Benzodiazepine Use, Cognitive Impairment, and Cognitive-Behavioral Therapy for Anxiety Disorders: Issues in the Treatment of a Patient in Need

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Cognitive-behavioral therapy (CBT) is effective in the treatment of anxiety disorders when used in conjunction with benzodiazepine pharmacotherapy and when used as a monotherapy. Patients using CBT alone have dropout rates similar to or lower than those patients undergoing other forms of therapy, including benzodiazepines. CBT also works well with patients who do not respond adequately to pharmacotherapy. Combined CBT and benzodiazepine treatment has additive effects when compared with benzodiazepine monotherapy; however, patients receiving combined therapy who subsequently discontinue benzodiazepine treatment experience a loss of efficacy compared with CBT and placebo, perhaps due to fear extinction being context dependent. To avoid this loss of efficacy, CBT may be administered alone or as a bridge between benzodiazepine use and discontinuation during a medication taper. The case report upon which this supplement is based questions the value of CBT for patients experiencing cognitive impairment due to an anxiety disorder, benzodiazepine medication, substance abuse, or a combination of these factors. This article addresses this concern and asserts that CBT is a valuable treatment option in these cases. *(J Clin Psychiatry 2005;66(suppl 2):34–38)*

The case report[1] that motivated this supplement was noteworthy for raising questions about when cognitive-behavioral therapy (CBT) should be added to benzodiazepine treatment for an anxiety disorder in a patient with cognitive impairment. The case report raises questions about the impact of benzodiazepines on cognitive functioning, the impact of impaired cognitive functioning on CBT outcome, and issues concerning the interactions between CBT and benzodiazepines for both acute and longer term outcome. In this article, we address each of these issues and argue for a crucial role for CBT in the treatment of anxiety disorders, particularly in individuals who are being considered for medication discontinuation. In the following sections, our strategy is to consider current use patterns for benzodiazepine treatment for panic disorder, and then to consider the evidence for combined CBT and benzodiazepine use. For this discussion, we rely heavily on studies of panic disorder, both because of its potential relevance to the case presented and also because the panic disorder literature is particularly well-developed relative to the issues to be considered. Following general consideration of combined treatment, we then consider the evidence for and implications of cognitive impairment for an individual taking benzodiazepines for phobic anxiety.

BENZODIAZEPINE TREATMENT FOR ANXIETY DISORDERS

Results from the Harvard/Brown Anxiety Research Project (HARP),[2] a prospective, longitudinal study of anxiety disorders, indicate that benzodiazepines were the most common class of drugs used for panic disorder over the past decade (1989–2001). Sixty-four percent of patients reported receiving a benzodiazepine at intake, and 58% reported receiving a benzodiazepine at the 10-year follow-up. In contrast, rates of selective serotonin reuptake inhibitor (SSRI) usage lagged well behind at the 10-year follow-up (33%).

A previous HARP investigation by Mueller et al.[3] examined a total of 343 participants who at intake were taking benzodiazepines, 29% of whom had a past or current history of alcohol use disorder. Examination of daily dose or the supplemental (p.r.n.) use of benzodiazepines over

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the first 12 months of follow-up revealed no significant differences between participants with alcohol use disorder and those without alcohol use disorder, suggesting that for these patients there was no evidence for differential dose escalation. In a subsequent examination of 12 years of follow-up data in HARP patients with comorbid alcohol dependence and anxiety disorders, there was no relationship between the use of benzodiazepines and the occurrence of a new alcohol use disorder (T. Mueller, M.D.; M. E. Pagano, Ph.D.; B. F. Rodriguez, Ph.D.; et al., manuscript submitted). Additionally, there was no temporal relationship between the onset of a new alcohol use disorder and the use of benzodiazepines. Moreover, little evidence exists that the intensity (dose, duration) of benzodiazepine use is associated with the onset, recovery, or subsequent recurrence of alcohol use disorder.[4,5] These data suggest that the relative risk of benzodiazepine use as a predictor of the onset or subsequent course of an alcohol use disorder is minimal. Accordingly, the case[1] presented here appears to represent an atypical or limited-event outcome, rather than the expected outcome for benzodiazepine use for panic disorder.

