'chological Medicine, 1988, 18, 365–374
nted in Great Britain

Cognitive impairment in long-term benzodiazepine users

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NOPSIS In view of the very extensive and often prolonged use of benzodiazepines in therapeutic actice, this study was designed to investigate whether or not cognitive ability is impaired in long-rm benzodiazepine users, and to determine the nature and extent of any deficit. Fifty patients rrently taking benzodiazepines for at least one year, thirty-four who had stopped taking nzodiazepines, and a matched control group of subjects who had never taken benzodiazepines or ho had taken benzodiazepines in the past for less than one year were administered a battery of uropsychological tests designed to measure a wide range of cognitive functions. It was found that ıtients taking high doses of benzodiazepines for long periods of time perform poorly on tasks volving visual-spatial ability and sustained attention. This is consistent with deficits in posterior ɔrtical cognitive function.

NTRODUCTION

is now widely acknowledged that the long-rm use of benzodiazepines often leads to hysical dependence (Lader, 1983*a*; Owen & yrer, 1983; Schopf, 1983). Withdrawal symp-ɔms can develop after as little as 6 weeks of ɔntinuous administration (Murphy *et al.* 1984) nd may persist for a year or longer (Ashton, 984; Higgitt *et al.* 1985). These include anxiety nd related symptoms, insomnia, depression, ches, pains and muscle spasms, gastro-intestinal isorders and increased sensitivity to sound, ght, touch, smell and taste (Petursson & Lader, 984; Ashton, 1984). Although our awareness nd understanding of the dependence-inducing ɔroperties of the benzodiazepines has increased n recent years, little is known about the ɔnsequences of long-term administration on ɔgnitive functioning. In view of the very xtensive and often prolonged use of benzo-liazepines in therapeutic practice (Balter *et al.* 1984) it is important to establish whether or not ɔgnitive ability is impaired in long-term benzo-liazepine users, and to determine the nature and xtent of any deficit.

Since the introduction of the benzodiazepines in the 1960s, a large number of controlled studies of normal subjects have provided clear evidence that single doses of these drugs impair cognitive functioning (McNair, 1973; Wittenborn, 1979; Hindmarch, 1980; Johnson & Chernik, 1982). In summarizing these findings, Lader (1983*b*) concluded that it is simple repetitive tasks, learning and memory which are affected by benzodiazepines, rather than well established higher mental functions involving visual-spatial, perceptual and verbal abilities.

Repeated-dose studies differ in the particular type of benzodiazepine, the dosages and the cognitive measures investigated, and are too few to draw general conclusions about effects on cognition. Diazepam is the most frequently investigated benzodiazepine and Digit Symbol Substitution (Wechsler, 1955) the most common measure of cognitive function to be used in these studies. After one or two weeks of continuous administration, performance on Digit Symbol Substitution has been shown to remain impaired when compared with subjects taking a placebo (Bond *et al.* 1983; Golombok & Lader, 1984), to counteract the improvement in performance expected by practice effects (Aranko *et al.* 1985), and to become significantly worse (Lader *et al.* 1980). Similar impairment has been found for the Symbol Copying Test (Bond *et al.* 1983), Reaction Time (Aranko *et al.* 1985; Brosan *et al.*

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1986) and tests of Syntactic Reasoning and Semantic Processing (Brosan *et al.* 1986).

In spite of these numerous short-term studies, the effects on cognition of longer-term administration of benzodiazepines are not known. In fact, very few studies have examined the long-term effects of these drugs on anxious patients, and those which have done so have followed-up the patients for only a few weeks after beginning a course of medication. Although benzodiazepines are often assumed to counteract the debilitating effects of anxiety on cognitive funtioning, Bond *et al.* (1974) found that patients' performance on cognitive tasks does not improve after several weeks of medication.

