, and characteristics of the subject population tested.<sup>5-7</sup> The memory task used is also of importance. For instance, recall tasks are more sensitive than recognition tasks, and verbal tasks are more sensitive than visual tasks.<sup>2</sup> In longitudinal studies, it was found that only partial tolerance to the amnesic effects develops; in verbal recall tests, tolerance to the effects of benzodiazepines was found on immediate but not delayed (15-20 minutes) recall in normal volunteers<sup>8</sup> as well as in patients with generalized anxiety disorder.9 Impaired delayed recall was also found in chronic benzodiazepine users after acute administration of the medication.<sup>10</sup>

Anesthetists welcome the amnesic effects since they cause patients to forget unpleasant operative procedures. However, in other situations, these effects are a reason for concern. In the large group of people who are taking benzodiazepines on a daily basis, anterograde amnesia may interfere with the ability to function optimally, and in patients taking benzodiazepines who are also being treated with psychotherapy, anterograde amnesia may impair remembrance of what happened during a therapy session.<sup>11</sup>

In a case report,<sup>12</sup> it has been suggested that anterograde amnesia also interferes with the efficacy of psychiatric consultation in patients admitted to the hospital after a suicide attempt with benzodiazepines. Since benzodiazepines are involved in almost half of the suicide attempts,<sup>13</sup> we decided to further explore possible memory impairment following a benzodiazepine overdose. We examined systematically whether anterograde amnesia occurs in a group of patients consecutively admitted to the hospital because of a suicide attempt involving benzodiazepines. We inves-

Received March 1, 1999; accepted Jan 16, 2000. From Ziekenhuis Rijnstate, Arnhem (Dr. Verwey); and the Departments of Psychology (Dr. Eling) and Psychiatry (Dr. Wientjes and Professor Zitman), University of Nijmegen, Nijmegen, the Netherlands.

Reprint requests to: Bas Verwey, M.D., Ziekenhuis Rijnstate, Postbus 9555, 6800 TA Arnhem, the Netherlands.

### **CME: ARTICLE**

tigated verbal recall with the 15-word test, because such a test has been applied frequently in the evaluation of benzodiazepine-induced anterograde amnesia. This test is thought to be highly sensitive to the presence of anterograde amnesia induced by benzodiazepines.<sup>14</sup> Scores on a highly standardized verbal recall test do not necessarily reflect clinically significant memory impairment. Therefore, we added a visual recognition task with a more immediately obvious relevance to clinical practice: a photo recognition test to investigate whether patients were able to recognize the face of the psychiatric resident who examined them. In clinical practice, it is often assumed that the degree of anterograde amnesia can be predicted from the degree of sedation as estimated by the psychiatrist. However, the results of laboratory studies are equivocal.<sup>5</sup> Therefore, in this study we also assessed the degree of sedation as estimated by the patient and the psychiatric resident who examined the patient and related these estimations to the degree of memory impairment.

#### **METHOD**

#### **Material and Procedure**

son site interesting the son of t From September 1, 1994, until November 25, 1996, all patients admitted to the Rijnstate general hospital (Arnhem, the Netherlands) because of attempted suicide by taking an overdose of benzodiazepines were prospectively studied. The medical ethics committee of the hospital approved the study.

#### Subjects

All patients with benzodiazepines in their blood were included. Additional use of other drugs and nondrug methods in the suicide attempt were not exclusion criteria, but all patients that had alcohol in their blood were excluded.

Also, patients meeting the following criteria were excluded: age younger than 18 years (because the tests used were not developed for younger people), a diagnosis of dementia or amnestic disorder before admission (cognitive dysfunction may interfere with the drug effects), alcohol dependence or abuse (cognitive dysfunction and impaired liver function may interfere with the drug effects), delirium according to DSM-IV criteria, and/or inability to read or understand test instructions and items on the verbal recall test.

#### Assessments

1. The "15-woorden" test (15-word test) is the Dutch equivalent of the Rey Auditory Verbal Learning test, a verbal recall test often used in research on

anterograde amnesia caused by benzodiazepines.<sup>15</sup> We adapted the procedure slightly by administering the list of words only once on day 1 and once on day 2. On both days, the research assistant instructed the patient in the use of a computerized version of the test. The patient was asked to remember words that were presented successively on the computer screen for a period of 2 seconds each. Immediately after the presentation of 15 unrelated words, the patient was asked to recall as many words as possible (immediate recall). After 15 minutes the patient was asked again to recall as many words as possible (delayed recall). The test was administered on days 1 and 2. To prevent learning, patients were presented different but equivalent lists on these days.

- 2. A photograph recognition test was used as a visual recognition test. The patient was presented with a series of 6 photographs of faces with a variety in the features such as hair, spectacles, and so on, 1 of which showed the resident in psychiatry who examined the patient. This procedure is used in formal police investigations in the Netherlands. The patient had to answer 3 questions: (1) Do you recognize anyone? (2) Who do you recognize? (3) How do you know this person? This test was administered on day 2 only. Patients who were known to the resident, possibly because of earlier suicide attempts, were excluded from this test.
- 3. Degree of sedation was rated on a 10-cm visual analogue scale (VAS). On day 1, the patient as well as the resident in psychiatry filled in this scale. A low score indicates a high level of sedation.
- 4. Blood alcohol concentration was measured with gas liquid chromatography.
- 5. Presence of benzodiazepines in blood was ascertained by the immunochemical method TDxFLx (Abbott Laboratories, Abbott Park, Ill.)