COMBINED CBT AND BENZODIAZEPINE TREATMENT

Cognitive-behavioral therapy is both an effective alternative to benzodiazepine treatment and a useful adjunctive or replacement treatment for individuals who have failed to respond adequately to benzodiazepine medication. Large-scale studies and meta-analytic reviews[6–11] indicate that CBT is an effective and tolerable treatment for anxiety disorders, with dropout rates that tend to be equal to or below those for medication alternatives, including benzodiazepines. Also, among the few and generally small-scale studies[12–14] of patients with panic disorder who have been referred to CBT after failing to respond adequately to medications, there is every indication that CBT works well with these patients; however, this evidence is based on benzodiazepines used alone or in combination with SSRIs in a fixed-dose format, and there are some concerns that p.r.n. (as needed) benzodiazepine use may inhibit CBT outcome to a greater extent than regularly scheduled use.[15]

Positive open studies indicating benefit for CBT added to benzodiazepine join evidence from a large-scale, randomized trial[16] comparing the acute benefits of combined CBT and benzodiazepine treatment, relative to these treatments offered with placebo or relaxation training, respectively. Additive effects were evident for some measures for acute treatment, but subsequent discontinuation of the benzodiazepine treatment was associated with loss of efficacy of the combined condition relative to CBT plus placebo.

This apparent attenuation of CBT efficacy wrought by discontinued benzodiazepine treatment is worthy of further explanation, particularly in relation to evidence on the nature of exposure effects coming from the animal laboratory. Specifically, there is consistent evidence that extinction of conditioned fears (brought by repeated exposure to the feared stimulus in the absence of aversive outcomes) is dependent on the context of extinction.[17] For example, if a fear is conditioned (e.g., pairing of tone and shock so that the animal shows evidence of fear in response to the tone) in one context (Context A), and then is extinguished in a second context (Context B), then the degree of fear that is evoked by later exposure to the once-feared cue (the tone) is dependent on the context in which it appears; if retested in Context A, there is relatively greater return of fear behaviors than in Context B. There is also greater return of fear if an animal conditioned to fear in Context A, then extinguished in Context B, is then tested in a novel context (Context C). These general findings are reliable for a range of contexts including the nature of the testing room (e.g., type and smell of the testing apparatus), as well as recent events and the passage of time (for review see Bouton[17]).

There is also evidence that contexts include the internal state of the animal, including drug context. It is these results that are most relevant to the issue of benzodiazepine discontinuation following medication treatment. For example, in animals, Bouton et al.[18] evaluated the effects of changing internal contexts as manipulated by use of benzodiazepine or saline injections. As with the previous studies, there was a greater return of fear when context was shifted between extinction and later testing.

We have applied these findings to interpreting the loss of efficacy when patients who completed CBT on medication later discontinue their medication.[19,20] This effect is evident not only in the Marks et al.[16] trial of combination treatment with benzodiazepine medication, but also in the large multicenter trial[21] of the relative and combined efficacy of CBT and imipramine. In both trials, combined treatment had some advantages over either monotherapy alone, but when the medication was discontinued (when the internal context was shifted), learned safety was compromised in the patients who had received the combined treatment, to a level below that for CBT alone. Patients who had not taken then-discontinued medication did not undergo a shift in internal context, and their maintenance of treatment gains was correspondingly stronger. There is also some evidence that attributions about the treatment context may account for some of the disruptive effects of benzodiazepine discontinuation in the Marks et al. trial.[16] Basoglu and associates[22] examined the link between attribution and relapse by asking patients who had responded to treatment how much they attributed their gains to medication versus their own efforts. Patients who had attributed their improvement to medication reported significantly more withdrawal symptoms and showed greater loss of gains during the tapering-off and treatment-free

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period compared to those who had attributed their gains to their own efforts (see also Biondi and Picardi[23]).

