Psychopharmacology (1991) 105:1–8
003331589100161Y

Psychopharmacology

Review

Benzodiazepines, memory and mood: a review

H. Valerie Curran

Department of Psychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

Received October 30, 1990 / Final version January 11, 1991

Abstract. The amnestic effects of benzodiazepines (BZs) have attracted considerable research interest. This reflects not only the clinical implications of memory failure for people prescribed these drugs but also the potential of BZs as tools in modelling organic memory problems. As well as impairing certain aspects of human memory functions, BZs affect mood states by reducing anxiety and inducing sedation. An unresolved issue is the extent to which the amnestic effects of BZs are separable from their sedative and anxiolytic effects. The present review focusses on this issue, first presenting a conceptual framework for evaluating the interrelationship between the various effects of BZs, and then summarising recent volunteer and patient research relevant to dissociating amnestic from other effects. Clinical implications are discussed in terms of the use of BZs alone or as adjuncts to psychotherapy for anxiety disorders, and attention is drawn to the need for more ecological validity in psychopharmacological research. Theoretical implications are explored in terms of BZs as tools in studying both memory failure and the relationship between mood and cognition.

Key words: Benzodiazepines – Memory – Mood state – Sedation

For the past 30 years, benzodiazepines (BZs) have been extensively prescribed throughout the western world as tranquillizers and sleeping pills. These drugs, however, not only act to reduce anxiety and induce sedation. They can also produce an apparent anterograde "amnesia". Amnesic effects were recognised early on by anaesthetists using BZs as premedicants (Brandt and Oakes 1965; Haslett and Dundee 1968; Pandit and Dundee 1970). Indeed, anaesthetists welcomed a premedicant drug which resulted in a patient forgetting unpleasant operative procedures. Many studies have since been carried out in which single doses of BZs have been given to non-anxious, volunteer subjects and significant impairments have been found in their performance on certain types of memory tasks (Curran 1986).

The amnesic effects of BZs have attracted considerable research interest for both practical and theoretical reasons. One practical reason is that many people take BZs on a daily basis and for them, memory loss could interfere with their ability to function optimally. Another relates to the fact that BZs are often given in combination with behavioural and cognitive treatments of anxiety. To the extent that such therapies involve specific types of learning, the conjoint use of drugs which impair a client's memory may well be counter productive.

Theoretical relevance derives firstly from the observation that some organic amnesias have certain features in common with the memory impairments induced by BZs. It has therefore been suggested that the administration of BZs to normal, healthy subjects may provide a useful model of organic amnesia, especially of Korsakoff's disease (Brown et al. 1982; Weingartner 1985). Secondly, because the study of amnesic patients has helped clarify our understanding of "normal" memory functions, it has been argued that the differential effects of BZs on memory may also help elucidate "normal" memory mechanisms (e.g. Mewaldt et al. 1983). Thirdly, as discussed later in this review, mood-altering drugs like BZs offer potential tools in the study of the interrelationship between cognition and mood.

Given both the practical and potential theoretical relevance of understanding the effects of BZs upon human memory, it is not surprising that research in this field has mushroomed in volume. Between 1986 and 1990, a "Medline" search reveals over 100 published studies which have assessed BZ effects on human memory. This work has helped to produce a clearer picture of the differential effects of BZs, such as which aspects of memory functions are impaired and which preserved, and how the manner in which memory is assessed can affect this.

At the same time, limitations to our understanding derive mainly from two related issues. The first is the question of specificity of effects: to what extent are the

"amnestic" effects of BZs isolated from their other effects – most notably those on arousal, on attention and on anxiety levels? The second is the question of ecological validity: how generaliseable are laboratory-based findings to the "real world", to the daily experience of people taking BZs? Even though the memory-impairing effects of BZs were recognised in the 1960s, we still know little today about how, on either a short-term or long-term basis, these drugs affect cognitive functions of patients who take them, or how these cognitive effects may interact with non-pharmacological treatments of anxiety. The aim of this review is both to summarise what we now know about the effects of BZs on memory and to identify our ignorance, focussing on the issues of specificity of effects and ecological validity.

A conceptual framework

The simplest conceptual framework we require to understand how any anti-anxiety treatment may affect cognition is presented in Fig. 1*a*. The interaction between cognition and mood has been widely documented (for reviews see Blaney 1986; Williams et al. 1988). Levels of anxiety may influence cognitive functioning not only quantitatively in terms of levels of performance (cf Eysenck 1984) but also qualitatively in that anxious people display an attentional bias towards threat-related information in the environment (Mathews and MacLeod 1985, 1986). Partly perhaps via this attentional bias, and/or directly through anxiety mood states themselves, levels of arousal will also be influenced. Similarly, levels of arousal may interact with aspects of cognitive functioning (Yerkes-Dodson 1908; Eysenck 1982).

