Anxiety Associated With Comorbid Depression

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Historically, the clinical term for mixed depression and anxiety was *anxious depression*. With the publication of DSM-III-R, 2 categories were established for the purpose of classifying disorders that involve both anxiety and depression, and that classification system is currently used in DSM-IV as well. These more specific diagnostic criteria have given us a much better understanding of the anxiety spectrum, but have created a need for a better understanding of the place of benzodiazepines in clearly defined indications on the anxiety spectrum. In spite of warnings about side effects, misuse, and dependence, benzodiazepines are frequently prescribed as adjunctive therapy to antidepressants for comorbid anxiety and depression. This article presents data on the prevalence, course, and outcome of comorbid anxiety and depression. It also compares efficacy data from trials of benzodiazepines used alone and in combination with antidepressants for the treatment of anxiety disorders comorbid with depression.
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With the publication of the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (DSM-III-R),[1] 2 categories were established for the purpose of classifying disorders that involve both anxiety and depression, which were previously called *anxious depression*. DSM-III-R acknowledged that 2 distinct disorders could coexist in a patient. The first category of the newer classification system, which is currently used in DSM-IV as well,[2] is a diagnosis of major depressive disorder in addition to a diagnosis of panic disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, or posttraumatic stress disorder. The second category is a diagnosis of mixed anxiety-depressive disorder, which can only be made if the criteria for any other anxiety or mood disorder are not currently met.

PREVALENCE AND CONSEQUENCES

Clinicians are well aware of the enormous epidemiologic prevalence of anxiety and depression and their consequences in terms of treatment and social costs. According to a study by Kessler et al.,[3] 58% of patients with lifetime major depressive disorder have 1 anxiety disorder. Most lifetime cases of major depressive disorder are secondary, and anxiety disorders are both the most common primary disorders associated with secondary major depressive disorder and the primary disorders predicting the greatest subsequent risk of secondary major depressive disorder. Data from the National Comorbidity Survey[4] showed that, of patients with lifetime generalized anxiety disorder, 62% also have major depressive disorder and 40% have dysthymia. There is also a high prevalence of comorbid anxiety and mood disorders in the primary care setting.[5]

The probability that depression will be comorbid with well-defined anxiety syndromes is nearly twice as high as the probability that depression will be comorbid with alcohol dependence.[6] Comorbidity increases severity and predicts a poorer outcome, and individuals who suffer from both anxiety and depression appear to experience a more chronic course and more impairment of social and occupational functioning than individuals with either anxiety or depression alone.[7] In a study of 327 patients diagnosed with depression according to DSM-III-R criteria, median recovery time for those with high anxiety ratings was 26 weeks compared with 13 weeks for those with low anxiety ratings.[8] Longer recovery times translate to increased social costs; therefore, more effective treatment strategies must be explored for patients suffering from comorbid anxiety and depression.

ANTIDEPRESSANT AND BENZODIAZEPINE COMBINATION THERAPY IN DEPRESSION

Antidepressants and benzodiazepines have individually demonstrated some success in treating both depression and anxiety. Selective serotonin reuptake inhibitor (SSRI) therapy, while highly effective for depression, resolves symptoms slowly and may increase anxiety or insomnia.

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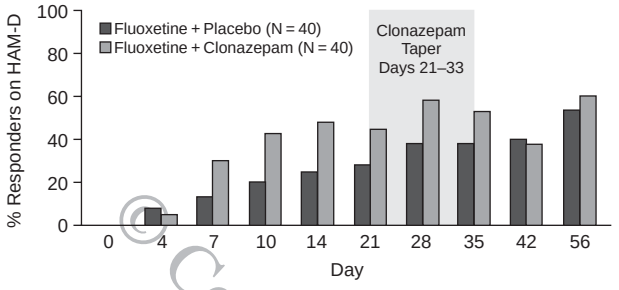
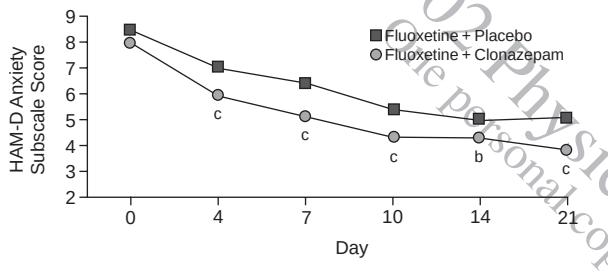
Figure 1. Improvement in HAM-D Scores in Patients With Major Depression Treated With Fluoxetine and Clonazepam or Fluoxetine and Placebo[a]