Tolerance to the sedative effects of benzodiazepines has been shown to develop after one or two weeks of continuous administration, so that any initial drowsiness normally disappears. In view of the generally held belief that tolerance develops to most benzodiazepine effects (Greenblatt & Shader, 1978), it is perhaps surprising that after repeated doses of a benzodiazepine, the performance on cognitive tasks of both normal subjects and anxious patients remains impaired. It is possible that it takes longer for tolerance to develop to cognitive tasks than to physiological responses and subjective feelings, and that existing studies have simply failed to allow sufficient time to elapse for tolerance to occur. Accumulation of the drug after repeated doses may augment cognitive impairment and tolerance may not become apparent until some time after a steady-state is reached. Alternatively, recent evidence suggests that tolerance is more likely to develop to some effects than to others (Petursson & Lader, 1984). Thus, it might be the case that tolerance does not develop to the cognitive effects of benzodiazepines, or that tolerance to these effects is minimal. This would have serious implications for patients taking these drugs for long periods of time. In Britain alone, at any point in time, one and a quarter million people have been taking benzodiazepines continuously for at least one year (Balter *et al.* 1984).

A study of psychomotor performance during withdrawal from long-term benzodiazepine treatment (Petursson *et al.* 1983) suggested that chronic medication might impair cognitive functioning. Those patients who had taken benzodiazepines in normal therapeutic doses for more than one year showed significantly poo psychomotor test performance than a cont group of normal subjects matched for age a sex. However, these findings remain inconclus because of the small size together with inadequate control group and the inclusion subjects who might be expected to perfo poorly for reasons other than benzodiazep intake. The present study was designed investigate the effects of long-term ben diazepine treatment on a battery of neu psychological tests designed to measure a w range of cognitive functions bearing in mind known short-term effects of these drugs. Neu radiological measures were also obtained a will be reported elsewhere.

METHOD

Subjects and design

One hundred and forty-five subjects took part the study. They were sampled from three grou (i) patients currently taking benzodiazepin (ii) subjects who had never taken ben diazepines or who had taken benzodiazepines the past for less than one year, and (iii) patie who had taken benzodiazepines in the past at least 1 year and who had withdrawn for least 6 months. Those currently taking ben diazepines ($N = 50$) were obtained through t records of several general practitioners the London area. In order to be included in t sample, they had to have taken benzodiazepir in normal therapeutic doses (defined as up 30 mg per day of diazepam or equivalent) for least one year. Subjects who had never be prescribed a benzodiazepine or who had tak these drugs in the past for less than one ye ($N = 61$), were recruited from voluntary orga izations and employment agencies. The group subjects who had taken benzodiazepines co tinuously for at least one year and who h successfully withdrawn from their medicati for at least six months ($N = 34$) was obtain from both general practice and the outsi agencies. No subject with a history of excessi alcohol use, epilepsy, brain injury, psycho illness, cerebrovascular accident, monoami oxidase inhibitors or major tranquillizers w included in the study.

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National Adult Reading Test (NART)

iis reading test assesses pre-morbid intel-gence in patients with dementia (Nelson, '82). In the present study it was used to ovide a measure of intellectual ability before e possible development of drug-related de-rioration. The NART comprises a list of 50 ords printed in order of increasing difficulty, l of which are 'irregular' with respect to the mmon rules of pronounciation. The subject as asked to read aloud down the list of words id the number of pronounciation errors was corded.

Cancellation Test

iis test provides a measure of sustained tention. Subjects were presented with a sheet paper with rows of numbers containing forty s in 400 numbers. They were instructed to ncel out all the 4's (Kornetsky *et al.* 1959). The ne taken in seconds to complete the test was corded.

Reaction Time

mple reaction time to identical visual stimuli, e number '1', presented on a computer screen as measured. The subject was instructed to old down a key to elicit the stimulus, and then move the hand off the key to the response key quickly as possible. After eight practice trials, e mean reaction time for 32 test trials was lculated.

Digit Symbol Substitution Test

iis subtest of the WAIS (Wechsler, 1955) gives measure of psychomotor function. It is a ding task in which symbols are substituted for mbers. The score was the number of items rrect in 90 seconds.

Symbol Copying Test

this test of motor speed the same symbols are ed as in the Digit Symbol Substitution Test it the subject has only to copy and not code em (Bond & Lader, 1972). The score was the mber of items correct in 90 seconds.

Block Design

iis sub-test of the WAIS (Wechsler, 1955) is a nstruction test which measures visuospatial organization. Subjects are instructed to use red and white blocks to construct replicas of nine red and white designs printed in smaller scale. A total score is obtained for each subject according to the speed and accuracy of completion of the designs.