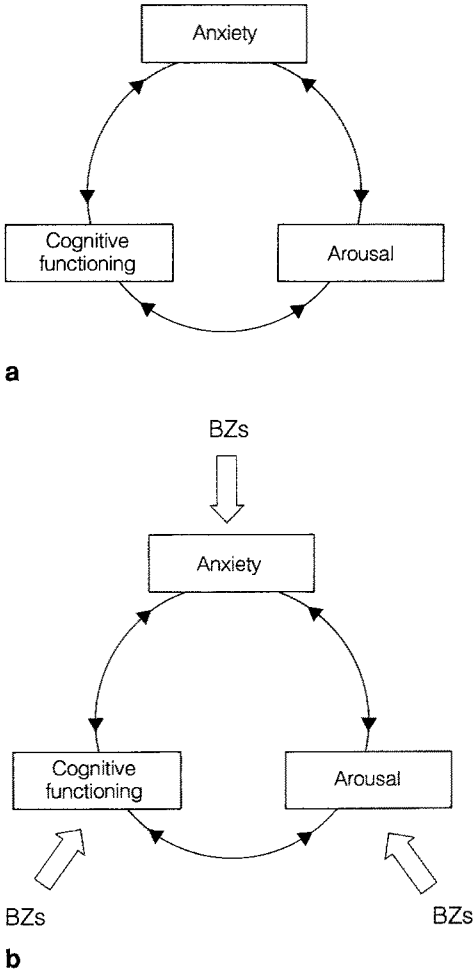

Fig. 1. a Simplified model of the interaction between anxiety, arousal and cognitive function. **b** How benzodiazepines may act on those factors

The effects of BZs within this framework are depicted in Fig. 1*b*. As anxiolytics, BZs may act directly on levels of anxiety. As sedative compounds, they may act directly to reduce levels of arousal. And as centrally acting drugs, BZs may directly influence cognitive functions. By acting on any or all of these three components, BZs may also influence the interaction between them.

Given this simple conceptual framework, it is clear that a change in cognitive functioning following administration of a BZ may be interpreted in several ways. For instance, it could be that the drug directly affected an aspect of cognition (e.g. impaired attentional or memory functions), or that it lowered arousal levels (e.g. sedated a subject such that information may not have been registered). Further, these effects may also depend on the individual's initial (pre-drug) levels of anxiety. For example, it is possible that, following a BZ, performance may improve in highly anxious subjects. When taken on a repeated basis, these various direct and interactional effects will also depend on the individual's tolerance to BZs, and tolerance to the anxiolytic, sedative and cognitive effects of BZs may not develop in parallel.

Acute effects of benzodiazepines

Anterograde "amnesia" is a consistent finding from volunteer studies of single doses of a BZ: information presented after the drug is administered is poorly remembered. In contrast, no study has found objective evidence of retrograde impairments of memory: information acquired before drug administration is retained intact. Very rarely, retrograde amnesic effects have been observed, but they have been linked to the patient being so deeply sedated as to having a degree of cerebral hypoxia (Dundee and Pandit 1972; McKay and Dundee 1980). The degree and duration of anterograde amnesia depends on several factors (the particular BZ taken; dosage and route of administration; the memory assessments used; the times post-drug at which information is presented and retrieval is required; characteristics of the subject population tested). Although there is considerable variation between studies in these factors, the relatively large number of studies carried out to date do allow some generalizations to be drawn out.

First, BZs do not impair performance on tasks which require remembering a few verbal items for a period of seconds. For example, performance on the digit span task is unaffected by BZs and so too is the recency effect in free recall tasks (Ghoneim and Mewaldt 1975; Ghoneim et al. 1981; Curran et al. 1987b). Few studies have

assessed short-term visual or spatial memory. On the Corsi block task, two BZs (oxazepam and lorazepam) impaired performance relative to placebo, but as this visuospatial task involves a motor response, this may have related to the effects of these drugs on motor speed (Curran et al. 1987b).

The above tasks are seen traditionally to tap short-term or primary memory as conceptualised in the "modal model" of memory (Atkinson and Shiffrin 1971). Indeed, most studies of BZs have been carried out implicitly or explicitly within the framework of the modal model. A more comprehensive view of short-term remembering is offered by the "working memory" model which posits more than one short-term store (Baddeley and Hitch 1974). Pivotal to the working memory model is the "central executive" mechanism which is responsible for general processing and for allocating processing resources to the particular task(s) at hand. The central executive is aided by two main subsystems – a store maintaining verbal information (the articulatory loop) and a store for visuospatial material (the visuospatial scratchpad). The central executive, which has a limited capacity, also mediates the exchange of information between long-term and short-term storage. The effects of BZs on working memory have not yet been assessed in detail. In a study comparing a benzodiazepine (lorazepam, 2 mg) with the anticholinergic drug, scopolamine, we found evidence that lorazepam impairs central executive function essentially by reducing the speed (but not the accuracy) with which information is manipulated (Curran et al. 1991). However, a recent study by Rusted and Eaton-Williams (submitted) found that diazepam (5, 10 mg) disrupted central executive function in terms of both speed and accuracy of processing. Differences between these two findings may reflect differing speed-accuracy trade-offs in the logic task used to assess central executive function rather than differences between lorazepam and diazepam. Future research on the effects of BZs on working memory is needed to clarify which aspects are impaired. It is possible that acute doses of BZs, perhaps partly via inducing sedation, may reduce central executive function which, in turn, will impair performance on a wide range of tasks.

BZs appear to affect different aspects of long-term memory in different ways. Although there is considerable debate among cognitive psychologists about how to characterise long-term remembering in terms of stores, systems and processes, one useful framework for discussing drug effects on memory is a three-way division of episodic, semantic and procedural memory (e.g. Tulving 1985). Episodic memory, as its name suggests, is the system concerned with remembering personally experienced episodes in our lives. It is an autobiographical memory which retains information such as what you had for supper last night or the circumstances in which you first met a close friend. In the laboratory, episodic memory is often assessed by seeing how much of a recently presented story, or a list of words or a series of photographs, a subject recalls or recognises. And what is found consistently is that BZs impair performance on these tasks.