#### Procedure

At Rijnstate hospital, all patients admitted because of a suicide attempt are seen by a psychiatric resident for a routine clinical interview at least 12 hours after admittance, provided the patient is sufficiently alert for psychiatric consultation. For this study, at the end of the interview, the psychiatric resident informed patients who had used benzodiazepines in the suicide attempt about the study and asked them to participate. When informed consent was obtained, a research assistant (an experienced consultation-liaison nurse) immediately started assess-

Recall	Day 1		Day 2		p Value
	Mean	SD	Mean	SD	(t test)
Immediate	4.91	1.76	6.00	1.93	.002
Delayed	3.02	1.82	4.26	1.77	.000

ments (day 1). Twenty-four hours later, the research assistant again performed assessments (as day 2).

#### Statistical Analysis

Data were analyzed using the paired t test; the level of significance was  $p \le .05$ . Relationships between memory variables and subjective sedation ratings were assessed using Pearson correlation coefficients.

#### RESULTS

Forty-seven patients were eligible for the study. Three refused to cooperate, and 1 had to be excluded because of insufficient cooperation. In this article, data on the remaining 43 patients (9 men and 34 women; mean  $\pm$  SD age = 39.1  $\pm$  12.4 years) are presented. The following benzodiazepines had been used: oxazepam (N = 16), temazepam (N = 11), diazepam (N = 10), clorazepate (N = 4), alprazolam (N = 6), flurazepam (N = 4), lormetazepam (N = 3), lorazepam (N = 1), clobazam (N = 1), flunitrazepam (N = 2), and zopiclone (N = 1). Eleven patients had used more than one benzodiazepine. Six patients had also used an antidepressant agent. Three others had taken a neuroleptic; 1 of them had used 3 neuroleptics.

#### Verbal Recall With the 15-Word Test

Immediate recall on day 1 was significantly lower than on day 2. Delayed recall was also significantly lower on day 1 than on day 2. The results are presented in Table 1.

#### Visual Recall With the Photograph Recognition Test

Less than half of the patients recognized the psychiatric resident from the photograph and knew that he was the one they spoke with the day before (the recognizers) (Table 2). Scores of the recognizers on the verbal recall test were not significantly different from the scores of the nonrecognizers. Likewise, the subjective ratings of sedation of the recognizers were not significantly different from the ratings of the nonrecognizers.

#### Sedation

On day 1, patients rated themselves as more sedated than the residents rated them, but the difference was not

Table 2. Results of Interviewer Recognition From Photograph (N = 35) <sup>a</sup>					
Question	Yes/Correct	No/Incorrect			
Do you recognize anybody?	22	13			
Who do you recognize?	20	2			
How do you know this person?	12	8			
<sup>a</sup> Some patients had previously re	ceived treatment	from the resident			

psychiatrist and therefore did not participate in the photograph recognition test.

significant (mean  $\pm$  SD VAS score = 5.09  $\pm$  2.22 and 5.80  $\pm$  2.15, respectively; p = .142). A low correlation was found between subjective ratings of the patients and immediate or delayed recall on day 1 (Pearson r = 0.12, p = .463 and Pearson r = 0.08, p = .576, respectively). A higher correlation was found between ratings of the resident and immediate and delayed recall on day 1 (Pearson r = 0.5, p = .00 and Pearson r = 0.47, p = .00, respectively). When the 9 patients who had also used antidepressants or neuroleptics were excluded, the results did not differ from those of the whole group.

#### DISCUSSION

This study is the first to demonstrate memory impairment in patients who made a suicide attempt by taking benzodiazepines. First of all, in a verbal recall test, patients performed more poorly on the first day of admittance to the hospital than on the second day in immediate and delayed recall. These results are in agreement with the existing wide body of literature in which verbal recall test results demonstrate memory impairment after the intake of benzodiazepines in a laboratory setting.<sup>5</sup> Secondly, impairment was found in a photo recognition task. This result is surprising because a number of factors make memory loss in this task less probable. Patients were in contact much longer with the psychiatric resident than with the words of the verbal recall test, given that psychiatric examination of these patients takes 45 minutes on the average.<sup>16</sup> Moreover, a psychiatric interview immediately after a suicide attempt is often a very emotional experience for the patient, implying that the interview and the interviewer are more meaningful and thus more likely to be remembered than the words of the verbal recall test. In addition, in laboratory studies visual tasks are much less sensitive than verbal tasks, and recognition tasks are less sensitive than recall tasks.<sup>3</sup> The results of our study also show that anterograde amnesia is not necessarily accompanied by a lowering of consciousness.

