

# Prevalence, Recognition, and Treatment of Comorbid Depression and Anxiety

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The management of depression is often complicated by comorbid psychiatric illness. Incomplete diagnoses or inadequate treatment can severely limit a patient's improvement. However, careful diagnosis and straightforward treatment can relieve suffering and restore function. This article will examine recent research investigating the coexistence of depression with a number of different anxiety disorders and review literature on the prevalence and recognition of depression with comorbid anxiety disorders. Finally, current data on treatment will be discussed, with a focus on optimal treatment approaches and duration of treatment.

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Comorbidity of depression with other psychiatric disorders is the rule, not the exception, in clinical practice. Often, patients with depression have a comorbid anxiety disorder, and the converse is true as well. Illnesses currently defined in the DSM-IV as depressive disorders include major depressive disorder, dysthymia, and depressive disorder not otherwise specified (Table 1). Illnesses currently defined in DSM-IV as anxiety disorders include panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder, social phobia or social anxiety disorder, and agoraphobia. The interplay between depressive symptoms and anxiety symptoms is complex (Figure 1).<sup>1</sup> Some patients have major depression without anxiety. Other patients have anxiety without depression. Some patients, particularly those seen in primary care, have a combination of symptoms of both anxiety and depression.

If not treated properly, patients with comorbid anxiety and depression have a worse outcome than patients with either illness alone. Thus, the most effective treatment requires attention to symptoms of both anxiety and depression. Usually, diagnostic theories inform treatment protocol, but as the newer antidepressants are successful for treating not just depression but also anxiety disorders, there may be less need to employ separate medication treatments for each disorder.

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## PREVALENCE

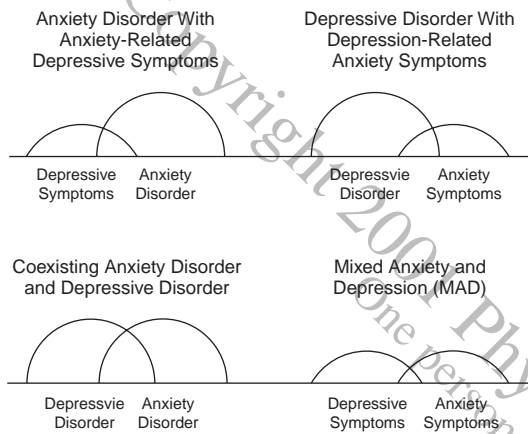
Epidemiologic studies have found that anxiety and depression often go hand in hand. In a study<sup>2</sup> of 260 patients with principal diagnoses of depressive disorders, 116 (59%) of 197 patients with major depression and 41 (65%) of 63 patients with dysthymia had at least 1 concurrent Axis I disorder. Most of these patients had comorbid anxiety disorders. In the National Comorbidity Survey (N = 8098) of noninstitutionalized civilian persons aged 15 to 54 years in the United States, Kessler et al.<sup>3</sup> found that 21% of respondents had 1 DSM-III-R disorder, 13% had 2, and 14% had 3 or more psychiatric disorders. This means that the major burden of psychiatric disorder in the United States is concentrated in 27% of the population, who have 2 or more disorders. In this sample, 58% of the respondents with lifetime depression had an anxiety disorder. The most frequently reported comorbid lifetime anxiety disorders were social phobia, simple phobia, and PTSD.<sup>4</sup>

The prevalence of depression is also increased among patients with anxiety disorders. The prevalence of depression, as well as other disorders, was greatly increased among people with PTSD compared with those without PTSD (Table 2).<sup>5</sup> A lifetime history of at least 1 affective or other disorder was found in 88% of men and 79% of women with PTSD.

Kessler et al.<sup>4</sup> concluded that major depression is prevalent in the U.S. general population and that most lifetime cases of major depression are secondary to other psychiatric illnesses (i.e., symptoms of other disorders predate symptoms of depression). Anxiety disorders are the most common primary disorders associated with secondary major depression and the ones with the greatest risk of subsequent secondary major depression.