In general, the more demands a task places on episodic memory, the clearer are the detrimental effects of BZs. So, for example, free recall tasks are more sensitive than cued recall or recognition tasks. Or again, the longer the delay between acquisition and retrieval, the greater the drug effect on performance. Overall, when direct assessments of memory are used, it seems that the experimental manipulations which affect the performance of normal (non-drugged) subjects produce a broadly parallel pattern of influences on the performance of subjects administered single doses of BZs. Thus if subjects are required to process information at different depths, from the relatively superficial (e.g. deciding whether a word is in capital letters or in small case) to the relatively deep (e.g. deciding whether a word belongs to a particular semantic category), BZs may mean fewer words are subsequently recalled but the pattern of recall will be the same as normal (i.e. deeper levels of encoding lead to better recall) (Curran et al. 1988).

It is well established that benzodiazepines do not impair the retrieval of information acquired before drug administration. Apparently paradoxically, several studies have shown that subjects given a BZ can actually remember word lists presented before the drug significantly better than subjects given placebo (Ghoneim et al. 1984; Hinrichs et al. 1984). This effect, however, is only found when one or more lists are presented post-drug. Without the interfering effects of post-drug lists, pre-drug lists are recalled equally by drug and placebo groups. Therefore, as Hinrichs et al. (1984) show convincingly, this "retrograde facilitation" effect is due to drug groups' impaired learning of post-drug lists which reduces retroactive interference on pre-drug learning.

Semantic memory is the system concerned with our stored knowledge of the world, our language, rules and concepts. Unlike information in episodic memory which is stored with reference to how, where and when that information was acquired, information in semantic memory is thought to be relatively decontextualised. In drug studies, semantic memory has been assessed almost exclusively by "word fluency" tasks: a subject is asked to produce as many instances of a category (e.g. occupations) and/or words beginning with a particular letter of the alphabet (e.g. F) as they can think of at a given time. BZs do not appear to affect performance on word fluency tasks (Curran et al. 1987b, 1991), although whether this reflects a sparing of semantic memory or a relative insensitivity of the task is not clear. Using a sentence verification task, we found neither lorazepam nor oxazepam affected accuracy of semantic retrieval although both BZs slowed retrieval speeds (Curran et al. submitted).

The contents of episodic and semantic memory are thought to be directly accessible to consciousness – we can bring to mind both personal episodes and impersonal facts. In contrast, procedural memory is expressed indirectly through skilled performance. So, for example, procedural memory includes our knowledge of perceptual and motor skills such as riding a bicycle, and more "intuitive" skills we may use in problem-solving. BZs have been found not to affect procedural learning in both perceptual-learning tasks (Lister and File 1984) and ana-

gram-solving tasks (Weingartner and Wolkovitz 1988). In perceptual-motor skill-learning tasks, such as the pursuit rotor (cf Curran et al. 1991) results are less consistent and this may relate to motor sedation.

Tasks assessing procedural memory in these ways are indirect tests of memory – remembering is inferred from changes in the performance of a skill. Another kind of indirect test of memory includes what is normally referred to as "priming": the influence of prior exposure on subsequent performance. For example, subjects might be asked to rate each of a series of words (e.g. cheese, dragon) according to how much they liked them. They might then be given an ostensibly unrelated task of completing lists of three letter word stems (e.g. CHE..., DRA...) with the first English word that comes to mind. Even though the stems may actually begin a dozen or more common words, the subject is more likely to complete those stems with the words they were exposed to in the previous rating task. Thus at no point is the subject asked to remember any words directly. His or her memory for the words is indexed indirectly through performance on the word stem completion task. One of the most intriguing findings in memory research over the past decade has been that amnesic patients may show preserved abilities on indirect tests of memory despite profound impairments on direct tests (for review, see Shimamura 1986). Few studies of BZs have assessed priming. Both Fang et al. (1987) and Danion et al. (1989) found diazepam (0.3 $mg \cdot kg^{-1}$, 0.2 $mg \cdot kg^{-1}$, respectively) did not affect performance on an indirect test of memory but produced the usual impairment on direct tests of memory. However, Brown et al. (1989) report precisely the opposite effect in a study of lorazepam: impairment on an indirect test (word stem completion) but not on a direct test (recognition).

Similarly, in a comparison of lorazepam (2 mg) with scopolamine (0.3, 0.6 mg) Schifano and Curran (submitted) found that lorazepam impaired verbal priming more than verbal recall whereas the higher dose of scopolamine produced the opposite pattern of effect. To further explore this surprising effect of lorazepam on word priming, Curran and Gorenstein (submitted) recently compared lorazepam (2 mg) with the closely related but much less potent BZ, oxazepam (30 mg). Significant differences between the two BZs were found on word-stem completion, but not word recall, with lorazepam again producing impairments of priming.

Taken together, the results of these studies suggest that there may be qualitative differences between the effects of different BZs on memory functions. They also suggest that priming can be disrupted by lorazepam. This is remarkable in that priming appears relatively unaffected by age (Parkin and Streete 1988), by alcohol (Hashtroudi et al. 1984), by scopolamine (Kopelman and Corn 1988) or by organic amnesia (Shimamura 1986). Clearly, more research is needed, using a wide range of priming tasks and different (single and repeated) dosages of lorazepam and other BZs, to clarify these effects. As Tulving and Schacter (1990) point out, priming is probably a ubiquitous occurrence in everyday life, and disruption of this nonconscious form of memory could have major implications for people's ability to function efficiently.