Verbal Recall Memory

Forty-nine randomly ordered words were presented individually for 2 seconds at 2 second intervals (Curran *et al.* 1986). The word list comprised seven categories with seven words in each. The categories were selected from those of Battig & Montague (1969) and the words were balanced across categories for frequency of use. Immediately the list had been presented, the subjects were instructed to write down as many of the words as possible in any order in 2 minutes. This procedure was repeated twice using the same words in a different random order each time. The total number of words correctly recalled over the three trials was calculated. To provide a measure of delayed recall, the subjects were asked to write down as many words as they could remember $1\frac{1}{2}$ hours later.

New Learning

The ability to learn new material was assessed from the Verbal Recall Test by subtracting the subject's score for trial 1 from the score for trial 3.

Visual Spatial Recognition Memory

This is a computerized spatial recognition test (Acker & Acker, 1982*a*). The subject is required to memorize a design and then to recognize that previously-seen design from a triad which includes two unseen designs. The interval between initial presentation of the stimulus and its re-appearance on the screen with two new designs is 1, 5 and 10 seconds. There are 36 trials altogether, with 12 at each of the three retention intervals. Total number correct and mean reaction time were scored.

Little Men

This is a computerized measure of spatial orientation (Acker & Acker, 1982*a*). A 'manikin' appears on the screen holding a baton in one hand. He may be facing away from the subject, on his feet or on his head, and the baton

may be in the right or left hand. Subjects are required to make a left/right discrimination for 32 trials. Total number of correct trials and mean response time were scored.

Visual Perceptual Analysis

This computerized measure of visual information processing examines the subject's ability to perceive small differences in complex abstract designs (Acker & Acker, 1982*a*). Three designs, two of which are identical, appear on the screen and the subject has to indicate the different one. The test has 32 trials, 16 'hard' and 16 'easy'. Total number correct and mean reaction time were scored.

Trail Making

This is a test of visual conceptual and visuomotor tracking (Reitan, 1958). The subject was asked to draw lines to connect consecutively numbered circles on one work sheet (Trail Making 'A'), and then to connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between the two sequences (Trail Making 'B'). Time taken in seconds to complete each part was recorded.

Bexley-Maudsley Category Sorting Test

This computerized test measures the subject's ability to use abstract concepts (Acker & Acker, 1982*b*) and has been adapted from the Wisconsin Card Sorting Test (Berg, 1948; Grant & Berg, 1948). The subject is required to use abstract concepts to solve a problem, and to change concepts as the computer alters the solution criteria of the problem. Four standard designs are presented incorporating three dimensions – the orientation of the elements, the number of elements and the type of elements. The subject has to assign serially presented test designs to one of the standard designs on the basis of orientation, number or type, and is told after each trial whether or not the response was correct. The computer takes the subject through two cycles of these three concepts. The following scores were obtained: (i) number of categories – total number of concepts achieved, (ii) total number of sorts to complete the test, (iii) total number of errors, and (iv) perseverations – number of errors which were repeated consecutively.

Controlled Word Association Test

This measure of verbal fluency requires subjects to say as many words as they can think of which begin with the letter 'F' in 60 seconds excluding proper nouns, numbers and words with the same prefix. This procedure is then repeated with the letters 'A' and 'S' (Benton, 1968). The sum of correct words in the three categories was scored.

Cognitive Failures Questionnaire (CFQ)

This scale measures self-reported failures in perception, memory and motor function (Broadbent *et al.* 1982). The subject is asked to indicate the frequency with which he or she has made such mistakes in the past 6 months on a 5-point scale ranging from 'never' to 'very often'. A total score is obtained by summing the score for each item.

State Anxiety Inventory

This scale provides a measure of the subject's level of anxiety at the time of testing. The subject is asked to rate 20 statements about how he or she feels at that particular moment on a 4-point scale ranging from 'not at all' to 'very much so' (Spielberger *et al.* 1970). A total score is obtained by summing the score for each item.

