The Effects of Benzodiazepines on Cognition

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Initially thought to be virtually free of negative effects, benzodiazepines are now known to carry risks of dependence, withdrawal, and negative side effects. Among the most controversial of these side effects are cognitive effects. Long-term treatment with benzodiazepines has been described as causing impairment in several cognitive domains, such as visuospatial ability, speed of processing, and verbal learning. Conversely, long-term benzodiazepine use has also been described as causing no chronic cognitive impairment, with any cognitive dysfunction in patients ascribed to sedation or inattention or considered temporary and associated with peak plasma levels. Complicating the issue are whether anxiety disorders themselves are associated with cognitive deficits and the extent to which patients are aware of their own cognitive problems. In an attempt to settle this debate, meta-analyses of peer-reviewed studies were conducted and found that cognitive dysfunction did in fact occur in patients treated long term with benzodiazepines, and although cognitive dysfunction improved after benzodiazepines were withdrawn, patients did not return to levels of functioning that matched benzodiazepine-free controls. Neuroimaging studies have found transient changes in the brain after benzodiazepine administration but no brain abnormalities in patients treated long term with benzodiazepines. Such findings suggest that patients should be advised of potential cognitive effects when treated long term with benzodiazepines, although they should also be informed that the impact of such effects may be insignificant in the daily functioning of most patients.

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The unique trajectory of benzodiazepines as a psychotropic class began with their improved safety profile relative to previous central nervous system depressants and the resulting widespread prescription by primary care physicians. However, physicians soon discovered through clinical experience the potential risks of dependence, withdrawal, and negative side effects, raising questions about the risk:benefit ratio of benzodiazepines. Research trends have paralleled these shifts in attitude toward benzodiazepines. After the introduction of benzodiazepines in the 1960s, early research of these agents focused on the anxiolytic effects of low-dose, short-term benzodiazepine administration, but by the 1980s, the focus had turned to the potential for tolerance and withdrawal in agents of this class. Much of benzodiazepine research in the 1990s was aimed at defining the specific effects of long-term use and examining the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex for ways to isolate benzodiazepine effects. Most recently, research has examined alternatives to benzodiazepines for the treatment of anxiety and sought a more comprehensive understanding of the variety of receptors involved in anxiety.

My interest in research concerning the cognitive effects of benzodiazepines was piqued when I treated a patient who was admitted to Massachusetts General Hospital after overdosing with the benzodiazepine lorazepam. (For the case report, see Table 1.[1]) Neuropsychiatric testing of this patient indicated a low IQ score that appeared incongruous with someone who had practiced law for several years. Prior to seeing this patient, I had met many patients who chronically took benzodiazepines, and I was aware of possible problems with withdrawal and tolerance but did not know that cognitive effects were also a possible, albeit controversial, consequence of long-term benzodiazepine use. This article presents my review of the literature on this issue.

ACUTE COGNITIVE EFFECTS OF BENZODIAZEPINES

Acute benzodiazepine administration has been known to produce sedation, drowsiness, psychomotor slowing, anterograde amnesia, and difficulties learning new material.[2,3] Early descriptions called the memory effects "traveler's amnesia," because normal subjects who took benzodiazepines were able to perform old tasks as usual (such as walking through an airport) but were unable to recall specific details that would have required the storage

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Table 1. Case Report of Patient With Cognitive Deficits Attributed to Benzodiazepines[a]

Ms. A was admitted to the Massachusetts General Hospital psychiatric unit after her family found her heavily sedated from having taken 18 mg of lorazepam. She was a white, middle-aged, divorced mother and lawyer who had been profoundly depressed since the loss of her job 2 months earlier. Her family and her new psychiatrist were afraid that this was a suicide attempt, but Ms. A insisted she was just trying to sleep, so every time she roused she took more lorazepam.