Specificity of effects of BZs

BZs do not only affect memory. Single doses also generally impair performance on attentional and on psychomotor tasks and generally lower subjective ratings of alertness. Given these global effects on a range of tasks and marked subjective sedation, one must question whether BZs have any specific effects on memory which are not simply by-products of their sedative effects.

How can we dissociate the sedative and amnesic effects of BZs? One simple approach might be a statistical one – to covary measures of sedation from measures of memory. When we have done this, we find that the differences between a BZ and a placebo in their effects on memory are diminished but are still significant, even though differences in psychomotor performance may disappear (Curran et al. 1987b, 1991). This may imply that sedation contributes to, but does not explain, the "amnesic" effects of BZs. The main limitation of this statistical approach is that covariance assumes a linear relationship between variate and covariate and the relation between memory and sedation may well be more complex than that.

A more satisfactory way of assessing sedative versus amnesic effects would be to show a dissociation between them experimentally.

The effects of BZs are thought to be mediated by facilitation of central GABA-ergic transmission via specific benzodiazepine receptors (Haefely 1985; Morre et al. 1985). If all of the effects of BZs are mediated in this way, then administration of a benzodiazepine antagonist such as flumazenil should reverse the sedative, psychomotor and amnesic effects of BZs. On the whole, however, studies with flumazenil have not yet produced a consistent pattern of results. O'Boyle et al. (1983) reported that co-administration of a high dose of flumazenil reversed sedation but only attenuated the amnesic action of diazepam. Complete reversal of amnesic effects by flumazenil has been reported in studies using lormetazepam (Dorow et al. 1987) and flunitrazepam (Gentil et al. 1989). Dunton et al. (1988) reported differential dosage effects of flumazenil on the amnesic actions of diazepam as compared with lorazepam. Ghoneim et al. (1989) found that the time course of flumazenil's reversal of diazepam differed for sedative compared with amnesic effects. Hommer et al. (1986) administered the antagonist before giving diazepam and this resulted in a blocking of attentional and sedative effects but amnesia remained. We found that flumazenil reversed the sedative and psychomotor effects of midazolam but not its amnesic effects in both normal volunteer subjects (Curran and Birch 1991) and patients undergoing day-care surgery (Birch and Curran 1990). It will be apparent from just this selection of studies that we do not yet have a clear picture of whether flumazenil reverses all the effects of all BZs or not. A fair conclusion is probably that sedative effects are much more easily reversed that amnestic effects. However, different researchers have used very dif-

ferent agonist/antagonist dosages, and other procedural differences make it difficult to compare across the various studies.

A third way to establish a dissociation between sedation and amnesia could be to show that two drugs produced the same effect on one measure (sedation or amnesia) but different effects on the other measure. In a study comparing two chemically similar BZs, oxazepam (15, 30 mg) with its chlorinated derivative, lorazepam (1, 2 mg) we found similar effects on measures of attention, sedation and psychomotor function but different degrees of memory impairments (Curran et al. 1987b). This may mean that the relation between sedation and amnesia varies depending on the particular benzodiazepine. In a similar vein, Smirne et al. (1989) compared three dose levels of flunitrazepam (1, 2, 4 mg) and found memory impairments even at the lowest dose, whereas accompanying attentional impairments were produced only by the higher doses.

A fourth way of dissociating sedation and amnesia could be to show that tolerance over repeated dose of BZs builds up differentially to the two effects. I shall discuss this mainly in the section on studies with anxious patients, but it is worth noting here the results of one carefully controlled study of a 3-week administration of diazepam to normal, volunteer subjects. Ghoneim et al. (1981) used 30 volunteers in three independent treatment groups administering each night: (i) placebo for 3 weeks; (ii) diazepam (0.2 $mg \cdot kg^{-1}$) for 3 weeks; or (iii) placebo for 3 weeks except for 1 night when the same dose of diazepam was given. Subjects were tested on days 1, 2, 18, 19, 21, and 28. This design allowed a comparison of acute with chronic effects of the drug.

No acute or chronic effects were found on a digit recall task. The immediate recall of 16 uncategorised words showed a clear impairment after a single dose of diazepam but this effect decreased over the 3-week treatment period. Thus, tolerance built up in terms of immediate memory. However, no tolerance effects were observed for delayed (15 min) recall of those words, which was significantly impaired compared with placebo at each testing session. All groups were again tested at 4 weeks when no differences in performance were found, so there were no residual memory effects following withdrawal. This implies that repeated doses of diazepam produce partial rather than complete tolerance to its memory decrement over a 3-week treatment period. In Ghoneim et al.'s (1981) study, no drug effects were found on a range of non-memory tasks (tapping rate, simple and choice reaction times and multiplication of numbers) or on subjective ratings of drowsiness, implying that the effects of diazepam on memory are not simply a by-product of altered levels of arousal. Few other studies have assessed the amnesic effects of daily BZs with volunteer subjects over a time interval resembling a normal treatment period.