**Table 1. Common Depressive and Anxiety Disorders That May Be Comorbid**

Depressive Disorders	Anxiety Disorders
Major depression	Agoraphobia
Dysthymia	Generalized anxiety disorder
Depressive disorder not otherwise specified	Obsessive-compulsive disorder
	Panic disorder
	Posttraumatic stress disorder
	Social phobia

**Figure 1. Relationship Between Depressive Symptoms and Anxiety Symptoms<sup>a</sup>**<sup>a</sup>Adapted from Stahl.<sup>1</sup>

## RECOGNITION

The recognition of psychiatric comorbidities markedly increased with the transition from DSM-III<sup>6</sup> to DSM-III-R, with the evolution of diagnostic nosology from a hierarchy-based classification system to a system in which an individual may simultaneously have more than 1 psychiatric disorder.<sup>2</sup> An additional development in DSM-IV was the open discussion and frank investigation of less than syndromal conditions like minor depression and mixed anxiety and depression. Mixed anxiety and depression (MAD) is a conceptualization of a syndrome that combines features of both anxiety and depression where neither would qualify as a predominant, stand-alone diagnosis.

The clinical features of MAD listed in the International Classification of Diseases, 10th edition (ICD-10),<sup>7</sup> include equally intense but subthreshold symptoms of anxiety and depression, autonomic overactivity, and psychic overactivity independent of other disorders and stressful life events (Table 2). Autonomic symptoms may include tremor, palpitations, and stomach churning. Boulenger and Lavallée<sup>8</sup> commented that a benefit of developing the ICD-10 MAD diagnosis is the tangible reunification of 2 syndromes: anxiety disorders and depressive disorders.

Whatever the diagnosis, the first step is recognition. In a World Health Organization (WHO) survey, Sartorius and

**Table 2. Comorbidity of Psychiatric Disorders With Posttraumatic Stress Disorder (PTSD)<sup>a</sup>**

Comorbid Disorder	Lifetime Rate (%)			
	Men		Women	
	PTSD	Non-PTSD	PTSD	Non-PTSD
Depression	48	12	48	19
Mania	12	1	6	1
Panic disorder	7	2	13	4
Social phobia	28	11	28	14
Generalized anxiety disorder	17	3	15	6
Any diagnosis	88	55	79	46

<sup>a</sup>Data from Kessler et al.<sup>5</sup>

colleagues<sup>9</sup> found that the recognition of depression in primary care was more likely in patients with a comorbid psychological disorder than in those with depression alone. The presence of any comorbid disorder increased the recognition and treatment of depression in these patients. Interestingly, when depressive or anxiety disorders were recognized, only half the patients received any drug treatment.

Patients who have anxious and depressive symptomatology are often disabled and need aggressive treatment. MAD is common in primary care settings, and the disability levels of patients with MAD are similar to those of patients who meet the DSM diagnostic criteria for a major depressive disorder or an anxiety disorder.<sup>10</sup> In the WHO multicenter study<sup>9,11</sup> of psychological problems in general health care, about 1500 consecutive primary care patients aged 18 to 65 years were screened at each of 15 primary care centers around the world. Selected patients (N = 5438) were asked to complete a series of rating scales (primary care version of the Composite International Diagnostic Interview, Social Disability Schedule, Brief Disability Questionnaire, self-rated Overall Health Status, and the General Health Questionnaire). Ormel et al.<sup>11</sup> reported that moderate-to-severe disability was consistently found in 4 to 5 times as many patients with psychiatric illnesses as patients without psychiatric illness. (Physical disease severity was an independent but weaker contributor to disability.) Sartorius and colleagues<sup>9</sup> found that 48% of all patients with full syndromal depressive and anxiety disorders had occupational dysfunction, compared with 39% of all persons with only depression.

