

Care of Depressed Patients With Anxiety Symptoms

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Anxiety frequently coexists with depression, either as a comorbid anxiety disorder or as anxiety symptoms accompanying a primary depressive disorder. Effective therapy for the treatment of depressive illness must include a consideration of anxiety symptoms, since anxiety has been estimated to be present in up to 96% of patients with depressive illness. Available data also indicate that depressed patients with significant anxiety may be at greater risk for suicide. Of particular clinical importance are symptoms of somatic anxiety: they are present in up to 86% of depressed patients, and the failure to treat them effectively can diminish the ability of a patient to function. Since the overall prognosis for recovery from a major depressive episode is less than optimal in patients with significant anxiety, treatments that can provide an effective and early relief of both depressive and anxiety symptoms are of paramount importance. Drugs with serotonin reuptake inhibition (such as selective serotonin reuptake inhibitors [SSRIs] or serotonin-norepinephrine reuptake inhibitors [SNRIs]) may produce transient increases in anxiety symptomatology presenting as jitteriness, agitation, insomnia, and gastrointestinal symptoms when treatment is initiated. Mirtazapine has intrinsic receptor-blocking properties (in particular, serotonin-2 [5-HT₂] receptor blockade) that can be linked to an early relief of anxiety symptoms during the treatment. The available data show that mirtazapine is superior to placebo in depressed patients with high baseline anxiety and/or agitation. Furthermore, mirtazapine was statistically significantly superior to both citalopram and paroxetine in alleviating anxiety symptoms early in treatment as assessed by changes from baseline on the Hamilton Rating Scale for Anxiety or the Hamilton Rating Scale for Depression anxiety/somatization factor, respectively. Mirtazapine provides early and effective relief of both depressive and anxiety symptoms, reducing the need for polypharmacy. These therapeutic actions of mirtazapine persist throughout the course of treatment.

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There is now ample evidence that depression and anxiety coexist as opposed to being completely separate entities. The 2 conditions show extensive overlap with respect to symptomatology,^{1,2} and a spectrum of disorders has been described,^{3,4} of which anxiety and depression are the 2 extremes.⁵

COMORBIDITY OF DEPRESSION AND ANXIETY

In a primary care population prevalence study,⁶ the majority of patients were found to have mixed anxiety-depressive syndrome (42.3%) or depression with comorbid anxiety (19.2%), with only 12.8% of the population having anxiety alone and 10.3% having depression alone. Anxiety alone included panic disorder, social phobia, obsessive-compulsive disorder, and generalized anxiety disorder (GAD). Depression alone included major depres-

sion and chronic depression. The distribution of all depressive and anxiety symptoms in this primary care population is shown in Figure 1. The comorbidity of major depression with anxiety disorders in the community was also determined in the National Comorbidity Survey over 12 months.⁷ The results are shown in Table 1. Major depression was comorbid with any anxiety disorder in one half of patients, whereas it was comorbid with GAD in only one sixth of patients.

The symptoms common to major depressive and anxiety disorders are shown in a Venn diagram (Figure 2).⁸⁻¹⁰ Anxiety disorder symptoms that were in common with the symptoms of depression included, among others, fear, panic attacks, difficulty in sleeping, and difficulty in concentrating. In one study of 200 patients with major depression, anxiety symptoms were quantified in terms of the percentage of patients who experienced these symptoms (Table 2).¹¹ Moderate worry (72%) and moderate psychic and somatic anxiety (62% and 42%, respectively) were the most commonly found symptoms. Similar results were found in another study, which showed that the most common anxiety states accompanying depression were panic disorder, GAD, and social phobia.¹²