Effects of anxiety

So far we have discussed the issue of specificity of BZ effects in terms of the interaction between sedation and memory. Unfortunately, we know very little of how anxiety levels may also interact to influence the effects of BZs on cognition (cf Fig. 1*b*). By using healthy volunteer subjects, most studies have not taken anxiety levels into account, either implicitly assuming that anxiety levels would be unaffected as subjects were "non-anxious" to begin with, or finding that measures of anxiety showed floor effects before drug administration.

Three studies have assessed the possible effects of anxiety levels on memory using single doses of BZs with volunteer subjects. Kohnen and Lienert (1980) manipulated anxiety experimentally by varying the degree of stress in the test situation. They showed that recall of objects was improved by 2 mg cloxazolam in stressful situations but impaired in a low-stress condition. Desai et al. (1983) found diazepam (5 mg) improved the performance of high anxiety volunteers but impaired that of low anxiety volunteers in recalling consonant sequences. However, a very different pattern of results is reported by Hartley et al. (1982): in a task requiring the retrieval and recognition of category exemplars, the performance of high anxiety volunteers was generally more impaired than that of low anxiety volunteers by 5 mg diazepam.

These disparate results have few, if any, implications for the effects of benzodiazepines on memory in clinically anxious patients. The decreased arousal produced by single doses of drug may be subject to tolerance effects such that the interaction of anxiety, performance and drug varies over a treatment period. On balance, the findings from studies of anxious patients taking BZs on a repeated basis (discussed below) indicate persisting memory impairments rather than any improvements.

Anxiety, cognitive bias and benzodiazepines

The past decade has seen significant advances deriving from the application of cognitive psychology to the investigation of anxiety and depression. This work has accumulated evidence that these emotional disorders are associated with biases in the cognitive processing of emotionally salient information. Evidence so far implies that anxious people display *attentional* biases such that they selectively attend to threat-related information. In contrast, most studies with depressed people indicate that they show a *memory* bias towards mood-congruent information (for reviews see Blaney 1986; Williams et al. 1988). Memory research with anxious subjects has produced equivocal results. Mogg et al. (1987) found no evidence of a memory bias towards threatening words with patients diagnosed as having generalised anxiety disorder. However, two studies have produced evidence for a memory bias in patients with panic disorder (Norton et al. 1988; McNally et al. 1989) and Nunn et al. (1984) report memory bias in agoraphobic patients.

If anxiety is associated with a bias towards processing threat-related information, an agent which changes anxious mood such as a BZ may also be capable of producing a change in cognitive bias. To date, no published study appears to have addressed the possibility of change in memory bias following a BZ, although two studies

have tried to assess attentional bias pre- and post- a BZ (Golombok et al. 1990; submitted). Unfortunately, in neither study (one with pre-operative patients; one with patients diagnosed as having generalised anxiety disorder) did the BZ (diazepam, 10 mg) produce a significant change in levels of state anxiety, and so the finding that there was no significant change in attentional bias is equivocal. Further, as Golombok et al. discuss, it is possible that cognitive bias is a relatively enduring, stable characteristic of highly anxious individuals (i.e. a "trait" feature) which remains stable despite transient changes in mood (i.e. "state" anxiety).

Effects of BZs on memory functions of anxious patients

In view of the fact that the amnesic effects of BZs were reported in the 1960s in the anaesthesiology literature, it is puzzling why so little is known in the 1990s about the cognitive effects of BZs on people who have taken these drugs daily for an anxiety disorder over a period of months or years. As has been pointed out elsewhere (Curran 1986; Koelega 1989), generalisability of volunteer studies to the patient population is limited by several factors, including the fact that the former involve young, non-anxious predominantly male subjects whereas the latter are predominantly older, anxious and female. In research with anxious patients, one is necessarily looking at a three-way interaction of mood state, drug and cognition.

Two studies have compared the memory functions of chronic users with various control groups. Golombok et al. (1988) used a measure of cumulative intake of BZs over years and found this was negatively correlated with level of learning over trials in a free recall task, as, too, was the actual dose of BZ taken on the day of testing. Lucki et al. (1986) found no difference in the performance of chronic BZ users and an anxious control group. However, they did find that chronic users were impaired on a delayed word recall task after taking one dose of a BZ.

Longitudinal studies of cognition with patients are very few. In a study by Morton and Lader (1990) patients diagnosed as having generalised anxiety disorder were administered a 4-week treatment of either lorazepam (mean end of treatment dosage, 1.7 mg bd) or a newer anxiolytic, alpidem (mean end of treatment dosage, 56 mg bd). Both treatments produced parallel reductions in levels of anxiety, and at 4 weeks there was no subjective or motor sedation. However, patients given lorazepam were significantly impaired at 4 weeks on a word recall task. [A single-dose volunteer study of the same drugs in the same laboratory had shown more profound effects of lorazepam on the same recall task which were accompanied by marked sedation (Curran et al. 1987a)]. Thus like the results of Ghoneim et al. (1981) with normal volunteers, the clinical study of Morton and Lader implies that tolerance to sedation develops before tolerance to amnesic effects.