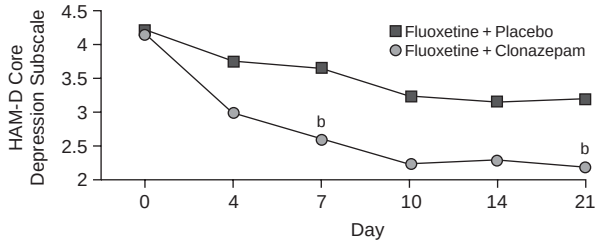
[a]Data from Smith et al.[10] Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Improvement in HAM-D Anxiety Subscale (items 9, 10, 11) Scores in Patients With Major Depression Treated With Fluoxetine and Clonazepam or Fluoxetine and Placebo[a]



[a]Adapted with permission from Londborg et al.[11]
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]$p < .01$.
[c]$p < .001$.

Figure 3. Improvement in HAM-D Core Depression Subscale (items 1, 2, 3, 7) Scores in Patients With Major Depression Treated With Fluoxetine and Clonazepam or Fluoxetine and Placebo[a]



[a]Adapted with permission from Londborg et al.[11]
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]$p < .01$.

The addition of a benzodiazepine to SSRI therapy may speed response and alleviate symptoms and side effects in patients suffering from depression.

A meta-analysis[9] examined 9 studies that compared treatment with an antidepressant alone with antidepressant and benzodiazepine combination treatment for 679 adult patients with major depression. Seven of the 9 studies used tricyclic antidepressants (TCAs), 1 study used mianserin, and 1 used fluoxetine. Those taking combination therapy were 37% less likely to drop out than those taking an antidepressant alone. Intent-to-treat analysis showed that the patients taking combination therapy were 63% to 38% more likely to show a response up to 4 weeks. Response was defined as a 50% or greater reduction in the depression scale score from baseline.

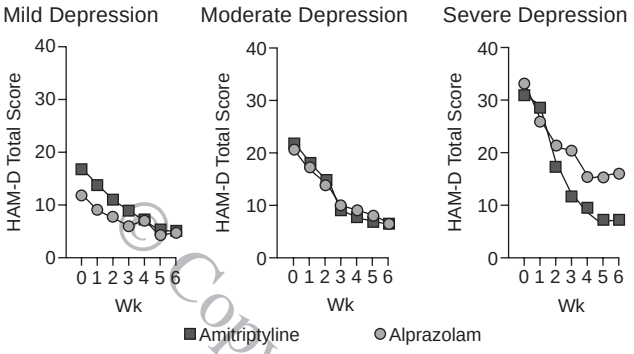
In another study,[10] 80 adult outpatients with major depression who were rated as moderately or markedly ill on the Clinical Global Impressions-Severity of Illness (CGI-S) scale underwent 8 weeks of double-blind, randomized treatment with fluoxetine at 20 mg/day, titrated to 40 mg/day if needed after 6 weeks. One half of the patients also received one 0.5-mg tablet of clonazepam at bedtime, adjusted to 2 tablets by day 10 if needed, and the remaining 40 patients received adjunctive placebo, likewise adjusted. Clonazepam and placebo were gradually withdrawn from treatment during days 21 to 33. Efficacy was evaluated by the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions-Improvement scale (CGI-I), and a patient rating of global improvement. Patients taking clonazepam in combination with fluoxetine improved significantly more, according to the HAM-D, during the first 3 weeks of treatment than patients taking fluoxetine with placebo (Figure 1).

Adverse events for the same study were reported by Londborg et al.[11] Patients were assessed by a HAM-D anxiety cluster, sleep disturbance cluster, and core symptoms cluster (Figure 2). Treatment-emergent anxiety was reported for 25% of placebo-treated patients and 7% of clonazepam-treated patients. Patients taking clonazepam also showed decreased anxiety and sleep disturbance as symptoms of depression (Figure 3) and partially suppressed SSRI side effects. Clonazepam and fluoxetine combination therapy also modestly reduced core symptoms of low mood and loss of interest. Because SSRIs usually require 2 to 4 weeks to achieve a response, a combination strategy may improve the effectiveness of SSRIs, particularly early in treatment, which can improve compliance. A combination strategy may also partially suppress SSRI side effects and reduce the risk of suicide.