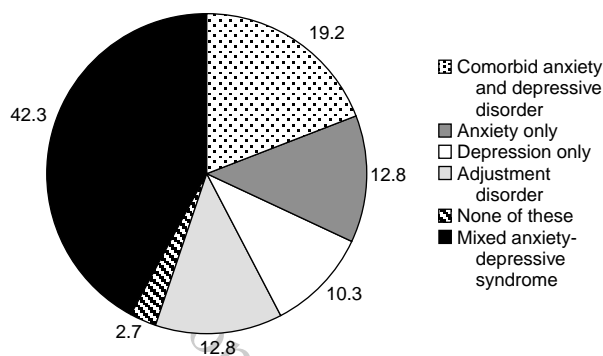
Recognition of anxiety and depressive disorders is now considered to be extremely important, since the comorbid condition of depression complicated by anxiety has a

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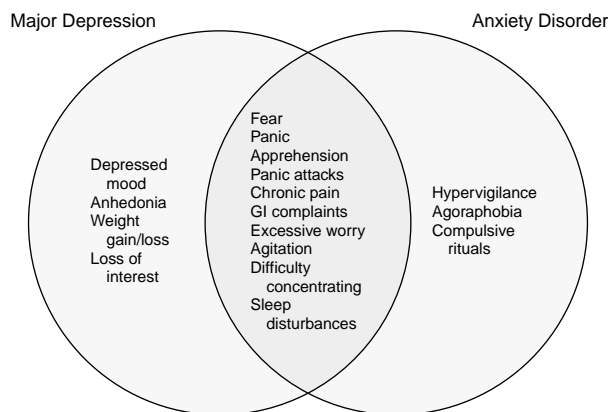
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Figure 1. Distribution of Depressive and Anxiety Symptoms in a Primary Care Population^a



^aData from reference 6.

Figure 2. Symptoms Common to Major Depression and Anxiety Disorders^a



^aData from references 8–10. Abbreviation: GI = gastrointestinal.

Table 1. Occurrence of Anxiety Disorders With Major Depression in the Community^a

Comorbid Anxiety Disorder	% Comorbid	Proportion
Any anxiety disorder	50.0	1/2
Panic disorder	9.9	1/10
Social phobia	21.3	1/5
Simple phobia	26.2	1/4
Generalized anxiety disorder	16.9	1/6

^aData from reference 7.

Table 2. Anxiety Symptoms in Major Depression^a

Symptom	% of Patients With Major Depression (N = 200)
Worry, moderate	72
Psychic anxiety, moderate	62
Somatic anxiety, moderate	42
Panic attacks	29
Phobic symptoms, moderate	19
Obsessive-compulsive symptoms	2

^aData from reference 11.

much poorer prognosis than that of depression alone.¹³ When patients display anxiety symptoms in depression, the illness tends to be more severe at baseline and there is more psychosocial impairment.⁸ Moreover, response to treatment is poorer and slower, and there is a greater likelihood of chronic illness and suicide.¹⁴ Although a high degree of hopelessness and complete or near total anhedonia are the most significant factors in suicide early in treatment, sleep disturbances, severe psychic anxiety, and a recent history of panic attacks are also highly significant.^{8,15,16}

Treatment-related issues that should be borne in mind while evaluating anxiety symptoms in a depressed patient include side effects of ongoing treatment, inadequate treatment of a medical or psychiatric disorder, and antidepressant discontinuation syndrome.

TREATMENT OF ANXIETY SYMPTOMS IN DEPRESSION

The treatment options for anxiety symptoms in depression, together with their probable outcomes, are summarized in Table 3. Treatment of anxiety symptoms in depression with a benzodiazepine has the disadvantage of leaving the underlying depression untreated. Selective serotonin reuptake inhibitors (SSRIs) have been used effectively to treat patients with depression and anxiety; however, drawbacks include early side effects of agitation and

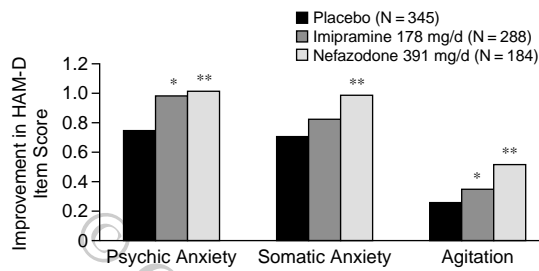
Table 3. Treatment Options for Anxiety Symptoms in Depression^a