Recently, we carried out a study with patients who had a diagnosis of "agoraphobia with panic" (Curran et al. submitted). They were allocated to two drug treatment groups, alprazolam or placebo. Dosages were flexible and at the end of treatment averaged 5.2 mg alprazolam (range 0.5–9 mg) and 8.2 capsules of placebo (range 5–10), each given in up to four divided doses per day. We assessed the patients on a range of cognitive and psychomotor indices at three time points: before treatment, after an 8-week treatment, and then again at a drug-free follow-up of approximately 24 weeks. At these assessment points, there was no evidence of subjective or motor sedation, and over the 8-week treatment anxiety levels changed equally in both groups. However, we found a highly significant impairment of performance on a word recall task at the end of treatment for patients given alprazolam. Further, at follow-up, scores on this task had only returned to baseline (pre-treatment) levels in the alprazolam group whereas placebo subjects had shown a significant improvement (a practice effect) over the three assessment times. An indirect test of memory using a word-stem completion task was administered at 8 weeks. This indirect test showed no treatment differences, parallelling findings from studies of single doses of diazepam and oxazepam with normal volunteers. Overall, therefore, this study showed that a two month administration of a BZ impaired patients' episodic memory in the absence of sedation.

In that study, subjects within each drug and placebo group were given one of two psychological treatments: graded in vivo exposure or progressive relaxation training. The two psychological treatment groups did not differ on objective measures, but they did differ on subjective ratings of everyday memory problems. To see if we could gain some information about patients' memory functions in everyday life, rather than in the laboratory, we asked them to complete a slightly adapted form of the Subjective Memory Questionnaire (Bennett-Levy and Powell 1980) at each assessment point. Subjects given exposure treatment rated fewer everyday memory failures than the relaxation group, in terms of how often they had forgotten things, both at the end of treatment and at follow-up. This difference was not reflected in the objective memory tests. It may be that subjective ratings of memory reflect mood state or feelings of self-efficacy more than actual memory functioning. Further, that there were no differences between drug and placebo groups in subjective memory may imply one of two things: either the episodic memory impairment shown in laboratory testing did not mean memory problems were experienced in daily life, or subjects were unaware of experiencing such problems. Memory questionnaires offer limited insight into real-life memory problems, although completion of questionnaires by significant others such as spouses may provide more reliable data (Baddeley et al. 1982).

Future research using repeated dosages of BZs over more than a few days is restricted by ethical considerations concerning dependence. However, research to date implies that repeated use of BZs over weeks does not lead to tolerance of episodic memory impairments. This has implications for the debate about the conjoint use of BZs with psychological therapies. There are several issues

involved in this debate, beyond that of memory impairment, including questions about whether pharmacologically lowered anxiety levels impede or promote therapy involving exposure to anxiety-inducing situations (cf Matthews et al. 1981; Hayward et al. 1989; Wardle 1990). But because BZs do not impair all aspects of learning, one would predict that BZ induced memory impairments would only impede cognitive-behavioural treatments to the extent that the latter involve episodic learning. For example, depending on several factors (e.g. particular BZ used, dosage, timing of therapy sessions with respect to drug ingestion) it is possible that a client may actually forget what she/he did during a therapy session. This would contribute negatively to therapy outcome. However, to the extent that such treatments involve procedural learning (e.g. classical conditioning, skill acquisition), one would not expect BZ-induced impairments.

Benzodiazepine-induced amnesia?

What, then, can we conclude about the effects of BZs on memory? In terms of acute dosage, the sedative effects of BZs may contribute to a range of performance impairments, including performance on tasks involving memory functions. These global changes may be due, in part at least, to impairment of attentional or central executive functions. But results so far do not rule out the possibility that episodic memory itself is disrupted, over and above sedation effects. If two measures (e.g. of "memory" and "sedation") show different effects of a drug, it can always be argued that the measures themselves are differentially sensitive, so ideally, one needs to show a double dissociation. The concept of sedation (or "arousal" or "activation") is itself ill-defined and the various subjective, psychomotor and psychophysiological measures of sedation do not inter-correlate well. It also seems likely that people may try to compensate for subjective sedation by increasing the effort expended in performance of a task. Such compensatory factors, or motivational factors, have received little attention as yet in research with psychotropic drugs.

The central issue remains of how changes in memory performance are interpreted in terms of the disruption of particular memory and/or non-memory processes. Results of studies in which BZs have been given on a daily basis over a period of weeks imply that tolerance develops differentially to sedative and amnesic effects. Indeed, tolerance may not develop fully to impairments of episodic memory. It is of clinical concern that significant memory impairments have been found after weeks of daily BZ use by anxious patients. Those impairments seem to be more pronounced on tasks relying heavily on contextual cues, such as word recall or paired associate learning, and this is similar to impairments observed in Korsakoff's disease (KD).

Unlike KD, BZs do not appear to produce retrograde impairments of memory. Further, priming is preserved in KD (cf Shimamura 1986) whereas there is some preliminary evidence that one BZ (lorazepam) may disrupt verbal priming as assessed by word completion, although other BZs (diazepam, oxazepam) do not. Weingartner (1985) suggested that BZ-induced memory impairments tend to parallel those of KD, whereas those of scopolamine are more akin to those of Alzheimer's disease. To date, however, it has proved difficult to dissociate the effects of these two types of compounds in terms of their effects on memory (Curran et al. 1991; Rusted and Eaton-Williams, submitted). Both compounds can produce sedation and psychomotor impairments as well as amnestic effects.

Future research is needed using detailed task analyses to establish more precisely the conditions under which different aspects of memory are disrupted or preserved. Whether BZs offer a useful model in the study of either organic amnesias or the mechanisms of "normal" memory will depend on identifying specific memory effects of these drugs as distinct from their anxiolytic and sedative effects. The potential of BZs and other psychotropic drugs as tools in the study of the interaction between mood and cognition has yet to be fulfilled.