BENZODIAZEPINE MONOTHERAPY IN DEPRESSION

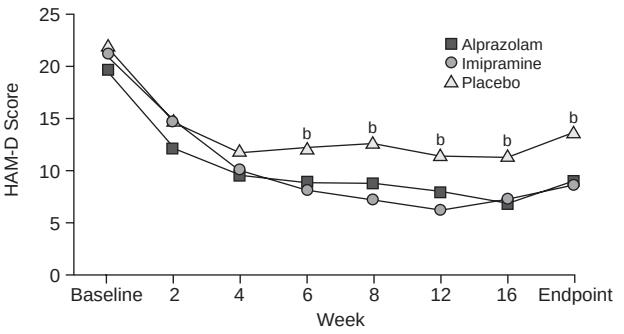
Alprazolam and standard antidepressants may have some similar mechanisms of action, such as a β-adrenergic receptor down-regulation. There are some data showing that benzodiazepines are as efficacious as amitriptyline in mild-to-moderate depression. Laakman et al.[12] conducted a randomized double-blind study in 342 mildly to moder-

Figure 4. Effect of Alprazolam and Amitriptyline on HAM-D Scores in Patients With Mild, Moderate, and Severe Depression as Defined by the CGI Scale[a]



[a]Reprinted with permission from Laakman et al.[13] Abbreviations: CGI = Clinical Global Impressions, HAM-D = Hamilton Rating Scale for Depression.

Figure 5. Sustained Improvement in Patients Treated With Alprazolam, Imipramine, or Placebo for Depression Comorbid With Panic Disorder[a]



[a]Data from Keller et al.[17] Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]$p \leq .05$.

ately depressed patients to investigate the antidepressant effectiveness and onset of action of lorazepam, alprazolam, and amitriptyline versus placebo. Of the intent-to-treat group, 257 completed 6 weeks of therapy. At 6 weeks, all active drugs showed similar efficacy according to the patients' HAM-D scores and were significantly superior to placebo. Compared with placebo, onset of efficacy was earlier with the benzodiazepines than with amitriptyline. An earlier study by Laakman et al.[13] also showed alprazolam as efficacious as amitriptyline in mild or moderate depression, but for severe depression alprazolam was inferior (Figure 4).

A meta-analysis[14] of 11 randomized controlled trials that compared low-to-medium doses of TCAs with alprazolam in depressed patients showed that the antidepressant effect of alprazolam was comparable to that of low-dose TCAs. There is no evidence, however, that alprazolam is comparable to TCAs at optimum doses in severely depressed patients or for long-term treatment. In another meta-analysis[15] of placebo-controlled benzodiazepine trials, patients with major depressive disorder taking alprazolam had a 27.1% greater response than patients taking placebo, which is an effect comparable to that of standard antidepressants. In addition, all benzodiazepines studied had an overall efficacy of 47% to 63%. However, alprazolam and other benzodiazepines have shown inferiority to TCAs in patients with endogenous or melancholic depression.[16]

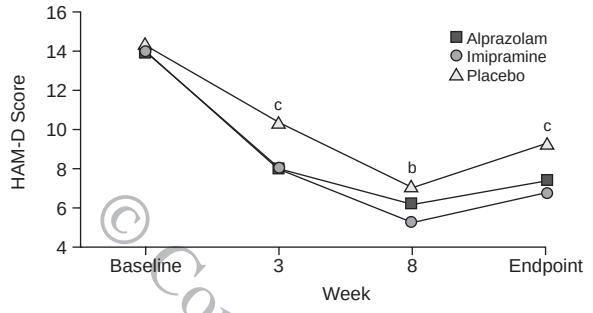
BENZODIAZEPINES IN COMORBID DEPRESSION AND PANIC DISORDER

Quite often, major depression and panic disorder coexist. Up to 60% of patients with depressive symptomatology also have anxiety, and 20% to 30% of patients with major depression as a presenting complaint also meet the criteria for panic disorder.[7] Conversely, an average of one third of patients meeting criteria for panic disorder experience an episode of major depression at some time during their lives. Although there are limited data evaluating the differences between primary and secondary depression in patients with panic disorder, evidence suggests that regardless of order of onset, patients with comorbid panic disorder and major depression are significantly more impaired than patients with either panic disorder or major depression alone. The available literature also indicates that acute treatment outcome for individuals with comorbid panic disorder and major depression is usually poorer than for individuals with either disorder alone.