A history revealed near lifelong symptoms of anxiety, characterized primarily by an overarching feeling of doom and certainty that the worst was about to happen. As a child, she had loved flying, but after losing her mother in a plane accident and experiencing a later rough flight of her own, she developed a profound phobia of flying. At the same time, her career required that she make frequent short flights, often leaving and returning the same day. It was during this period that she developed the strategy of having 2 drinks and taking several lorazepam tablets before flying.

The benzodiazepine was prescribed by her primary care physician; however, she had begun seeing a psychiatrist 5 years prior during her marital trouble and had had brief trials of both antidepressants and mood stabilizers. At the time of admission, she was taking lorazepam, typically 5 mg, for sleep and flying. She denied increasing the dosage or using the lorazepam other than as prescribed until the presenting events. She had, in fact, recently switched psychiatrists and was attempting to taper her lorazepam use. She currently had prescriptions for 10 mg of zolpidem h.s. and 4 mg of lorazepam h.s.

Her speech was slightly slurred on admission. She was irritable but cooperative. Within 1 day of hospitalization, she was more organized and euthymic, showing no symptoms or signs of withdrawal while taking 3.5 mg of lorazepam and 10 mg of zolpidem. She began taking a selective serotonin reuptake inhibitor, and her dose of lorazepam was tapered to 3 mg with a plan to continue a slow taper to discontinuation. She was educated about cognitive-behavioral therapy (CBT), which she said had previously been recommended by an anxiety disorders clinic.

Basic neuropsychiatric testing showed a surprisingly low IQ score that did not correlate with that of a lawyer. The testing psychologist suggested that Ms. A's alcohol and benzodiazepine use had likely contributed to this cognitive inefficiency, which may interfere with future treatment with CBT. Ms. A and her family adamantly denied alcohol abuse, saying that except for flights, she drank only socially and then rarely more than 2 drinks. Magnetic resonance imaging showed no brain atrophy but did reveal a pituitary microadenoma, which endocrinologists began to treat.

[a]Reprinted with permission from Stewart.[1]

of new information as it occurred (such as details of events that took place en route).[3] It has been argued that such memory loss can be attributed to the sedative effects that impair attention and therefore memory.[3] However, different rates of tolerance to sedation versus amnesia, as well as different rates of reversal of the 2 effects in the presence of the benzodiazepine antagonist flumazenil, suggest distinct phenomena, despite the fact that sedation and amnesia are mediated by the same GABA-benzodiazepine receptor subunit.[3]

CHRONIC COGNITIVE EFFECTS OF BENZODIAZEPINES

Unfortunately, anxiety disorders are frequently chronic, mandating an understanding of the potential consequences of long-term benzodiazepine use. Many of the acute benzodiazepine effects do not appear to be problematic for patients taking benzodiazepines long term.[4,5] After reviewing numerous studies using various benzodiazepines and experimental paradigms, Buffett-Jerrott and Stewart[4] observed that patients are likely to develop a tolerance to sedation and impaired attention. Lucki et al.[5] found similar results in their study of patients who were taking benzodiazepines long term (average length 5 years), and the authors offered that although tolerance may develop to sedation and psychomotor effects, the desired anxiolysis persists. The literature is divided, however, on the persistence of cognitive effects in patients taking benzodiazepines long term.

Does Long-Term Benzodiazepine Treatment Impair Cognition?

Among the cognitive dysfunctions that have been reported in patients taking benzodiazepines long term are impaired visuospatial and visuomotor abilities[6,7]; decreased IQ, motor coordination, psychomotor speed, speed of information processing, verbal learning, and concentration[2,6–9]; and delayed response time.[9] Chronic effects of rebound anxiety, psychic drug dependence, and an altered perception of the self, environment, and relationships have also been described.[10] Of these possible cognitive effects, visuospatial impairments have been those most specifically linked to long-term use.[9] Populations proposed to be at high risk for cognitive changes include patients requiring high doses of benzodiazepines, male patients, elderly patients, and patients with concurrent drug and alcohol use or psychotropic medications with anticholinergic properties.[3,9]