Option	Potential Outcomes
Treat with a benzodiazepine	Underlying depression remains untreated; benzodiazepine dependence
Treat with an SSRI	SSRI side effects (eg, activation, agitation, sleep disturbances) exacerbate anxiety symptoms
Treat with SSRI + benzodiazepine	Positive, but risks drug-drug interaction and dependence; more costly
Treat with mirtazapine	Positive; improvement in depression with early relief from symptoms of anxiety

^aAbbreviation: SSRI = selective serotonin reuptake inhibitor.

anxiety. Treatment with an SSRI alone can exacerbate the anxiety symptoms, so it is important with comorbid patients to administer a low dose and to titrate slowly, as well as to aggressively manage treatment-emergent anxiety to avoid premature discontinuation of medication.¹³ Combined benzodiazepine and SSRI treatment is effective, but there is the potential risk of a drug-drug interaction and of benzodiazepine dependence developing. Tricyclic antidepressants and monoamine oxidase inhibitors, although proven to be effective in treating both anxiety and depres-

Figure 3. 5-HT₂ Blockade: The Importance on Anxiety and Agitation Items in the HAM-D^a

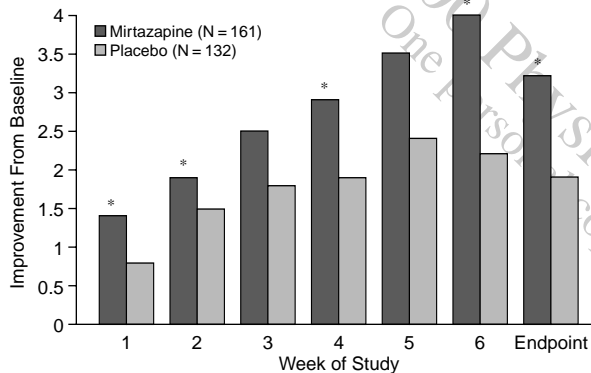


^aData from reference 22. Abbreviation: 5-HT₂ = serotonin-2
HAM-D = Hamilton Rating Scale for Depression.

* $p \leq .05$.

** $p < .01$ vs. placebo. Endpoint (last-observation-carried-forward analysis).

Figure 4. Mirtazapine: Mean Improvement in HAM-D Anxiety/Agitation Item^a



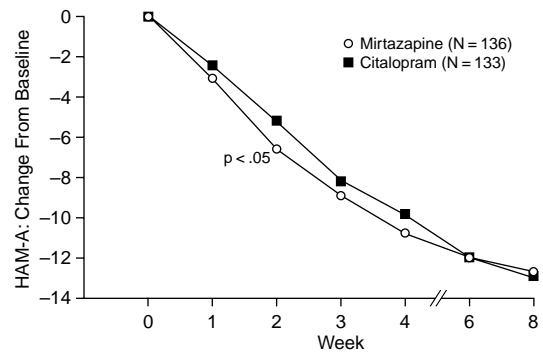
^aAdapted from reference 23, with permission.

* $p \leq .05$.

sive symptoms, have numerous adverse effects, making them second choice therapies.¹³ In addition, they are known to interact with many other pharmacologic agents.

Treatment with the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine shows improvement in depression with early relief from symptoms of anxiety. Mirtazapine is a specific antagonist of pre-synaptic α_2 -adrenoceptors and α_2 -heteroceptors located on serotonergic nerve terminals, which results in an increased release of both norepinephrine and serotonin (5-HT).¹⁷ In addition, mirtazapine has a low affinity for 5-HT_{1A} receptors, but potently blocks 5-HT₂ and 5-HT₃ receptors. This direct enhancement of noradrenergic and 5-HT_{1A} receptor-mediated serotonergic neurotransmission is thought to be responsible for the antidepressant activity of mirtazapine,¹⁸ whereas the 5-HT₂ and 5-HT₃ blockade may account for mirtazapine's low incidence of anxiety and agitation. Clinical trials have shown that mirtazapine is similar to

