

Benzodiazepines for anxious depression

These agents should be more frequently considered as monotherapy for this indication

Benzodiazepines' potential antidepressant properties and their role in the treatment of depression were fairly extensively examined during the 1980s and early 1990s. There were various reasons for this investigation—from the adverse effects of available antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors) to the delay of action of the existing antidepressants and treatment resistance of a significant portion of depressed patients. Benzodiazepines had already been used in the treatment of depressive disorders for decades, but not as monotherapy or main treatment agents, but rather in combination with existing antidepressants to alleviate initial or persistent anxiety, and to help with insomnia. Some authors¹ felt that specific benzodiazepines, such as alprazolam, were effective in mild and moderate depression, although not as effective as TCAs for patients with endogenous or melancholic depression. Others² proposed that benzodiazepines, particularly alprazolam, may be a useful treatment option for patients for whom antidepressants are contraindicated, poorly tolerated, or ineffective. Petty et al² suggested that the antidepressant efficacy of benzodiazepines was consistent with the then-entertained γ -aminobutyric acid theory of depression.

A shift from benzodiazepines to antidepressants

The evidence for using benzodiazepines in anxious depression was based on results of several studies, but it has not



AYELET-KESHET/SHUTTERSTOCK

Richard Balon, MD

Professor of Psychiatry and Anesthesiology
 Departments of Psychiatry and Behavioral Neurosciences
 and Anesthesiology
 Wayne State University School of Medicine
 Detroit, Michigan

Disclosure

The author reports no financial relationships with any company whose products are mentioned in this article, or with manufacturers of competing products.



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When abuse of benzodiazepines occurs, it is almost always in the context of abusing other substances

been adequately analyzed, summarized, and promoted. Then, after the arrival of the selective serotonin reuptake inhibitors (SSRIs) (fluoxetine arrived in the United States in 1987, and paroxetine and sertraline arrived in 1992), interest in benzodiazepines gradually waned. Within a few years, the SSRIs were also approved for various anxiety disorders. The SSRIs were heavily promoted not only for the treatment of depressive disorders, but also anxiety disorders, and were touted as well-tolerated medications without abuse potential. Benzodiazepines, on the other hand, were frequently described as less effective and having a substantial abuse potential.

Looking back, these claims were not properly substantiated. Berney et al³ concluded in a systematic review that comparative data of a high level of proof for using newer antidepressants in anxiety disorders rather than benzodiazepines were not available. Then, 5 years later, Offidani et al⁴ demonstrated in a systematic review and meta-analysis that benzodiazepines were more effective and better tolerated in the treatment of various anxiety disorders than TCAs. In addition, in a few studies comparing benzodiazepines with newer antidepressants such as paroxetine and venlafaxine, benzodiazepines were either comparable or showed greater improvement and fewer adverse effects than these antidepressants. Similarly to Berney et al,³ Offidani et al⁴ concluded that the change in the prescribing pattern favoring newer antidepressants over benzodiazepines for the treatment of anxiety disorders occurred without supporting evidence.

As far as abuse potential, the American Psychiatric Association Task Force on Benzodiazepine Dependency concluded that benzodiazepines do not strongly reinforce their own use and are not widely abused.⁵ When abuse occurs, it is almost always in the context of abusing other substances. The Task Force also noted that physiological dependence develops when benzodiazepines are used chronically; dependence being defined mostly in terms of symptoms of discontinuance.⁵ Thus, benzodiazepines need to be used appropriately,

not in extremely high doses, and under medical supervision.

Nevertheless, the judgment, right or wrong, was out—benzodiazepines were deemed problematic and to be avoided. This has become, unfortunately, a pattern of many prescribing psychiatrists' practice.

What about benzodiazepines for anxious depression?

Recently Benasi et al⁶ filled the void by investigating data from studies using benzodiazepines as monotherapy in depressive disorders (I was one of the co-authors of this study). They conducted a systematic review of 38 published randomized controlled trials that used benzodiazepines as a monotherapy vs placebo, antidepressants, or both. Patients in these trials were primarily diagnosed with depressive disorder or anxious depression. The majority of these studies used alprazolam as the benzodiazepine (other benzodiazepines used were adinazolam, bromazepam, chlordiazepoxide, and lorazepam) and imipramine or amitriptyline as the antidepressant comparator (other antidepressants used were desipramine, dothiepin, doxepin, and only one newer antidepressant, fluvoxamine, in one study). There was a lack of significant differences in response rate between benzodiazepines and placebo, and between benzodiazepines and TCAs.

