Cognitive Therapy and Research, Vol. 15, No. 6, 1991, pp. 459-467

The Effects of Diazepam on Anxiety-Related Cognition[1]

Susan Golombok,[2] Andreas Stavrou, and John Bonn
The City University, London

Karin Mogg
University of Cambridge

Stephen Critchlow
St. Bartholomew's Hospital, London

John Rust
Goldsmith's College, University of London

It has generally been assumed that the therapeutic action of benzodiazepines results from the effect of these drugs on mood. We suggest, however, that in reducing anxiety, benzodiazepines may have a direct effect on anxiety-related cognitions. The investigation was designed to examine the question of whether anxiety-related cognitive bias is reduced by diazepam in subjects selected according to DSM-III(R) criteria for generalized anxiety disorder (American Psychiatric Association, 1987). A modification of the Stroop color-naming task was used to measure bias toward the processing of threatening material. The results demonstrate that the reduction in anxiety shown by anxious patients after diazepam is not accompanied by a reduction in cognitive bias toward the processing of threatening material. This suggests that diazepam fails to reduce anxiety-related cognitive bias in clinically anxious subjects. It would seem, therefore, that diazepam alleviates anxious mood rather than cognitive manifestations of anxiety.

KEY WORDS: diazepam; anxiety; cognition; benzodiazepine.

[1]We would like to thank Malcolm Lader and Andrew Mathews for their help in developing this research. We would also like to thank the Medical Research Council for supporting the investigation.
[2]Address all correspondence to Dr. Susan Golombok, Clinical & Health Psychology Research Unit, The City University, Northampton Square, London EC1, England.

In recent years a number of studies have demonstrated that anxious subjects show a cognitive bias favoring the processing of threatening information — that is, people who are anxious selectively attend to information in their environment concerning personal threat or danger. Mathews and MacLeod (1985) found that patients with generalized anxiety disorder took longer to complete a Stroop color-naming task involving threatening words than a nonanxious control group. This finding has been replicated in similar comparisons of anxious patents and normal controls using different measures of selective processing of threat-related material (MacLeod, Mathews, & Tata, 1986; Mathews & MacLeod, 1986, Mogg, Mathews, & Weinman, 1989).

Benzodiazepine medication is the most widely used treatment for anxiety disorders. It has generally been assumed that the therapeutic action of benzodiazepines results from the effect of these drugs on mood via GABA receptors which are present in a number of systems of the brain (Tallman & Gallager, 1985). However, the finding that anxious individuals show a cognitive bias favoring the processing of threatening information has raised the question of whether, in reducing anxiety, benzodiazepines reduce the tendency of anxious individuals to selectively attend to threat.

Parrott and Sabini (1989) suggest that drugs affect not only emotion but cognition as well. Lazarus (1991) also proposes that drug effects on mood result from cognitive activities such as appraisal. Little evidence exists either to support or refute this claim, and interest in the issue has focused on the treatment of depression rather than anxiety. Simons, Garfield, and Murphy (1984), in a study of cognitive therapy vs. pharmacotherapy for the treatment of depression, found that depression was alleviated by both forms of treatment, and that antidepressant medication led to the same pattern of cognitive change as cognitive therapy on a variety of cognitive measures. On the basis of these findings, they argued that cognitive change follows clinical improvement after drug treatment. In a later discussion of the mechanisms by which pharmacotherapy may lead to cognitive change in depressed patients, Hollon, De Rubeis, and Evans (1987) postulated not only that cognitive change after antidepressants results from clinical improvement, but also that clinical improvement may result from a direct effect of drug treatment on cognition. Beck (1984) also argued that pharmacotherapy alleviates depression through a direct effect on cognition by reducing the negative bias which is characteristic of cognitive processing in depressed patients.