References

Atkinson RC, Shiffrin RM (1971) The control of short-term memory. Sci Am 225:82–90

Baddeley A, Hitch G (1974) Working memory. In: Bower G (ed) Recent advances in learning and motivation, vol 8. Academic Press, New York

Baddeley A, Sunderland A, Harris J (1982) How well do laboratory-based psychological tests predict patients performance outside the laboratory? Ageing 19:141–148

Bennett-Levy J, Powell GE (1980) The subjective memory questionnaire (SMQ). An investigation into the self-reporting of "real-life" memory skills. Br J Clin Psychol 19:177–188

Birch B, Curran HV (1990) The differential effects of flumazenil on the psychomotor and amnesic actions of midazolam. J Psychopharmacol 4:29–34

Blaney PH (1986) Affect and memory: a review Psychol Bull 99:229–246

Brandt AL, Oakes FD (1965) Preanesthesia medication: double-blind study of a new drug, diazepam. Anesth Analg 44:125

Brown J, Lewis V, Brown MW, Horn G, Bowes JB (1982) A comparison between transient amnesias induced by two drugs (diazepam and lorazepam) and amnesia of organic origin. Neuropsychologia 20:55–70

Brown MW, Brown J, Bowes J (1989) Absence of priming coupled with substantially preserved recognition in lorazepam induced amnesia. J Exp Psychol 41A:599–617

Curran HV (1986) Tranquillising memories: a review of the effects of benzodiazepines on human memory. Biol Psychol 23:179–213

Curran HV, Birch B (1991) Differentiating the sedative, psychomotor and amnesic effects of benzodiazepines: a study with midazolam and the benzodiazepine antagonist, flumazenil. Psychopharmacology 103:519–523

Curran HV, Allen DA, Lader M (1987a) The effects of single doses of alpidem and lorazepam on memory and psychomotor performance in normal volunteers. J Psychopharmacol 2:81–89

Curran HV, Schiwy W, Lader M (1987b) Differential amnesic properties of benzodiazepines: a dose response comparison of two drugs with similar elmination half-lives. Psychopharmacology 92:358–364

Curran HV, Schiwy W, Eves F, Shine P, Lader M (1988) A "levels of processing" study of the effects of benzodiazepines on human memory. Hum Psychopharmacol 3:21–25

Curran HV, Schifano F, Lader M (1991) Models of memory dysfunction? A comparison of the effects of scopolamine and