RESULTS

Benzodiazepine intake

A global measure of benzodiazepine intake (BZI) was calculated for each subject by multiplying the length of time for which the subject had taken a particular benzodiazepine with its dose for each benzodiazepine taken, and then summing these scores. Length of time was measured in months and the dose was categorized as (i) less than the minimum therapeutic dose, (ii) maintenance dose, (iii) maximum therapeutic dose, and (iv) above the maximum therapeutic dose. A global measure of antidepressant intake (ADI) was calculated in the same way as for BZI.

As the subjects who had been prescribed benzodiazepines ranged from those who had taken a large dose for a long period of time to those who had a relatively low intake, the data were analysed by regression techniques which

:d the continuous nature of the degree of ɔdiazepine intake (BZI), the independent ble in this investigation.

ysis of subjects still taking benzodiazepines he matched control group

nts currently taking benzodiazepines and cts who had never taken these drugs or had so in the past for less than 1 year were ded in the first part of the analysis to look e effects of chronic benzodiazepine use on itive functioning. In selecting the sample, :cts with different levels of benzodiazepine :e were balanced for age, further education NART score, all of which are known to t test performance. Pearson product-ıent correlation coefficients between each of : variables and BZI showed no significant ionship with benzodiazepine intake, con-ing that the subjects had been successfully :hed for age, number of years of further :ation and NART score, the measure of pre-bid IQ.

:elations

ı of the test variables was regressed on BZI the significance of the beta coefficients are ɔrted in their standardized form as Pearson duct-moment correlation coefficients in le 1. Those tests for which a significant tionship was found are the Cancellation Test : 0·23; $P < 0·01$), Digit Symbol Substitution : −0·27; $P < 0·01$), Symbol Copying ($r =$ ·19; $P < 0·05$), Block Design ($r = -0·22$; : 0·01), New Learning ($r = -0·23$; $P < 0·01$), le Men ($r = -0·22$; $P < 0·01$) and Visual ceptual Analysis ($r = -0·27$; $P < 0·01$), such t subjects with a high benzodiazepine intake ıwed significant impairment on these tests.

ıltiple regression

e seven variables which were found to be nificantly related to benzodiazepine intake re entered into a multiple regression analysis ng stepwise extraction. Two components re found to be predictive of BZI. One was ıracterized by Visual Perceptual Analysis (P 0·01). There were indications from changes in nificance levels that Symbol Copying, Block :sign and Little Men were closely related to s component. The other component was extracted with the Cancellation Test ($P < 0·02$) and was related to Digit Symbol Substitution and New Learning.

Table 1. *Correlations between benzodiazepine intake (BZI) and test variables*

	Pearson's r	Significance
Cancellation Test	0·23	$P < 0·01$
Reaction Time	0.10	NS
Digit Symbol Substitution	−0·27	$P < 0·01$
Symbol Copying	−0·19	$P < 0·05$
Block Design	−0·22	$P < 0·01$
Verbal Recall	−0·11	NS
Delayed Recall	−0·12	NS
New Learning	−0·23	$P < 0·01$
Spatial Recognition	−0·11	NS
Spatial Recognition Reaction Time	0.05	NS
Little Men	−0·22	$P < 0·01$
Little Men Reaction Time	0·11	NS
Visual Perceptual Analysis	−0·27	$P < 0·01$
Visual Perceptual Analysis Reaction Time	0·09	NS
Trail Making 'A'	0·14	NS
Trail Making 'B'	0·09	NS
Bexley–Maudsley Category Sorting		
N of Categories	−0·03	NS
N of Sorts	0·05	NS
N of Errors	0·12	NS
Perseverations	0·17	NS
Word association	−0·03	NS
Cognitive Failures Questionnaire	0·14	NS

State anxiety

It was not possible to balance subjects for level of anxiety during testing as those subjects who had a high benzodiazepine intake were also the most anxious. State Anxiety was found to be significantly correlated with benzodiazepine intake at the 1 % level, thus raising the possibility of its effect as a contaminating variable between BZI and test performance. As shown in Table 2, correlations between State Anxiety and the tests themselves were found to be significant only for the Cancellation Test ($r = -0·23$; $P < 0·05$) and the Symbol Copying Test ($r = 0·20$; $P < 0·05$). For both of these variables it would be necessary, therefore, to eliminate the effect of State Anxiety before interpreting any relationship with benzodiazepine intake. However, partial correlations controlling for State Anxiety showed a strong significant relationship between BZI and both the Cancellation Test ($r = 0·35$; $P < 0·01$) and the Symbol Copying Test ($r = -0·27$; $P < 0·02$)