In a study of the effects of the benzodiazepine diazepam on cognitive processing in normal subjects with high state anxiety (Golombok, Mathews, MacLeod, & Lader, 1990), bias toward the processing of threatening information was not found to be reduced by the drug. However, no significant

difference was shown between diazepam and placebo in reducing state anxiety. Thus it remains possible that the failure to demonstrate that diazepam reduced anxiety-related cognitive bias simply reflected the failure of the drug to reduce anxiety levels in the nonclinical subjects who had high levels of state anxiety. From the few published reports of the effects of benzodiazepines on state anxiety in normal populations, it appears that it is not unusual for these drugs to fail to reduce state anxiety in such subjects (Debus & Janke, 1980; Parrott & Kentridge, 1982; Wilkinson, 1985).

The present study was carried out to overcome this problem. As we would expect anxiety to be reduced by diazepam in currently anxious patients, the investigation was designed to examine the question of whether anxiety-related cognitive bias is reduced by diazepam in subjects selected according to DSM-III(R) criteria for generalized anxiety disorder (American Psychiatric Association, 1987). Selective processing of threatening information was investigated using a modification of the Stroop color-naming task. This task has been shown to be sensitive to differences in cognitive processing between currently anxious patients and nonanxious control subjects, with anxious patients showing a bias toward the processing of threatening material (Mathews & MacLeod, 1985). As clinically anxious patients show a bias toward both physically and socially threatening material, some of the target words were related to physical or social threat while others were completely unrelated to danger. The Stroop procedure was essentially the same as that used by Mathews & MacLeod (1985), the only difference being that the present study required four versions of the task so that the cards had to be constructed using a larger pool of words.

METHOD

Subjects

The study was designed to compare the effects of diazepam and placebo in currently anxious patients and a matched nonanxious control group. The subjects were outpatients at the Department of Psychological Medicine at St. Bartholomew's Hospital in London who had been diagnosed with generalized anxiety disorder by a psychiatrist according to the DSM-III(R) classification. There were 24 subjects, 8 male and 16 female, aged between 20 and 66 years. The control group was recruited from the nonacademic staff at City University, London, and was matched with the anxious patients for age, sex, and IQ as measured by the Mill Hill Synonyms Scale (Raven, 1965). None of the patients or controls had taken psychotropic drugs or had received psychiatric treatment in the 6 months preceding the study.

Design

The subjects were tested according to a cross-over design on two separate occasions 1 week apart under double blind conditions. Each subject was administered 10 mg diazepam on one occasion and a placebo on the other in identical capsules, so that half of the subjects in each group received diazepam on the first testing session. Each subject was tested after a light breakfast. A Stroop color-naming task was administered to each subject immediately before taking the capsule and 1 hour afterward. Four parallel versions of the task were constructed, and presented in a balanced order within the design to reduce practice effects. The State Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) was also completed pre- and post-drug/placebo and was administered before the Stroop task at both testing sessions to monitor changes in anxious mood.

Measures

The stimulus words were chosen from a pool of physically threatening words, socially threatening words, and neutral control words matched for word length and word frequency according to ratings developed by Carroll, Davies, and Richman (1972). These words were randomly ordered and rated on a 5-point scale by 10 independent assessors in terms of the extent to which the word was considered to relate to physical or social threat, and how intrinsically threatening the word was considered to be. Forty physically threatening words (e.g., accident, violence) and forty socially threatening words (e.g., hopeless, unloved) were then selected. These two sets of words were comparable in terms of threat value. The 80 control words were not associated with threat.

In order to provide four parallel versions of the test material, the 40 physical threat words and the 40 social threat words, together with their matched control words, were randomly divided into four sets of 10 physical threat words and 10 social threat words each with a set of matched neutral control words. All four sets of words were matched for word length and word frequency. For each version, four cards (30 cm × 21 cm) were designed which contained either physical threat words, physical control words, social threat words, or social control words. The words on each card were written in letters 1 cm high in eight columns across the page, each column containing the complete set of words in randomized order. The 80 words on each card were presented in four colors (green, orange, blue, and red) with 20 words in each color. The colors were randomly allocated to words

Table I. Time Taken (in Seconds) by Patients and Controls to Color-Name Threat vs. Nonthreat Words Before and After Diazepam and Placebo

	Pre		Post	
	Threat	Non-threat	Threat	Non-threat
Patients				
Diazepam	69.2	66.1	75.3	70.5
Placebo	68.9	67.0	65.7	62.6
Controls				
Diazepam	59.2	57.2	61.0	59.6
Placebo	59.5	57.2	54.6	54.0

with the constraint that no color should appear consecutively in the same row.