A multisite study[17] of 126 patients meeting DSM-III-R criteria for panic disorder and for a concurrent major depressive episode of mild-to-moderate severity, dysthymia, or depressive disorder not otherwise specified compared alprazolam with imipramine and placebo to discern the influence of varying degrees of depression on the comparative efficacy of each drug. A double-blind, parallel, random assignment design was utilized over 16 weeks. At endpoint, depression and anticipatory anxiety were significantly reduced in both the alprazolam and the imipramine group, and alprazolam demonstrated efficacy similar to that of imipramine for the treatment of mild-to-moderate depression according to patients' HAM-D scores (Figure 5). Phobic measures were significantly improved by alprazolam compared with both imipramine and placebo early in the study.

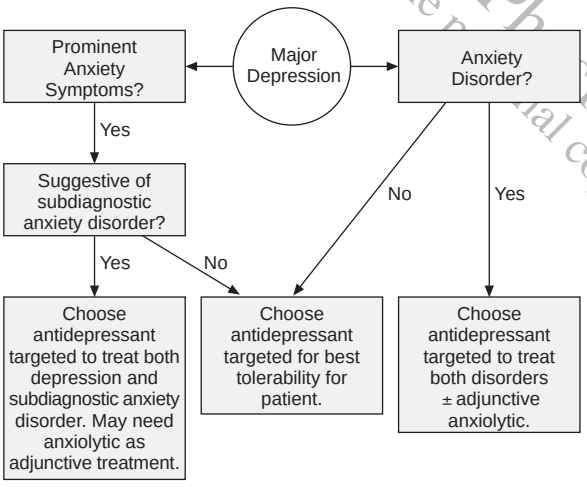
The Cross-National Collaborative Panic Study[18] was initiated to study the effects of alprazolam in the treatment of patients with panic disorder and secondary depression. Results from this study showed that depressive symptoms did not adversely influence antipanic response to medication, and alprazolam and imipramine showed similar efficacy in reducing symptoms of depression over a sustained

Figure 6. Efficacy of Alprazolam and Imipramine in Reducing Symptoms of Depression Secondary to Anxiety According to HAM-D Scores[a]



[a]Data from Klerman.[18] Abbreviation: HAM-D = Hamilton Rating Scale for Depression.
[b]$p \leq .01$.
[c]$p \leq .001$.

Figure 7. Proposed Treatment Algorithm for Anxiety and Depression[a]



[a]Reprinted with permission from Lydiard and Brawman-Mintzer.[7]

time period, according to HAM-D scores (Figure 6). These results further support the important role of benzodiazepines in treating the spectrum of combined depression and anxiety disorders.

PROPOSED TREATMENT ALGORITHM FOR COMORBID ANXIETY AND DEPRESSION

When a patient presents with a mixture of anxiety and depressive symptoms, the clinician should choose an antidepressant that is targeted to treat both major depressive disorder and anxiety disorder as a first-line treatment (Figure 7). An anxiolytic, such as one of the benzodiazepines discussed here, may be used as adjunctive therapy, which may not only improve anxiety symptoms, but also speed the patient's response. If a patient suffers from depression without anxiety, the antidepressant should be used alone.

CONCLUSION

Anxiety and mood disorders are not only extremely common, but they also coexist at some point in the lives of the majority of individuals who suffer from either anxiety or mood disorders. When anxiety and depression co-occur, the prognosis for recovery from the acute episode, as well as the longer-term prognosis, is affected adversely. Patients seeking treatment for depressive and anxiety disorders, especially panic disorder, need relief from symptoms as quickly as possible. Benzodiazepines have demonstrated a propensity to enhance and possibly accelerate the action of SSRIs and TCAs when used as adjunctive therapy in patients with both depressive and anxiety symptoms. Alprazolam appears to have antidepressant properties when used alone in patients with mild-to-moderate depression. Benzodiazepines are an effective option alone or in combination with antidepressants for providing fast onset of action, increased compliance, and hopefully a better prognosis for patients with comorbid anxiety and depression.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil, Endep, and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), imipramine (Surmontil, Tofranil, and others), lorazepam (Ativan and others).

Disclosure of off-label usage: The author has determined that, to the best of his 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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