Because 9 patients had used psychopharmacologic agents in addition to benzodiazepines, we also studied those who had only taken benzodiazepines. The results described above were also found in this subgroup of patients who made a suicide attempt with benzodiazepines only, and it makes it more probable that benzodiazepines are the main factor in the memory disturbances. The fact that the type of memory loss found here is typical for benzodiazepines also implies that the role of benzodiazepines is an important factor. However, these arguments do not exclude the possibility that the impairment of memory results from the turmoil caused by acute admittance to the hospital and the diagnostic and treatment procedures in the acute treatment ward. On the other hand, stress can also induce the amelioration of memory. Only a comparison between patients having made a suicide attempt with benzodiazepines and patients having made an attempt without benzodiazepines can provide a definite answer. At least in our hospital, such a control group is difficult to obtain because most suicide attempters use benzodiazepines, and patients who do not use them almost always leave the hospital within a few hours after arrival without having been seen by a psychiatrist.

Notwithstanding these shortcomings, the results support the hypothesis that the efficacy of psychiatric consultation in patients who made a suicide attempt with benzodiazepines can be compromised by memory impairment, even in patients who do not seem to be sedated. With many patients who have made a suicide attempt, arrangements for follow-up care and rules of life have to be negotiated. It is, of course, very important that the patients remember these arrangements later on. In accordance with case reports, our study lends support to the notion that patients who made a suicide attempt with benzodiazepines are likely to forget such arrangements. This is even true if the patient does not look sedated during the interview and seems to be cooperative with and responsive to the psychiatrist. Therefore, it is preferable to make arrangements later, although this is not always possible in clinical practice. We recommend providing essential information in writing as well and, whenever possible, drawing significant others into the discussions about the arrangements that have to be made.

*Drug names:* alprazolam (Xanax and others), clorazepate (Tranxene), diazepam (Valium and others), lorazepam (Ativan and others), oxazepam (Serax and others), temazepam (Restoril and others).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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### Instructions

Physicians may receive up to 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 456 and correctly answering at least 70% of the questions in the posttest that follows.

- 1. Read each question carefully and circle the correct corresponding answer on the Registration form.
- 2. Type or print your full name and address and Social Security, phone, and fax numbers in the spaces provided.
- 3. Send the Registration form along with a check, money order, or credit card payment in the amount of \$10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
- 1. Anterograde amnesia means:
- hy sic a. Diminished capacity to learn new information
  - b. Diminished capacity to retrieve old information
  - c. Diminished capacity to rehearse new information
  - d. Diminished capacity to consolidate old information
- 2. Anterograde amnesia is not a common finding in volunteers after a single dose of the following drug:
  - a. Diazepam
  - b. Lorazepam
  - c. Paracetamol
  - d. Midazolam
- 3. What is the prevalence of benzodiazepine use among people hospitalized because of a suicide attempt?
  - a. 10%
  - b. 20%
  - c. 35%
  - d. 50%
- 4. Choose the right statement about tests used to demonstrate anterograde amnesia induced by benzodiazepines:
  - a. Visual tests are more sensitive than verbal tests.
  - b. Recall tests are more sensitive than recognition tests.
  - c. Recall tests have shown tolerance to the amnestic effects.
  - d. Test have shown that sedation is the main factor of the amnestic effects.

4. For a credit certificate to be issued, answers must be postmarked by the deadline shown on the CME Registration form. After that date, correct answers to the posttest will be printed in the next issue of the Journal.

All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the Journal issue after the submission deadline. The Physicians Postgraduate Press Office of CME will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

- 5. Which test is most commonly used to demonstrate anterograde amnesia in users of benzodiazepines? a. 15-word test
  - b. Minnesota Multiphasic Personality Inventory (MMPI)
  - Symptom Checklist-90 (SCL-90)
  - d. Wechsler Adult Intelligence Scale (WAIS)
- 6. A consulting psychiatrist who visited a patient within suicide attempt with benzodiazepines should take into account that the next day:
  - a. The patient may not recognize the consulting psychiatrist.
  - b. The patient may not remember what he had discussed with the psychiatrist.
  - c. The patient may neither recognize the psychiatrist nor remember what was discussed.
  - d. The patient will recognize the psychiatrist and remember what was discussed.
  - 7. When making arrangements for follow-up care for patients who attempt suicide by benzodiazepine overdose, the psychiatrist:
    - a. Should ask the patient to repeat the arrangements immediately after they were explained to her or him
    - b. Should provide the information in writing
    - c. Should inform the patient about the consequences of memory impairment
    - d. Should only discuss the arrangements with the family of the patient

#### Answers to the December 1999 CME posttest

1. b 2. a 3. d 4. b 5. b 6. d 7. b 8. d

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#### Keeping a copy for your files

Retain a copy of your answers and compare them with the correct answers, which will be published after the submission deadline.

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- 5. Achievement of educational objectives:
  - A. Enabled me to describe the potential cognitive effects of benzodiazepines in patients admitted to the hospital after a suicide attempt with benzodiazepines.
    □ Yes □ No
  - B. Enabled me to develop a strategy for an initial psychiatric interview in a patient who has attempted suicide with benzodiazepines. □ Yes □ No
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- Does the information you received from this CME activity change the way you will manage your patients in the future?
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10. How much time did you spend completing this CME activity?

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