Table 2. *Correlations between state anxiety and test variables*

	Pearson's *r*	Significance
Cancellation Test	−0·23	$P < 0·05$
Reaction Time	−0·02	NS
Digital Symbol Substitution	0·05	NS
Symbol Copying	0·20	$P < 0·05$
Block Design	0·05	NS
Verbal Recall	0·05	NS
Delayed Recall	0·03	NS
New Learning	−0·05	NS
Spatial Recognition	−0·02	NS
Spatial Recognition Reaction Time	−0·04	NS
Little Men	0·05	NS
Little Men Reaction Time	−0·12	NS
Visual Perceptual Analysis	0·02	NS
Visual Perceptual Analysis Reaction Time	−0·18	NS
Trail Making 'A'	−0·11	NS
Trail Making 'B'	−0·07	NS
Bexley-Maudsley Category Sorting		
N of Categories	0·18	NS
N of Sorts	−0·18	NS
N of Errors	−0·15	NS
Perseverations	−0·02	NS
Word association	−0·04	NS
Cognitive Failures Questionnaire	0·36	$P < 0·001$

after State Anxiety had been removed. Not surprisingly, the most anxious subjects also had high scores on the Cognitive Failures Questionnaire ($r = 0·36$; $P < 0·001$).

Antidepressants and short-term benzodiazepine effects

Pearson product-moment correlation coefficients were calculated between antidepressant intake (ADI) and each of the 21 test variables to examine the effects of antidepressant medication on test performance. As only one significant relationship was found, between ADI and Digit Symbol Substitution ($r = 0·18$; $P < 0·05$), it is reasonable to reject this result as spurious, and to conclude that our data did not show a significant relationship between antidepressant intake and poor performance on the test battery. Similarly, our findings cannot be accounted for by the short-term effects of benzodiazepines. Only one variable, New Learning ($P < 0·05$), was shown to be significantly correlated with the dose taken on the day of testing.

Analysis of subjects who had withdrawn from benzodiazepines

The subjects who had withdrawn from long-term benzodiazepine medication were compared with patients who were still taking these drugs to examine whether stopping benzodiazepines is followed by a return to normal cognitive functioning. The patients still on medication were found to have a significantly higher mean BZI score than those who had withdrawn. In order to balance the two groups for benzodiazepine intake, patients with a high BZI score who were still taking these drugs had to be excluded. Subsequently, no significant differences in cognitive functioning were found between the groups. A further comparison between those who had withdrawn from medication and subjects who had never taken benzodiazepines also failed to show differences in performance.

DISCUSSION

It seems from the results that the long-term use of benzodiazepines is associated with cognitive impairment. Two areas of functioning appear to be affected. The first is visual-spatial ability, as measured by Visual Perceptual Analysis, which tends to be related to Symbol Copying, Block Design and Little Men. The second concerns attention or, more specifically, the ability to sustain attention on a repetitive task under time pressure. This is characterized by a deficit in performance on the Cancellation Test, and relates to the Digit Symbol Substitution Test and New Learning. There was no evidence of impairment in global measures of intellectual functioning such as memory, flexibility and simple reaction time.

This pattern of impairment is consistent with deficits in posterior cortical cognitive function. The tests which showed impaired performance are those which are generally affected by parietal, posterior temporal and occipital rather than frontal lesions (Kolb & Whishaw, 1980). The finding that patients function normally on tests which are indicative of frontal damage, such as Verbal Fluency and Card Sorting, suggests that benzodiazepines have a specific effect on the posterior cortex. It could be argued that because three of the measures of visual-spatial ability

have a motor component, these tests are simply identifying motor impairment. However, Visual Perceptual Analysis, a purely perceptual measure, had the highest weighting in the multiple regression analysis. In addition, simple reaction time as well as reaction time for Visual Perceptual Analysis were not affected. It could also be argued that only the tests of visual-spatial ability and sustained attention were sensitive enough to pick up the effects of benzodiazepines. This is not the case, however, as it was the most sensitive tests, such as Verbal Recall Memory and the Bexley-Maudsley Category Sorting Test, which showed no deficit.