Alternatively, long-term benzodiazepine use has been reported as being unassociated with cognitive dysfunction. Specifically, psychomotor function, motor speed, sustained attention, and verbal memory did not differ significantly between patients who took benzodiazepines long term and patients who were drug-free or did not take benzodiazepines long term.[5] Often, even when cognitive effects have been observed in patients taking benzodiazepines, the effects are attributed to sedation or impaired attention[4]; additionally, several studies report memory changes only when benzodiazepines have reached their peak plasma level, suggesting that specific cognitive changes are temporary and linked to time since last dose.[4] It has also been suggested that some benzodiazepines may have less effect on memory than others. For example, implicit memory (i.e., long-term, unconscious memory requiring previous experience to perform a task) has been reported to be impaired by lorazepam but not by oxazepam and diazepam.[4]

Complicating the issue of the cognitive effects of long-term benzodiazepine treatment are cognitive changes associated with anxiety itself and patients' lack of awareness

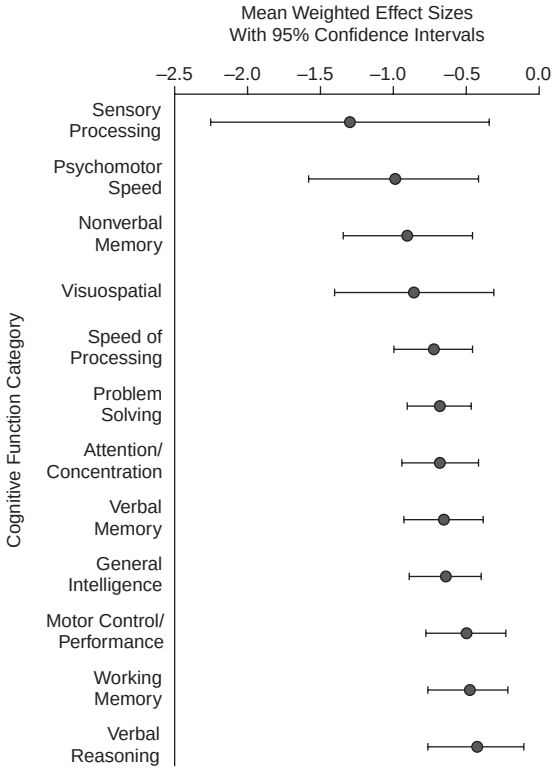
of their own possible cognitive dysfunction. Anxiety disorders have been shown to impair attention and concentration,[11] so arguably relief of anxiety may improve cognition. However, benzodiazepine-free subjects with anxiety disorders have performed at the same level as controls without anxiety disorders in measures of spatial, language, and memory functions.[8] Therefore, debate remains as to whether or at what level anxiety impairs cognitive performance. Research also indicates that patients using benzodiazepines are unaware of or underestimate their memory deficits.[3,4] It is unclear whether patients' inability to identify memory impairment is because they are unaware of their forgetfulness or because they deem what they cannot remember to be insignificant. It may be that many laboratory measures of cognitive function do not accurately assess the functional memory demands of daily life.[3,4]

To address the diversity of results regarding the cognitive effects of long-term benzodiazepine treatment, Barker and colleagues[9,12] recently designed 2 meta-analyses of literature published between 1980 and 2000 to determine whether there is a significant presence of cognitive decline with long-term benzodiazepine use[9] and, if so, whether cognitive decline is reversible after withdrawal of benzodiazepines.[12] In their introduction to the first meta-analysis,[9] the authors acknowledged the small number of studies and addressed the limitations of comparing studies with different methodologies. The most obvious problems in comparing studies include variable definitions of long-term use with a wide range of doses and duration of use represented, poorly defined coexisting drug and alcohol use, and the heterogeneity of psychiatric diagnoses in both subjects and controls. Also, some studies do not define the length of time from benzodiazepine dose to cognitive testing, which may create problems differentiating acute from chronic effects.