In more than half of the studies comparing benzodiazepines with TCAs and/or placebo, benzodiazepines were significantly more effective than placebo and as effective as TCAs. In 11 studies, TCAs were better than benzodiazepines, while benzodiazepines were better than TCAs in one study. In 12 studies, benzodiazepines were associated with a faster onset of action than TCAs. Adverse effects occurred more frequently with TCAs, with the exception of drowsiness and cognitive impairment, which occurred more frequently with benzodiazepines. The findings of the meta-analysis (22 studies) confirmed the low response of anxious depression to psychotropic medications, whether TCAs or benzodiazepines. There was no demonstrated superiority of antidepressants over benzodiazepines for anxious depression. Thus, clearly, benzodiazepines



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are a bona fide therapeutic option for anxious depression and so far, there is no indication that antidepressants are preferable for this indication.

However, it is important to note that there are almost no studies comparing benzodiazepines to newer antidepressants for anxious depression. One double-blind 6-week study of 112 patients⁷ compared fluvoxamine with lorazepam for mixed anxiety and depression in general practice. There were no significant differences between treatments at any point in the study. Lorazepam produced more sedation, while fluvoxamine produced more nausea and vomiting.

We clearly need randomized controlled trials comparing benzodiazepines with newer antidepressants in anxious depression. However, as in the case with anxiety disorders, these types of trials are strikingly missing.

Any clinical wisdom?

Anxiety could be a serious clinical problem in the treatment of patients with depressive disorder(s). We have not always paid

enough attention to anxiety and related issues in depressed patients. Interestingly, anxiety has not been listed among symptoms of major depression disorder (MDD) in several editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Only and finally did DSM-5⁸ add a specifier “with anxious distress” for both MDD and persistent depressive disorder (dysthymia), although this specifier still avoids the word “anxiety” in the description of its symptomatology.

It is difficult to disentangle whether the anxiety is part of depressive disorder symptomatology or whether it is a comorbid anxiety disorder. As I noted in a previous article,⁹ psychiatric comorbidity is a confusing phenomenon. Nevertheless, anxiety and depression are highly comorbid or co-symptomatologic. In a study by Kessler et al,¹⁰ 45.7% of survey responders with lifetime MDD had ≥ 1 lifetime anxiety disorder. Similarly, in a STAR*D study,¹¹ in Level 1, 53.2% of patients had anxious depression.

Kessler et al¹⁰ raised an interesting question about the importance of temporally

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A meta-analysis found that for treating anxious depression, antidepressants were not superior to benzodiazepines



Benzodiazepines for depression

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Benzodiazepines need to be prescribed appropriately, carefully weighing their risks and benefits

primary anxiety disorders as risk markers vs causal risk factors for the onset and persistence of subsequent MDD, including the possibility that anxiety disorders might primarily be risk markers for MDD onset and causal risk factors for MDD persistence. As is well-known, mood disorders should be treated as soon as possible after they are diagnosed, and should be treated vigorously, addressing the major symptomatology.

These findings emphasize the need to pay more attention to anxiety in depressed patients (especially those newly diagnosed) and for forceful treatment of anxious depression. Importantly, in the STAR*D study,¹¹ remission in anxious Level 1 (treated with citalopram) depressed patients was significantly less likely and took longer to occur than in patients with nonanxious depression. In addition, ratings of adverse effects frequency, intensity, and burden, as well as the number of serious adverse events, were significantly greater in the anxious depression group. Similarly, in Level 2 (either switched to bupropion, sertraline or venlafaxine, or citalopram augmented with bupropion or buspirone), patients with anxious depression fared significantly worse in both the switching and augmentation options. One wonders if Level 1 patients treated with benzodiazepines, and Level 2 patients switched to benzodiazepines or offered augmentation with them would not have fared better, especially in view of the fact that many old and new antidepressants have significant adverse effects and are difficult to discontinue due to withdrawal symptoms such as dizziness, vertigo, and, in case of newer antidepressants, brain “zaps.” Benzodiazepines certainly have serious withdrawal symptoms, including anxiety, rebound insomnia, and withdrawal seizures, especially when discontinued abruptly and when the dose was high. Thus, as is the case for many other medications (eg, steroids, anticoagulants, and some antidepressants), benzodiazepines must be tapered carefully in order to avoid discontinuance signs and symptoms. Because

benzodiazepines have been involved in nearly one-third of overdose-related deaths (either separately or in combination with opioids), and the FDA strongly warns against co-prescribing benzodiazepines and opioids, they need to be prescribed appropriately, carefully weighing their risks and benefits.¹²

Because the analysis by Benasi et al⁶ demonstrated that benzodiazepines seem comparably effective as antidepressants in anxious depression, we should be considering using benzodiazepines as monotherapy for this indication more frequently and vigorously, considering their similar efficacy, faster onset of action, and better tolerability, while also considering their risks. Clinicians use them in combinations anyway. We also need rigorous trials comparing benzodiazepines with newer antidepressants for anxious depression.

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