These interpretations of multicenter trial data are also consistent with human studies that have manipulated internal context (drug) effects in a controlled fashion.[24] In an elegant study, Mystkowski et al.[24] investigated shifts in internal context brought by the double-blind ingestion of either caffeine or placebo in a sample of spider-phobic individuals undergoing exposure treatment. After extinction in either the caffeine or placebo condition, maintenance of fear reduction from exposure was assessed 1 week later under congruent (e.g., caffeine extinction and caffeine testing or placebo extinction and placebo testing) or incongruent (caffeine extinction and placebo testing or the reverse) conditions. Patients tested under the incongruent condition had greater return of fear.

Taken together, the body of evidence provided by animal studies,[17,18] limited study of internal context effects in phobic humans,[24] and the pattern of results of multicenter trials[16,21] are consistent in indicating a risk for relapse brought by combination treatment relative to CBT alone, under conditions of an internal context shift brought by the later discontinuation of pharmacotherapy.

Two immediate solutions to this risk of relapse are evident: (1) patients may continue pharmacotherapy chronically (trying to avoid a context shift) or (2) care can be taken to insure that CBT is used to "bridge the gap" across the internal context shift (that is, CBT would be applied during and after a taper in medication). Certainly, for the treatment of panic disorder, there is evidence for strong maintenance or extension of treatment gains when CBT is applied in a discontinuation program. By fading medication use in the context of CBT, patients are provided with successful experiences with exposure across internal contexts—the result is strong maintenance of treatment gains as evaluated in studies of both benzodiazepine[25–27] and SSRI[28,29] treatment. This method of fading medication use in the context of exposure is exactly the way some psychopharmacologists apply benzodiazepine treatment—as a temporary rather than a chronic approach to phobic avoidance. Benzodiazepines are prescribed for initial exposure attempts, but are faded over time, so that the patients achieve successful exposure during and after medication discontinuation. However, given evidence of strong acceptability and tolerability of CBT for large samples of anxiety patients,[6–11] it is not clear whether many patients truly "need" introduction of benzodiazepines in the first place.

In summary, studies of CBT for anxiety disorders, particularly panic disorder, provide evidence that CBT should be considered an efficacious strategy for an anxiety patient already taking benzodiazepines. CBT can be added with plans for continued benzodiazepine use; conversely, there is evidence that CBT can be used to provide patients with a long-lasting alternative to benzodiazepine use. These considerations are apt for general issues of combined CBT and benzodiazepine treatment, but what of concerns of the effects of memory impairment, potentially associated with benzodiazepine use?

BENZODIAZEPINES AND NEUROPSYCHOLOGICAL DYSFUNCTION

Transient effects following intake of a single dose of a benzodiazepine include increased sedation, impairments in reaction times and psychomotor skills that involve focused attention and visuomotor coordination, and impairment in some functions of working memory.[30,31] Perhaps one of the most consistently reported effects of a single dose intake of a benzodiazepine on memory is a dose-dependent transient impairment in the acquisition (learning) of new information presented after drug administration (for review see Curran[32]). Following intake, benzodiazepine-participants learn fewer words in tests presenting multiple learning trials than placebo participants.[30] Likewise, benzodiazepine-administered participants also have difficulties in free recall of information presented after drug administration upon short and long delays, or recognizing this information on recognition tests[31]; however, there is evidence that individuals develop some tolerance to the psychomotor, cognitive, and amnesic effects of benzodiazepines after several weeks of intake.[31] Studies of individuals with long-term benzodiazepine use for months or years suggest that full tolerance to the amnesic effects of benzodiazepine may not occur. For example, Curran and Birch[33] found impaired memory during and after 2 months of treatment with alprazolam, and residual impairments were still manifest several weeks after drug withdrawal. Consistent with this finding, Bergman et al.[34] and Tonne et al.[35] reported impairment in verbal or nonverbal learning and memory following chronic benzodiazepine use for several years. In addition, longer intake at higher dosages appears to be associated with more difficulties in verbal learning.[36] Studies investigating benzodiazepine effects have failed to exclude patients with serious psychiatric conditions, in particular anxiety disorders for which benzodiazepines are often prescribed. Memory impairment observed after chronic benzodiazepine treatment may reflect effects of anxiety disorders themselves rather than effects of chronic benzodiazepine treatment.