Among these limitations, heterogeneity of psychiatric diagnosis is perhaps the most significant in evaluating the meaning of results. Subjects are often selected for benzodiazepine use, not necessarily for psychiatric diagnosis, and since benzodiazepines are prescribed for a wide variety of conditions, it may be that patients with different disorders will also vary with regard to side effects and risk:benefit ratio. Furthermore, Barker et al.[9] noted that subjects are frequently recruited from withdrawal clinics, which may create a sampling bias because such subjects typically have heightened concern about problems attributable to benzodiazepine use.

For the first meta-analysis,[9] English-language, peer-reviewed studies were collected from computerized databases and then selected for inclusion if they had a control group or within-subjects design, produced original calculable results, and reported on subjects with benzodiazepine use of at least 1 year. The final analysis included 13 studies. The range in duration of benzodiazepine use among the studies was between 1 and 34 years, with a mean duration of use of 9.9 years. The average dose was equivalent to a 17.2-mg/day dose of diazepam. Such findings emphasize that many people are taking benzodiazepines for substantial lengths of time and at substantial doses.

Figure 1. Cognitive Function in Patients Taking Benzodiazepines Long Term[a]

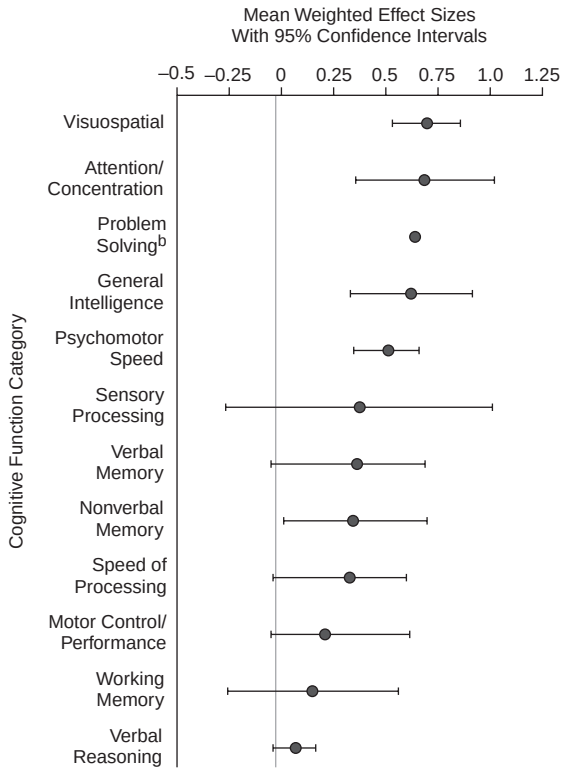


[a]Reprinted with permission from Barker et al.[9] A negative effect size indicates patients performed worse than controls.

The authors[9] divided the measured cognitive functions into 12 domains suggested by a neuropsychiatric textbook as follows: visuospatial, attention/concentration, problem solving, general intelligence, psychomotor speed, sensory processing, verbal memory, nonverbal memory, speed of processing, motor control/performance, working memory, and verbal reasoning. Although many of the studies used several batteries to measure a certain cognitive function, each study was allowed to contribute only 1 averaged and weighted effect size per cognitive domain.

The results of the meta-analysis[9] suggested significant cognitive decline in all 12 domains (Figure 1). Several variables in attributes of studies, subjects, tests used, and results presented were recorded and evaluated for additional trends. The authors offered these as trends of interest but suggested they be cautiously interpreted: a correlation between time since last dose and psychomotor speed, greater effect size reported in studies performed after 1994, and greater degree of cognitive decline in studies in which > 40% of the patients were male.

