A recent systematic review and meta-analysis that compared benzodiazepines with antidepressants for anxiety disorders has triggered a debate among clinicians about first-line treatments, efficacy for specific disorders, and adverse effects.

Offidani and colleagues\(^1\) gathered data through 2012 on published, controlled, and direct comparisons between benzodiazepines and antidepressants for anxiety disorders but were hindered, they said, by a “paucity of studies.” Their review encompassed 22 studies, 18 of which compared TCAs, such as amitriptyline, clomipramine, or imipramine, with benzodiazepines. Of the remaining studies, 3 compared SSRIs or SNRIs with benzodiazepines and 1 compared the MAOI phenelzine with benzodiazepines. Eleven studies in the meta-analysis compared a benzodiazepine with a TCA for the treatment of panic disorder with or without agoraphobia.

While there has been a shift in recent years toward using such newer antidepressants as SSRIs and SNRIs as first-line treatments for anxiety disorders instead of benzodiazepines, Giovanni Andrea Fava, MD, Clinical Professor of Psychiatry at the State University of New York at Buffalo and one of the review’s coauthors, questioned whether the shift is warranted. “There is no evidence to suggest that antidepressant drugs are more effective than benzodiazepines in anxiety disorders,” he said. “Certainly, benzodiazepines have fewer side effects.”

In their review, the authors cited results for various anxiety disorders. “In mixed anxiety, GAD [generalized anxiety disorder], and social phobia, a superior efficacy of TCAs did not clearly emerge,” they said. They acknowledged that studies “with mixed anxiety were difficult to evaluate because of the heterogeneous features of the samples and the confounding effects of depressive symptoms.” The meta-analysis of treatments for panic disorder showed “less efficacy” and tolerability of TCAs than benzodiazepines, according to the review authors.

In trials that compared benzodiazepines with the newer antidepressants, the benzodiazepines “resulted in comparable or greater improvements and fewer adverse events in patients suffering from GAD or panic disorder,” Offidani and colleagues added. Hackett and colleagues\(^2\) compared diazepam and venlafaxine extended-release in 540 patients with GAD. Results showed no significant differences in response rates between groups, but discontinuations and adverse effects were more frequent in patients treated with venlafaxine.

Feltner and colleagues\(^3\) compared lorazepam, paroxetine, and placebo for treatment of patients with GAD. “Both active treatments were effective in reducing anxiety-related psychiatric symptoms, while somatic features improved significantly only in patients taking lorazepam.”

Nardi and colleagues\(^4\) conducted a randomized, open-label, naturalistic 8-week study to compare the efficacy and safety of treatment with clonazepam and paroxetine in patients with panic disorder with or without agoraphobia. Clonazepam resulted in fewer weekly panic attacks at week 4 and greater clinical improvements at week 8. Anxiety severity was significantly reduced with clonazepam at weeks 1 and 2, with no difference in panic disorder severity. Patients treated with clonazepam had fewer adverse events than patients treated with paroxetine. The most common adverse effects were drowsiness/fatigue (57%), memory/concentration difficulties (24%), and sexual dysfunction (11%) in the clonazepam group and drowsiness/fatigue (81%), sexual dysfunction (70%), and nausea/vomiting (61%) in the paroxetine group.

Offidani and colleagues also cited a long-term follow-up study by Nardi and colleagues\(^5\) that compared the efficacy and safety of clonazepam and paroxetine over 3 years of treatment. Long-term treatment with clonazepam led to a small but significantly better Clinical Global Impression of Improvement rating than treatment with paroxetine. Both treatments similarly reduced the number of panic attacks and severity of anxiety. Patients treated with clonazepam had...
significantly fewer adverse events than those treated with paroxetine (28.9% vs 70.6%; P < .001). On the basis of their systematic review and meta-analysis, Offidani and colleagues concluded that the change in the prescribing pattern that favors newer antidepressants over benzodiazepines in the treatment of anxiety disorders “has occurred without supporting evidence.”

Fava, who is also Professor of Clinical Psychology at the University of Bologna in Italy, believes the shift to the newer antidepressants was for “purely commercial reasons.” He told Psychiatric Times, “The shift from benzodiazepines to antidepressants is one of the most spectacular achievements of propaganda in psychiatry. . . . The use of antipsychotics for anxiety disorders follows the same lines.”

In an editorial citing the systematic review, Karl Rickels, MD,6 founder of the Mood and Anxiety Disorders Section at the University of Pennsylvania and Stuart and Emily B. H. Mudd Professor of Behavior and Reproduction in Psychiatry, called for more comparison studies and contended that “no evidence for the superiority of the newer antidepressants over benzodiazepines, in terms of both efficacy and safety, exists for either short-term or long-term treatment.”

Peter Roy-Byrne, MD, Professor of Psychiatry at the University of Washington and one of the contributors to the American Psychiatric Association’s Practice Guideline for the Treatment of Panic Disorder (2009), criticized the study by Offidani and colleagues as being of limited value for informing clinical practice today. “I think it is a flawed study, for the simple reason that it compares benzodiazepines with older antidepressants.”