The finding that benzodiazepines appear to selectively impair posterior cognitive function raises the question of why these drugs show such a specific effect. The effects of benzodiazepines are generally believed to be mediated through benzodiazepine receptors in the central nervous system. However, there is no evidence that either the density, i.e. the number, or the affinity, the strength with which a benzodiazepine binds to a receptor, of benzodiazepine receptors is greater in the posterior cortex (Braestrup & Nielsen, 1985). Research on the mode of action of benzodiazepines may be at too early a stage to explain the specificity of their effects on cognitive functioning.

It may, of course, be the case that the poor performance of long-term benzodiazepine users is not due to the medication itself but to other factors which are common to these patients. In particular, the anxiety for which benzodiazepines are prescribed is associated with impaired performance on tests of cognitive ability. However, anxiety-related impairment was demonstrated for only two of the tests and, when the effects of anxiety had been accounted for the deficit in performance remained. Moreover, if our findings could be explained by anxiety, we would expect poor performance on all of the tests, especially on high demand tasks. In reviews of the literature on the effects of anxiety on performance, Eysenck (1984) and Hockey (1979) concluded that the more difficult the task, the more detrimental the effect of anxiety. Difficult tasks are considered to make high demands on the short-term storage of information. In the present investigation, therefore, we would expect to find a deficit in tasks which depend on efficient short-term storage such as the Memory tests and Card Sorting, and this was not so.

We were careful to exclude subjects from our sample with medical or psychiatric conditions which might have confounded the results. Another exclusion criterion was previous psychotropic medication to ensure that any possible drug effect could be clearly attributed to benzodiazepines. Many patients who had taken benzodiazepines for long periods of time had also been prescribed tricyclic antidepressants, so that not only would their exclusion have significantly reduced the sample size, but it would also have changed the nature of the sample to such an extent that it would no longer have been representative of long-term benzodiazepine users. This made it necessary to examine the possibility that our findings were due to the effects of antidepressants rather than benzodiazepines. However, the lack of effect of antidepressants on test performance was striking.

It is impossible to determine how long it is safe for a patient to continue to take benzodiazepines, or at what dose, before cognitive ability will begin to deteriorate. Nevertheless, it is clear from the inspection of our data that taking a low dose for short time has little effect, while a high intake is almost certainly harmful. When those on medication were divided into three groups according to benzodiazepine intake, with equal numbers in each, the average BZI score for the 'low intake', 'medium intake' and 'high intake' patients respectively was 67, 209 and 465. An example of medium intake would be 6 years of continuous medication at a dose towards the upper limit of the therapeutic range. The data are not precise enough to indicate a cut-off point. As with alcohol, the effect is cumulative – the higher the intake, the greater the risk (Ron, 1983).

The findings of the comparison between subjects who had stopped taking benzodiazepines and those still on medication remain inconclusive. Those who were no longer taking these drugs had had a comparatively low intake of benzodiazepines and were, therefore, unlikely to have shown much impairment while on medication. In order to determine whether or not patients who do become impaired return to normal cognitive functioning when they withdraw, it would be necessary to investigate patients who had withdrawn from a high

benzodiazepine intake. However, the fact that our sample comprised only subjects with a low intake suggests that few of those with a high intake manage to withdraw.

It is difficult to conclude whether or not the cognitive effects of the long-term use of benzodiazepines are different in nature from the effects of a single dose or a short course of these drugs. A particular problem is that the tests used in short-term studies fail to tap a wide range of cognitive abilities. A study of the effects of 15 mg clorazepate dipotassium using the same battery of tests as the present investigation showed only the Cancellation Test and Reaction Time to be significantly impaired (Moodley *et al* 1985), which suggests that the short and the long-term effects of these drugs might be different. The development and course of cognitive impairment are also uncertain because of the dearth of information between the first few weeks of medication and one year of continuous administration. Patients may become tolerant to the cognitive effects of these drugs before further impairment develops. Alternatively, cognitive ability might slowly deteriorate from the start. However, the *degree* of impairment does appear to be greater after chronic medication. In short-term studies it is usual for subjects to act as their own control which increases the sensitivity to the effects of the drug. The 'between-subjects' design in the present investigation has an error term which is inflated by individual differences in performance, so that a greater drug effect is needed for significance to occur.