MEMORY IMPAIRMENT IN ANXIETY DISORDERS

Neuropsychological studies of panic disorder have provided mixed evidence for impairments in learning and memory. For example, Lucas et al.[37] found impaired verbal and nonverbal learning and memory in patients with panic disorder. Memory impairments remained statistically significant when effects of anxiolytic medications

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were statistically controlled. Asmundson et al.[38] showed that unmedicated, nondepressed patients with panic disorder exhibited difficulties in learning a 16-item shopping list over 5 learning trials presented in the California Verbal Learning Test, whereas Gladsjo et al.[39] failed to find evidence for neuropsychological impairment in patients with panic disorder. Recent findings by our group[40] suggest that impairments in learning and long-term memory in patients with panic disorder are associated with the disorder itself, rather than long-term benzodiazepine intake. That is, we compared groups of patients with panic disorder who had either taken benzodiazepines for several months or were medication free. Although verbal learning and memory were preserved in both patient groups, patients with panic disorder were impaired in nonverbal learning and memory. However, benzodiazepine-medicated patients did not differ from medication-free patients with panic disorder.

In summary, the available evidence on the nature of memory functioning in benzodiazepines in individuals with anxiety disorders does not provide a firm answer on whether the anxiolytic actions of benzodiazepines provide a balance to the potential amnesic actions of benzodiazepines. What is certain is that patients taking benzodiazepines chronically do effectively learn CBT and achieve treatment benefit. However, these findings do not address whether CBT efficacy is seriously compromised by cognitive impairment. To address this question, it is helpful to consider research on substance use disorders, where this issue has been more consistently investigated.

SUBSTANCE ABUSE, COGNITIVE DYSFUNCTION, AND PSYCHOSOCIAL TREATMENT OUTCOME

Examination of the substance use literature, particularly for alcohol abuse disorders, is especially relevant to the case[1] presented for this series. In the case series, alcohol use in conjunction with benzodiazepine use, and cognitive impairment, were essential features. The alcohol literature provides consistent evidence of neurocognitive impairments from alcohol abuse (for review see Bates et al.[41]). However, does this impairment translate to poorer treatment outcome?

Despite clear expectations for compromised treatment effects, research on this topic has been limited and characterized by inconsistent findings.[41] There are some indications of poorer response to treatment for patients with worse cognitive impairment, but other studies[41,42] do not provide consistent findings. Some of this inconsistency may be due to heterogeneity of treatments being investigated. For example, among structured cognitive-behavioral treatments, as compared to supportive or motivational treatments, select learning or memory deficits may have a clearer role in modulating treatment. In addition, treatment engagement does appear to have a more reliable link to cognitive impairment as assessed by treatment dropout[42–44] and poorer motivation to change substance-use patterns.[45,46] Accordingly, given findings of neuropsychological impairment in the patient presented,[1] treatment with CBT may need to attend particularly to motivational factors and the meaning of poor initial treatment adherence, should it occur.[44]

OVERALL SUMMARY AND CONCLUSIONS

In this article, we considered different perspectives on whether CBT is likely to be successful in a patient taking benzodiazepines and suffering from cognitive impairment. By reviewing the more general combination treatment literature, we found evidence for the benefit of CBT when added to chronic benzodiazepine treatment for panic disorder. We also discussed that CBT may be particularly important for patients for whom benzodiazepine discontinuation may be indicated; patients with panic disorder are able to maintain or extend their treatment gains when benzodiazepines are discontinued in the context of CBT. Moreover, given recent research[47,48] on the extension of treatment strategies from CBT for panic disorder to substance use disorders, this strategy is particularly encouraged. Finally, we provided evidence that findings of cognitive impairment are no reason to refrain from a CBT referral, although there is evidence that treatment adherence may require additional attention.

Drug names: alprazolam (Xanax and others), imipramine (Tofranil and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, imipramine is not approved by the U.S. Food and Drug Administration for the treatment of panic disorder.

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