lorazepam on memory, psychomotor performance and mood. Psychopharmacology 103:83–90
Danion J-M, Zimmermann M-A, Willard-Schroeder D, Grange D, Singer L (1989) Diazepam induces a dissociation between explicit and implicit memory. Psychopharmacology 99:238–243
Desai N, Taylor-Davies A, Barnett DB (1983) The effects of diazepam and oxprenololon short-term memory in individuals of high and low state anxiety. Br J Clin Pharmacol 15:197–202
Dorow R, Berenberg D, Duka T, Sauergrey N (1987) Amnestic effects of lormetazepam and their reversal by the benzodiazepine antagonist Ro 15–1788. Psychopharmacology 93[4]:507–514
Dundee JW, Pandit SK (1972) Anterograde amnesic effects of pethidine, hyoscine and diazepam in adults. Br J Clin Pharmacol 44:140–148
Dunton AW, Schwam E, Pitman V, McGrath J, Hendler J, Siegel J (1988) Flumazenil: US clinical pharmacology studies. Eur J Anaethesiol S2:81–95
Eysenck MW (1982) Attention and arousal: cognition and performance. Springer, Berlin Heidelberg New York
Eysenck MW (1984) A handbook of cognitive psychology. Lawrence Erlbaum Associates, London
Fang JC, Hinrichs JV, Ghoneim MM (1987) Diazepam and memory: evidence for spared memory function. Pharmacol Biochem Behav 28:347–352
Gentil V, Tavares S, Gorenstein C, Bello C, Mathias L, Gronich G, Singer J (1990) Acute reversal of flunitrazepam effects by Ro 15–1788 and Ro 153505: inverse antagonism, tolerance, and rebound. Psychopharmacology, 100:54–59
Ghoneim MM, Mewaldt SP (1975) Effects of diazepam and scopolamine on storage, retrieval and organisational processes in memory. Psychopharmacology 44:257–262
Ghoneim MM, Mewaldt SP, Berie JL, Hinrichs V (1981) Memory and performance effects of single and 3 week administration of diazepam. Psychopharmacology 73:147–151
Ghoneim MM, Hinrichs JV, Mewaldt SP (1984) Dose-response analysis of the behavioural effects of diazepam: I. Learning and Memory. Psychopharmacology 82:291–295
Ghoneim MM, Dembo JB, Block RI (1989) Time course of antagonism of sedative and amnesic effects of diazepam by flumazenil. Anesthesiology 70:899–904
Golombok S, Moodley P, Lader M (1988) Cognitive impairment in long-term benzodiazepine users. Psychol Med 18:365–374
Golombok S, Mathews A, MacLeod C, Lader M (1990) The effects of diazepam on cognitive processing, Hum Psychopharmacol 5:143–147
Haefely W (1985) Tranquillisers. In: Grahame-Smith, DG Cowen PJ (eds) Psychopharmacology, 2, part 1. Preclinical psychopharmacology. Elsevier, Amsterdam
Hartley LR, Spencer J, Williamson J (1982) Anxiety, diazepam and retrieval from semantic memory. Psychopharmacology 76:291–293
Hashtroudi S, Parker ES, DeLisi E, Wyatt RJ, Mutter SA (1984) J Exp Psychol Learn Mem Cognit 10:156–161
Haslett WHK, Dundee JW (1968) Studies of drugs given before anaesthesia: XIV: two benzodiazepine derivatives, chlordiazepoxide and diazepam. Br J Anaesth 40:250
Hayward P, Wardle J, Higgitt A (1989) Benzodiazepine research: current findings and practical consequences. Br J Clin Psychol 28:307–327
Hinrichs JV, Ghoneim MM, Mewaldt SP (1984) Diazepam and memory: retrograde facilitation produced by interference reduction. Psychopharmacology 84:158–162
Hommer DW, Breier A, Paul SM, Davis M, Weingartner H (1986) Ro 15–1788, a specific benzodiazepine antagonist, blocks the sedative, anxiolytic and attentional but not the amnestic effects of diazepam in humans. Abstracts of the 25th ACNP Annual Meeting, Washington
Koelega HS (1989) Benzodiazepines and vigilance performance: a review. Psychopharmacology 98:145–156
Kohnen R, Lienert GA (1980) defining tranquilizers operationally by non addictive effect in experimental stress situations. Psychopharmacology 68:291–294
Kopelman MD, Corn TH (1988) Cholinergic "blockade" as a model for cholinergic depletion. Brain 111:1079–1110
Lister RG, File SE (1984) The nature of lorazepam-induced amnesia. Psychopharmacology 83:183–187
Lucki I, Rickels K, Geller AM (1986) Chronic use of benzodiazepines and psychomotor and cognitive test performance. Psychopharmacology 88:426–433
McKay AC, Dundee JW (1980) Effect of benzodiazepines on memory. Br J Anaesth 52:1247–1257
McNally RJ, Foa EB, Donnell CD (1989) Memory bias for anxiety information in patients with panic disorder. Cognit Emot 3:47–53
Mathews A (1988) Anxiety and the processing of threatening information. In: Hamilton V et al. (eds) Cognitive perspectives on emotion and motivation. Martinus Nijhoff, Dordrecht
Mathews A, MacLeod C (1985) Selective processing of threat cues in anxiety states. Behav Res Ther 23:563–569
Mathews A, Macleod C (1986) Discrimination of threat cues without awareness in anxiety states. J Abnorm Psychol 95:131–138
Matthews AM, Gelder MG, Johnson DW (1981) Agoraphobia: nature and treatment. Tavistock, London
Mewaldt SP, Hinrichs JV, Ghoneim MM (1983) Diazepam and memory: support for a duplex model of memory. Mem Cognit II:557–564
Mogg K, Mathews A, Weinman J (1987) Memory bias in clinical anxiety. J Abnorm Psychol 96:94–98
Morre M, Bachy A, Keane PE (1985) Differential CNS binding of benzodiazepines. Supplément Actualités Médicales Internationales – Psychiatrie 2:28–32
Morton S, Lader MH (1989) Studies with alpidem in normal volunteers and anxious patients. Pharmacopsychiatry 23:120–123
Norton GR, Schaefer E, Cox BJ, Dorward J, Wozney K (1988) Selective memory effects in non-clinical panickers. J Anxiety Disorders 2:169–177
Nunn JD, Stevenson RJ, Whalan G (1984) Selective memory effects in agoraphobic patients. Br J Clin Psychol 23:195–201
O'Boyle C, Lambe R, Darragh A, Taffe W, Brick I, Kenny M (1983) RO 15–1788 antagonizes the effects of diazepam in man without affecting its bioavailability. Br J Anaeth 55:349–355
Pandit SK, Dundee JW (1970) Preoperative amnesia: the incidence following the IM injection of commonly used premedicants. Anaesthesia 25:493–499
Parkin J, Streete S (1988) Implicit and explicit memory in young children and adults. Br J Psychol 79:361–367
Shimamura AP (1986) Priming effects in amnesia: evidence for a dissociable memory function. Q J Exp Psychol 38A:619–644
Smirne S, Ferini-Strambi L, Pirola R, Tancredi O, Franceschi M, Pinto P, Bareggi SR (1989) Effects of flumitraxepam on cognitive functions. Psychopharmacology 98:251–256
Tulving E (1985) How many memory systems are there? Am Psychol 40:385–398
Tulving E, Schacter DL (1990) Priming and human memory systems. Science 247:301–306
Wardle J (1990) Behaviour therapy and benzodiazepines: allies or antagonists? Br J Psychiatry 15:163–168
Weingartner H (1985) Models of memory dysfunctions. Ann Acad Sci 444:359–369
Weingartner H, Wolkowitz OM (1988) Pharmacological strategies for exploring psychobiologically distinct cognitive systems. Psychopharmacology [suppl]:S125
Williams JMG, Watts FN, MacLeod C, Mathews A (1988) Cognitive psychology and the emotional disorders. Wiley, Chichester
Yerkes RM, Dodson JD (1908) The relation of strength of stimulus to rapidity of habit formation. J Comp Neurol Psychol 18:459–482