## TREATMENT

Effective treatment can restore functioning in those who are disabled by psychiatric illnesses. Treatment of comorbid anxiety-depression has the potential for greatly lowering workplace costs of psychiatric disorders.<sup>11</sup> Therapeutic approaches to comorbid depression and anxiety include pharmacologic and psychosocial options (Table 3). The pharmacologic choices include benzodiazepines, azapirones, antidepressants, or combined treatment. Antidepressants are a safer alternative to benzodiazepines in pa-

**Table 3. Therapeutic Approaches to Comorbid Depression and Anxiety**

Pharmacologic	Psychosocial
Benzodiazepines	Cognitive-behavioral therapy
Azapirones	Interpersonal psychotherapy
Antidepressants	Other
Combined	

**Table 4. Efficacy of Antidepressants in Anxiety<sup>a</sup>**

Data	Panic Disorder	Generalized Anxiety Disorder	Social Phobia	Obsessive-Compulsive Disorder	Posttraumatic Stress Disorder	Mixed Anxiety and Depression
Efficacious	MAOIs SSRIs TCAs	Venlafaxine TCAs SSRIs	MAOIs SSRIs	SSRIs	SSRIs	SSRIs
Some evidence of efficacy	Venlafaxine Nefazodone	Trazodone Nefazodone Mirtazapine	Venlafaxine Bupropion Nefazodone	MAOIs	Venlafaxine MAOIs TCAs Bupropion Nefazodone Trazodone Mirtazapine	Venlafaxine MAOIs TCAs Nefazodone Trazodone Mirtazapine
Not effective	Trazodone Bupropion		TCAs	TCAs Trazodone		
No data	Mirtazapine	MAOIs Bupropion	Mirtazapine Trazodone	Venlafaxine Nefazodone Bupropion Mirtazapine		Bupropion

<sup>a</sup>Adapted from Lydiard and Brawman-Mintzer.<sup>12</sup> Abbreviations: MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

tients who might become dependent on the latter agents. Studies of anxiety and depression have examined the efficacy and safety of various medications. Since evidence shows that antidepressants in the selective serotonin reuptake inhibitor (SSRI) class have been found to be effective in treating anxiety disorders across the board (Table 4), SSRIs should be considered first-line treatment for patients with anxiety and depression. Psychosocial treatments include cognitive-behavioral therapy, interpersonal psychotherapy, and other treatments.

Laws et al.<sup>13</sup> studied 112 general practice patients with mixed anxiety and depression who were treated for 6 weeks with the SSRI fluvoxamine or the benzodiazepine lorazepam. Entry criteria of this multicenter, double-blind, parallel-group study included baseline scores of 11 or greater on the Clinical Anxiety Scale (CAS) and a 21 on the Montgomery-Åsberg Depression Rating Scale (MADRS). The 2 agents were equally effective, with continual improvement over baseline on MADRS, CAS, and global ratings shown at each assessment. Lorazepam produced more sedation, but it improved anxiety more quickly in an elderly subgroup. Fluvoxamine produced more nausea early in the study, which resolved during treatment. Laws and colleagues concluded that their results supported antidepressants as first-line treatment in mixed anxiety and depression.

Lydiard et al. performed an open-label<sup>14</sup> study of sertraline for patients with anxious depression, defined by a Hamilton Rating Scale for Depression (HAM-D) anxiety factor score of 7 or greater. Patients who presented with depression and anxiety had a similar endpoint response rate—but a lower remission rate—to sertraline than patients who presented with depression without prominent baseline anxiety.

Sertraline treatment resulted in greater than 50% reduction in the baseline HAM-D anxiety factor scores in 71% of patients. Among depressed patients without an anxious subtype at baseline, 79% responded and 74% remitted after sertraline treatment; however, among depressed patients with baseline anxiety, 83% responded to sertraline but only 63% remitted. This result suggests that patients with both anxiety and depression may require more intensive treatment to reach remission.

Fava and colleagues<sup>15</sup> investigated SSRI treatment of anxious depression. In the 108 patients with DSM-IV major depression and HAM-D anxiety factor scores of 7 or higher, greater improvement in anxiety was seen in the sertraline and fluoxetine groups than in the paroxetine group in the first week. Overall, efficacy and tolerability were similar among the drugs, with sertraline treatment having more nonstatistically significant responders and remitters in this head-to-head study. Rates of response (a 50% or greater decrease in the HAM-D score) were 86% with sertraline, 77% with paroxetine, and 73% with fluoxetine. The remission rates were 62% for sertraline, 50% for paroxetine, and 53% for fluoxetine.