Procedure

The four versions were presented so that a quarter of the subjects in both the patient and the control group received version 1 in the pretest, a quarter received version 2, and so forth. The order of presentation of physical threat, physical control, social threat, and social control cards was fully balanced within the patient and control groups. Each subject was given the four cards in turn to hold at a comfortable position for reading and asked to name the word colors as quickly as possible without making errors and without attending to the word content. The time taken to complete each card was recorded in milliseconds using a stopwatch. The difference in time taken to color-name threat and nonthreat cards provided a measure of selective attention to threatening material.

RESULTS

The data were analyzed using a four-factor analysis of variance with both between- and within-subjects factors. The between-subjects factors were group (patients vs. controls) and drug (diazepam vs. placebo). The within-subjects factors were time (pre vs. post) and valence (threat vs. nonthreat). Mean times to color-name each word card are shown in Table I.

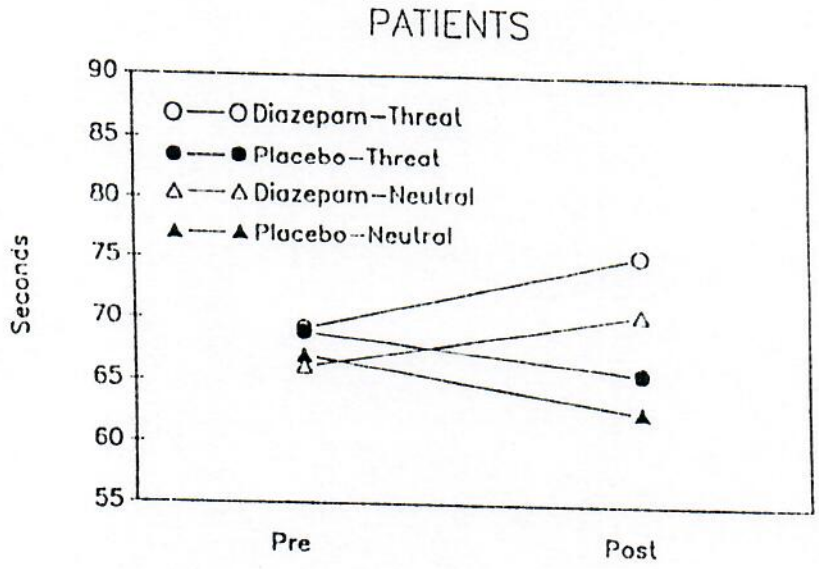

Fig. 1. Time taken (seconds) by patients to color-name threat vs. nonthreat words before and after diazepam and placebo.

A significant main effect was found for Group [$F(1, 46) = 8.8$, $p < 0.01$] showing that patients took longer overall to complete the color-naming task than the controls (patients = 68.2 sec; controls = 57.8 sec). There was also a significant main effect for Valence [$F(1, 46) = 26.8$, $p < 0.0001$], with subjects in each group taking longer to color-name threat than nonthreat words (patient threat = 69.8 sec; patient nonthreat = 66.5 sec; control threat = 58.6 sec; control nonthreat = 57.0 sec). The Group × Valence interaction approached significance [$F(1, 46) = 3.0$, $p < 0.1$], indicating a trend toward longer color-naming response latencies for threat than nonthreat by the patients compared with the controls. This is consistent with previous research indicating a cognitive bias following threat in anxious patients, so that a reasonable case can be made for the use of a one-tailed test producing a $p < 0.05$ significance level. In addition, there was a significant Drug × Time interaction [$F(1, 46) = 22.4$, $p < 0.001$], which demonstrated an overall effect of diazepam on slowing color-naming response times. However, the Group × Valence × Drug × Time interaction was not significant [$F(1, 46) = 0.1$, $p = 0.79$], so that diazepam did not reduce cognitive bias toward the processing of threat shown by anxious patients (see Figs. 1 and 2).