The older antidepressants, he explained, have a greater adverse effect burden than the newer ones, so it is much easier to show some advantage for benzodiazepines in comparison studies. In addition, TCAs are now rarely used for anxiety disorders.

**First-line treatment?**

Fava and Roy-Byrne disagreed about using benzodiazepines as first-line treatment for anxiety disorders. “Benzodiazepines should be considered first-line pharmacological treatment for all anxiety disorders with the possible exception of obsessive-compulsive disorder,” said Fava, adding that drugs generally should not be the first-line treatment for anxiety disorders, because psychotherapy is very effective.

“I don’t think anybody anymore realistically thinks benzodiazepines should be used as first-line [pharmacological] treatments,” Roy-Byrne countered. He also questioned the practice of using benzodiazepines to help reduce anxiety during the initial weeks of treatment with antidepressants when anxiolytic effects have yet to occur. “In my experience, except in rare cases, using low doses of antidepressants and being in contact with patients frequently enough to answer their questions and provide them reassurance is usually sufficient to help them get used to the antidepressant over time. It introduces more logistic complications to put them on a benzodiazepine and then to take them off of it six or eight weeks later.”

The most common use of benzodiazepines, Roy-Byrne said, is in combination with antidepressants for individuals who have had suboptimal responses to antidepressants. He uses benzodiazepines as “second-line” treatments for patients with anxiety disorders, but continues them for the long term only if he sees substantial clinical improvement. “Most of the time it is not worthwhile to use them to just take the edge off symptomatic distress,” he said, noting that behavioral treatment might be a better alternative.

While he prescribes benzodiazepines for anxiety disorders in some of his patients, Roy-Byrne said GAD is “the absolute worst anxiety disorder” for which to use benzodiazepines, because GAD is a difficult diagnosis to make and is often comorbid with other disorders. “Using benzodiazepines for PTSD over the long term is also likely to produce more harm than good, though very short-term use in recently traumatized patients is a sound practice.” He said that it is better to use benzodiazepines for panic disorder and social anxiety disorder, “because they are easier to diagnose and less likely to be confused with other disorders, such as personality disorder or a subacute alcohol problem.”

**Advantages and drawbacks**

Both Fava and Roy-Byrne were asked about the advantages and drawbacks of benzodiazepines for anxiety disorders. “Benzodiazepines are fast-acting and very well-tolerated drugs with few side effects and interactions with other medications. Their drawbacks are cognitive effects and dependence,” said Fava.

According to Roy-Byrne, the advantages of benzodiazepines “are that they are extremely potent and work very well. A disadvantage is that you can become physically dependent on them, although to be fair, there is also a withdrawal syndrome with antidepressants.” Other disadvantages include cognitive and psychomotor impairments, abuse potential, and most importantly, the possibility, not yet conclusively demonstrated, of a reduced response to CBT. Benzodiazepines tend to be anti-CBT
treatments.
“Whereas CBT is very good for anxiety because it toughens you up, improves your coping ability, and lets you become more resilient to stress, benzodiazepines do the exact opposite,” he said. “It has not been extensively investigated, but it is probably true that benzodiazepines may sometimes interfere with CBT programs. CBT requires some anxiety that individuals need to experience upon exposure to desensitize themselves over time. But if they take a potent anti-anxiety drug, they just won’t be anxious.”
“I agree that in some investigations, notably the London-Toronto study [by Nardi and colleagues5], use of benzodiazepines decreased the efficacy of CBT,” said Fava. The same effect is seen with antidepressants in panic disorder and social phobia.8,10 Furthermore, “long-term outcome studies of panic disorder treated by behavioral methods disclosed a detrimental effect of antidepressants and not benzodiazepines.”11 Antidepressants also entail the risk of a switch into an undiagnosed bipolar course, particularly in younger patients.
With regard to the newer antidepressants for anxiety disorders, Roy-Byrne said “they are well-tolerated and they work more slowly than benzodiazepines, so they don’t provide patients with a clear-cut signaling link between taking a pill and feeling an anti-anxiety affect.” There aren’t many drawbacks with the antidepressants, other than the sexual dysfunction associated with most of the agents.

Studies
The most common reason for using benzodiazepines is to add them to antidepressants when treating anxiety disorders that have not optimally responded to an initial antidepressant. According to Roy-Byrne, there is currently no published study comparing this strategy with switching the antidepressant, although a report of the study is in press, which may provide needed information in this debate.
Fava and Rickels call for further comparison studies, conducted, when possible, by non-industry sources. “A well-conducted comparison trial of a benzodiazepine and a newer antidepressant simply does not exist, neither for acute nor chronic treatment,” Rickels said.
In an editorial on whether benzodiazepines still have a role in treating patients with anxiety disorders, Baldwin and Talat12 said, “There is a persisting need for placebo-controlled combination studies in acute treatment; for placebo-controlled augmentation studies after non-response, for example, after unsuccessful treatment with a selective serotonin reuptake inhibitor or cognitive behavior therapy; and for well-designed relapse prevention studies.”

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