It seems clear that two of the three areas of cognitive functioning which Lader (1983*b*) found to be impaired after short-term benzodiazepine administration – the ability to perform simple repetitive tasks and the ability to learn new material – are also impaired after chronic medication. However, performance on a variety of memory tasks, the third area which is impaired after short-term administration, showed no obvious deficit for long-term users. In a recent review of the effects of benzodiazepines on memory, Curran (1986) describes a close association between sedation and memory impairment. This would suggest that as patients became tolerant to the sedative effects of benzodiazepines, memory deficits would diminish, which may well explain why the memory impairment found after short-term administration is not apparent in chronic users.

A major discrepancy between the short and long-term effects of benzodiazepines is in visual-spatial ability. Lader (1983*b*) concluded that such a well established higher mental function is not impaired by the short-term use of these drugs, yet poor visual-spatial ability was found to be the greatest problem among chronic users. The tests of visual-spatial performance in the present investigation appear, in general, to require more elaborate processing of information than those used in short-term studies. It may be the case that benzodiazepines interfere with complex perceptual analysis, rather than with simpler visual-perceptual skills. Otherwise, it seems likely that deterioration of visual-spatial ability develops only after benzodiazepines have been taken for a long period of time.

It remains possible that cognitive impairment in chronic benzodiazepine users is not a direct consequence of these drugs but, instead, results from an intervening factor. In particular, it could be argued that patients with the highest benzodiazepine intake are also the most anxious, and that the anxiety for which the benzodiazepines are prescribed is responsible for their poor performance. However, the lack of relationship in this investigation between anxiety and test performance rules this out as an explanation for our findings. Neither can the results be attributed to the acute affects of benzodiazepines taken at the time of testing as dose was also shown to be unrelated to cognitive impairment. It is also important to point out that subjects at risk for brain damage for reasons other than benzodiazepine intake were not included in the sample. We cannot exclude pre-existing impairment as a possible explanation but this is not likely in view of the significant correlation between impairment and benzodiazepine intake. Moreover, the subjects were matched for pre-morbid IQ. It seems, therefore, most likely that cognitive impairment in long-term benzodiazepine users is caused by the drugs themselves rather than extraneous factors.

The finding that patients taking high doses of benzodiazepines for long periods of time perform poorly on tasks involving visual-spatial ability and sustained attention, implies that these patients are not functioning well in everyday life. Furthermore, the lack of relationship between benzodiazepine intake and the Cognitive Failures Questionnaire, a subjective measure of impairment, suggests that they are not

aware of their reduced ability. This is in line with clinical evidence that patients who withdraw from their medication often report improved concentration and increased sensory appreciation, and that only after withdrawal do they realize that they have been functioning below par (Curran & Golombok, 1985). The cognitive effects of long-term administration of benzodiazepines may not simply be debilitating but may also be dangerous. Although benzodiazepines have not been directly implicated in road traffic accidents, Hindmarch (1986) estimated that up to 10% of drivers involved in car accidents had been taking psychoactive drugs, and that psychoactive drugs are responsible for the loss of 200000 lives world-wide on the roads each year. It is not clear what proportion of these drug-takers are long-term benzodiazepine users. However, benzodiazepines are the most commonly prescribed psychoactive drugs, and many patients continue their medication for long periods of time. It appears, therefore, that not only are long-term benzodiazepine users at risk of dependence, but that cognitive impairment also represents a very real hazard.

Thanks are due to the following GPs for their support: Professor M. Salkind and colleagues, Dr R. Meyrick and colleagues, Dr Y. Cooper and colleagues, and Dr C. Pickard. We appreciate the neuropsychological expertise and guidance of Tony Canavan. We are also grateful to Clare Acker for her advice on automated testing. The study was funded by the Medical Research Council.

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