When Demartinis et al.<sup>16</sup> completed an analysis of pooled data from 2 8-week, double-blind, placebo-controlled sertraline treatment studies, they found that anxiety symptoms responded in 80% of the 154 patients who met criteria for the anxious subtype of depression. Anxious depression was defined as a score of 7 or less on the anxiety-somatization item of the HAM-D.

Brady et al.<sup>17</sup> examined the results from 2 multicenter, 12-week, double-blind studies of sertraline (50–200 mg/day) and placebo to assess whether the comorbidity of mood or anxiety disorders affected treatment outcome in patients with DSM-III-R PTSD. In these 2 PTSD trials, comorbidity rates of depression were 50% and 37%, and comorbid anxiety disorders occurred in 20% and 16% of

**Table 5. Strategies for Optimizing Response in Anxious Depressed Patients**

Start at half the usual depression dosage
Titrate the medication slowly
Tell the patient about all potential problems with the drug
Reassure the patient about the illness and treatment
Increase the dosage as necessary
Combine drug treatments
Augment medication with psychosocial treatment
If necessary, switch to a different antidepressant

study participants. The Davidson Trauma Scale total score and the total severity score of the Clinician-Administered PTSD Scale were used to assess treatment outcome in the patients (N = 208, N = 187). In both trials, patients' PTSD improved significantly more with sertraline than with placebo, even in patients with comorbid anxiety or depression.

Newer antidepressants have also been studied in patients with comorbid depression and anxiety. Fawcett and Barkin<sup>18</sup> conducted a meta-analysis of 8 randomized, double-blind studies of mirtazapine in patients (N = 161) with major depression and symptoms of anxiety, compared with amitriptyline (N = 92) and placebo (N = 132). Mirtazapine was comparable to amitriptyline and superior to placebo for the treatment of major depression with anxiety symptoms. In a meta-analysis of 6 venlafaxine studies, Rudolph and colleagues<sup>19</sup> found that venlafaxine treatment resulted in improvement in both anxiety symptoms and depression of a magnitude similar to that of imipramine and trazodone and superior to that of placebo. A meta-analysis<sup>20</sup> of 6 randomized, placebo-controlled, double-blind trials of nefazodone in patients (N = 817) with major depression and symptoms of anxiety and agitation demonstrated that nefazodone was as effective as imipramine in relieving depression, and both drugs were superior to placebo, irrespective of baseline anxiety levels. Nefazodone-treated patients experienced improvement in agitation symptoms earlier than those taking imipramine or placebo. Nefazodone was also superior to imipramine and placebo on improvement in somatic anxiety.

### OPTIMAL TREATMENT APPROACHES

When treating patients who have comorbid depression and anxiety, there are some things that clinicians can do to optimize the chance of successful outcomes (Table 5). Start the chosen agent at half of the usual dosage used for treating depression, and titrate slowly. Tell the patient before beginning treatment about the potential side effects of the drug. Offer the patient reassurance that the disorders are treatable and that if the first agent fails, others are available. In order to optimize response, it may be necessary to increase the dose of the antidepressant to as much as the patient can tolerate. If this is ineffective, consider

switching to another antidepressant or combining psychosocial and pharmacologic treatment.

### CONCLUSION

Data show that mixed anxiety and depression, although prevalent and disabling, is treatable. The clinician's success in treating anxious depression lies in carrying out a few important steps. First, identify the patient's specific disorder(s) and/or subdiagnostic symptoms. Next, choose a treatment medication on the basis of efficacy and tolerability. Then, we need to educate our patients about (1) the time it takes to heal, (2) the potential side effects of our treatments, (3) the fact that most side effects resolve with time, and (4) the collaborative approach to treatment, which will lead to significant relief of symptoms and recovery. Many times patients with comorbid depression and anxiety require higher doses of medication and more intensive treatment to achieve remission than those without comorbid symptomatology.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, fluvoxamine is not approved by the U.S. Food and Drug Administration for the treatment of major depression, anxiety disorders, and obsessive-compulsive disorder; sertraline and fluoxetine for social phobia and mixed anxiety and depression; venlafaxine for anxiety disorders, except generalized anxiety disorder; amitriptyline, bupropion, imipramine, mirtazapine, nefazodone, and trazodone for anxiety disorders; and paroxetine for mixed anxiety and depression and PTSD.

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