Figure 2. Cognitive Function After Withdrawal From Benzodiazepines in Patients Previously Taking Benzodiazepines Long Term[a]



[a]Reprinted with permission from Barker et al.[12]
[b]The effect size for problem solving could not be calculated because only 1 test in this category was used.

The Barker et al. group followed up their first meta-analysis by addressing a question that naturally ensues: if long-term benzodiazepine use affects cognition, are these cognitive changes reversible upon withdrawal of benzodiazepines? In their introduction to the second meta-analysis,[12] they cited conflicting reports in the literature concerning change in cognitive function after benzodiazepine withdrawal, including descriptions of rapid recovery of function,[13] recovery that remained worse than the control group,[7] improvement in specific tasks,[14] and impairments in cognitive function up to 6 years after withdrawal.[15]

Using the same set of studies used in the first meta-analysis[9] except for 1 that did not adequately present follow-up data, Barker et al. again assembled an averaged and weighted effect size to represent studies' results as they fit into the same 12 areas of cognitive function.[12] The results of the second meta-analysis are 2-fold. The accumulated data suggested that there is improvement in all areas of cognitive function after benzodiazepine withdrawal at follow-up testing (Figure 2). However, the data also indicated that improvement never rises to the level of cognitive performance of non–benzodiazepine-using controls. The authors acknowledged that the data from the meta-analysis can be used to support these conclusions only up to 6 months after benzodiazepine discontinuation (the average length of postwithdrawal assessment was 3 months) and speculated that some cognitive effects might take longer than 6 months to improve. The group stated it was unlikely that ongoing deterioration in function was due to a return of or an increase in anxiety symptoms after withdrawal because they observed that, of the 10 studies that recorded outcomes from mood and anxiety scales, 7 studies reported that scores remained stable or improved when scores from prewithdrawal and postwithdrawal were compared. Barker et al. made the final recommendation that because of potentially permanent cognitive deficits or cognitive deficits that may take months to improve, patients should be informed of the possible long-term cognitive changes prior to initiation of benzodiazepine treatment.

Are Benzodiazepines Associated With Physiologic Changes in the Brain?

Given the degree of cognitive changes reported with benzodiazepine treatment, several researchers have proposed that anatomic or physiologic changes in the brain should be demonstrable in patients with cognitive changes due to benzodiazepine use. Positron emission tomography research is sparse but thus far seems to indicate that changes are measurable only during benzodiazepine use and then disappear shortly after dose administration without having a measurable effect on function. For example, although cerebral blood flow to the prefrontal cortex was found to be lower in the presence of midazolam, there was no difference in cerebral blood flow to functioning regions of the brain used during memory tasks between unmedicated controls and patients who took midazolam.[16] Therefore, despite benzodiazepine-induced changes in the prefrontal cortex, the brain was still able to perform cognitive functions. Computed tomographic (CT) scans of patients taking benzodiazepines long term were compared with those of age- and sex-matched controls by Busto et al.,[17] but the authors found no difference in brain atrophy in the 2 groups and concluded that long-term benzodiazepine use does not appear to be associated with brain abnormalities as assessed by CT.

CONCLUSION

Although controversy exists, much of the literature suggests that cognitive dysfunction is an effect of long-term benzodiazepine treatment.[2,6–9] After withdrawal of benzodiazepines, patients recover in many cognitive domains, but these patients often are still impaired when compared with control groups.[12] Thus, clinicians may find it necessary to advise patients of the potential for cognitive

effects of long-term treatment, especially since patients may experience cognitive impairment without realizing it. However, the clinical impact of cognitive changes may be insignificant in most patients in terms of daily functioning, as trial measures may not reflect actual cognitive needs for daily living. When considering long-term benzodiazepine treatment, as is the case with any treatment, potential side effects must be weighed against potential benefits.

Drug names: diazepam (Valium and others), flumazenil (Romazicon and others), lorazepam (Ativan and others), oxazepam (Serax and others), zolpidem (Ambien).

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

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