State and trait anxiety scores are presented in Table II. An analysis of variance was carried out to examine the effect of diazepam on state anxiety. The between-subjects factors were group (patient vs. control) and drug (diazepam vs. placebo) and the within-subjects factor was time (pre vs. post).

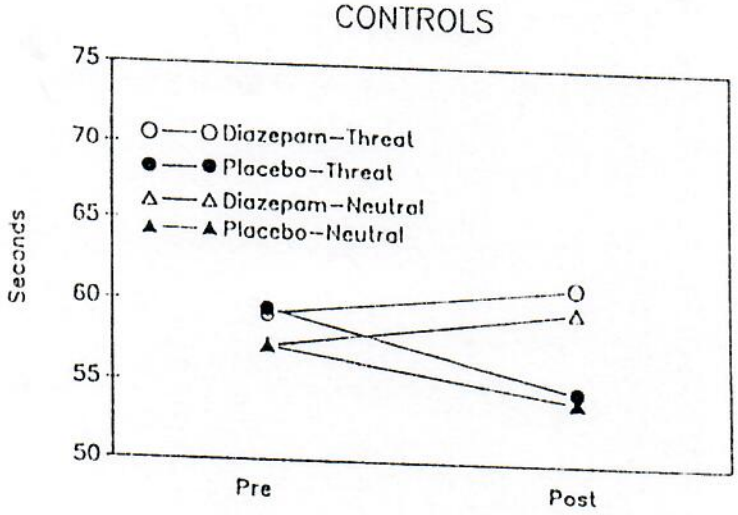

Fig. 2. Time taken (seconds) by controls to color-name threat vs. nonthreat words before and after diazepam and placebo.

A significant main effect was found for group [$F(1, 46) = 17.7$, $p < 0.0001$], which demonstrated that the patients were more anxious than the controls. A significant main effect was also found for time [$F(1, 46) = 13.5$, $p < 0.001$], showing that both patients and control subjects became less anxious between the first and second testing sessions. The Group × Time interaction approached significance [$F(1, 46) = 3.6$, $p < 0.1$], the patients showing a tendency toward a greater reduction in anxiety than the controls (patients pre = 47.5; patients post = 42.8; controls pre = 34.1; controls post = 35.7). The Group × Drug × Time interaction also approached significance [$F(1, 46) = 2.8$, $p < 0.1$], showing a trend toward a reduction in anxiety in patients after diazepam but not in controls.

DISCUSSION

The results of this study demonstrate that the reduction in anxiety shown by anxious patients after diazepam is not accompanied by a reduction in cognitive bias toward the processing of threatening material. This suggests that diazepam fails to reduce anxiety-related cognitive bias in clinically anxious subjects. It would seem, therefore, that diazepam alleviates anxious mood rather than cognitive manifestations of anxiety.

This finding is in line with the traditional view of the mode of action of benzodiazepines. The suggestion by Parrott and Sabini (1989) and by Lazarus (1991) that psychotropic drugs affect mood-related cognition as well as emotion is not supported by our findings. It remains possible that

Table II. State Anxiety Scores of Patients and Controls Before and After Diazepam and Placebo

	Pre	Post
Patients		
Diazepam	47.4	41.7
Placebo	47.4	44.0
Controls		
Diazepam	33.7	33.4
Placebo	34.3	31.4

a repeated-dose study would demonstrate that diazepam reduces cognitive bias following a reduction in anxious mood. However, there is no evidence from our investigation to support the suggestion in the depression literature by Hollon et al. (1989) and Beck (1984) that drug treatment may have a direct effect on cognition. Although it may be that antidepressants affect cognitive bias while benzodiazepines do not, it is important to remember that the literature on the effects of drug treatment on depressive cognition is mainly speculative, and the data which do exist come from self-report measures.

It could be argued that the failure to demonstrate a diazepam-induced reduction in cognitive bias simply reflects an insufficient decrease in state anxiety after the drug. The decrease in state anxiety in patients after diazepam compared with control subjects only reached significance at the 10% level and may not have been large enough to produce a statistically detectable reduction in cognitive bias. However, inspection of the data gives no indication whatsoever that diazepam reduced selective attention to threatening words in anxious patients (see Fig. 1). It is also worth noting that the 10-mg dose administered is the maximum single dose considered to be within the normal therapeutic range. Moreover, the drug clearly produced cognitive impairment in the subjects (as opposed to an effect on cognitive bias), as demonstrated by the very marked overall slowing on the color-naming task following the administration of diazepam.

The failure of diazepam to reduce cognitive bias in anxious patients suggests that benzodiazepines are ineffective in reducing the tendency for anxious patients to perceive everyday events as threatening or to selectively attend to threatening information in their environment. Clearly, there are limits to the extent to which it is possible to draw conclusions from negative results. However, taking the findings of the current study together with our earlier investigation it seems that, although diazepam causes cognitive

impairment as reflected by an overall slowing on the color-naming task, there is no indication that cognitive bias is reduced in any way. It remains possible that other measures of anxious cognition would change as a result of diazepam treatment, and further studies are needed to clarify this issue. However, on the evidence so far we would need to conclude that in reducing anxiety benzodiazepines affect emotional rather than cognitive pathways.

REFERENCES

American Psychiatric Associaiton (1987). *Diagnostic and statistical manual of mental disorders, Third Edition (Revised).* Washington, D.C: APA.

Beck, A. (1984). Cognition and therapy. *Archives of General Psychiatry, 41,* 1112-1114.

Carroll, J., Davies, P., & Richman, B. (1972). *Word frequency book.* New York: American Heritage.

Debus, G., & Janke, W. (1980). Methods and methodological considerations in measuring anti-anxiety effects of tranquillising drugs. *Progress in Neuro-Psychopharmacology, 4,* 391-404.

Golombok, S., Mathews, A., MacLeod, C., & Lader, M. (1990). The effects of diazepam on cognitive processing. *Human Psychopharmacology, 5,* 143-147.

Hollon, S., De Rubeis, R., & Evans, M. (19878). Causal mediation of change in treatment for depression: Discriminating between non-specificity and non-causality. *Psychological Bulletin, 102,* 139-149.

Lazarus, R. S. (1991). Cognition and motivation in emotion. *American Psychologist, 46,* 352-367.

MacLeod, C., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal psychology, 95,* 15-20.

Mathews, A., & MacLeod, C. (1985). Selective processing of threat cues in anxiety states. *Behavior Research and Therapy, 23,* 563-569.

Mathews, A., & MacLeod, C. (1986). Discrimination of threat cues without awareness in anxiety states. *Journal of Abnormal Psychology, 95,* 131-138.

Mogg, K., Mathews, A., & Weinman, J. (1989). Selective processing of threat cues in anxiety states: A replication. *Behavior Research and Therapy, 27,* 317-323.

Parrott, A., & Kentridge, R. (1982). Personal constructs of anxiety under the 1,5-benzodiazepine derivative clobazam related to trait anxiety levels of the personality. *Psychopharmacology, 78,* 353-357.

Parrott, W., & Sabini, J. (1989). On the "emotional" qualities of certain types of cognition: A reply to arguments for the independence of cognition and affect. *Cognitive Therapy and Research, 13,* 49-65.

Raven, J. (1965). *Guide to using the Mill Hill Vocabulary Scale with the Progressive Matrices Scale.* London: H. K. Lewis.

Simons, A., Garfield, S., & Murphy, G. (1984). The process of change in cognitive therapy an pharmacotherapy for depression. *Archives of General Psychiatry, 41,* 45-51.

Spielberger, C., Gorsuch, A., & Lushene, A. (1970). *Test manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press.

Tallman, J., & Gallager, D. (1985). The GABA-ergic system: A locus of benzodiazepine action. In M. Cowan, E. Shooter, C. Stevens, & R. Thompson (Eds.), *Annual Review of Neuroscience, 8,* 21-44.

Wilkinson, C. (1985). Effects of diazepam (valium) and trait anxiety on human physical aggression and emotional state. *Journal of Behavioral Medicine, 8,* 101-114.