Figure 5. Mirtazapine Versus Citalopram: Changes From Baseline on HAM-A Scale^a



^aData from reference 24. Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

tricyclic antidepressants in its interaction with noradrenergic and serotonergic transmission and overall efficacy^{19,20}; in addition, it also demonstrated the absence of cholinergic, adrenergic, and serotonergic side effects, together with safety in case of overdose.²¹

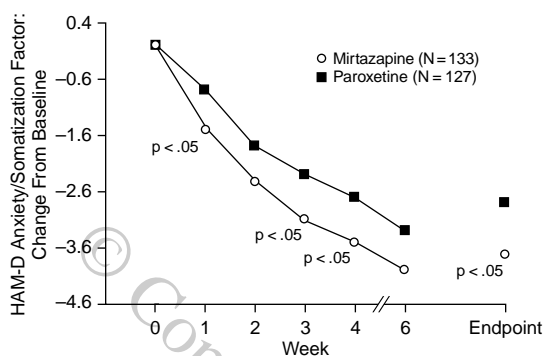
A study by Fawcett et al.²² of the antidepressants imipramine and nefazodone in depressed patients noted the effect of 5-HT₂ blockade on anxiety and agitation items on the Hamilton Rating Scale for Depression (HAM-D) (Figure 3). There was an improvement for psychic anxiety, somatic anxiety, and agitation in both antidepressant groups, but more so for nefazodone. Similar improvement in the HAM-D anxiety/agitation item was seen with mirtazapine in a recent meta-analysis of 8 placebo-controlled studies (Figure 4).²³ The mirtazapine-treated patients experienced a significant ($p \leq .05$) reduction in the symptoms of anxiety at weeks 1, 2, 4, 6, and endpoint compared with those receiving placebo.

The improvement on the Hamilton Rating Scale for Anxiety (HAM-A) with mirtazapine was compared with that produced by citalopram, and improvement on the HAM-D anxiety/somatization factor (change from baseline) with mirtazapine compared with that produced by paroxetine and fluoxetine, in 3 separate clinical trials in depressed patients.²⁴⁻²⁶ The clinical trial comparing mirtazapine with citalopram was 8 weeks in duration, whereas the other 2 trials lasted 6 weeks each. Mirtazapine consistently reduced anxiety symptoms more than did any of the other antidepressants, and its effect persisted throughout the course of treatment (Figures 5-7).

CHOOSING A TREATMENT OPTION

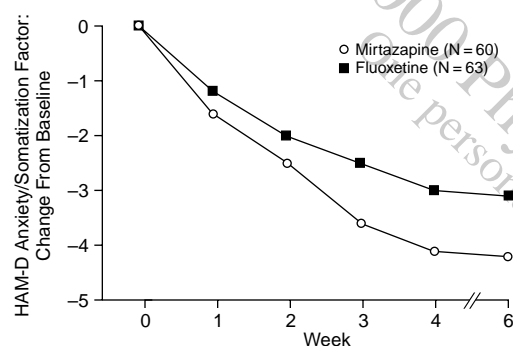
The rapid improvement in anxiety symptoms seen in depressed patients treated with mirtazapine could have important implications when choosing antidepressant therapy for depressed patients with significant anxiety

Figure 6. Mirtazapine Versus Paroxetine: HAM-D Anxiety/Somatization Factor^a



^aData from reference 25.

Figure 7. Mirtazapine Versus Fluoxetine: HAM-D Anxiety/Somatization Factor^a



^aData from reference 26.

symptoms.²³ Factors to consider in the choice of an antidepressant in the management of depression complicated by anxiety symptoms include the following: early reduction of anxiety symptoms, minimal side effects, good compliance, quality of life, and the potential for maximum dosing. The antidepressants currently used to treat major depression with anxiety features differ in their effects upon the various neurotransmitter systems, producing both clinically beneficial and adverse effects.^{10,23} Where possible, monotherapy should be attempted first with a drug capable of treating depression as well as anxiety disorders. Mirtazapine is an effective antidepressant with anxiolytic properties that may offer a promising alternative to currently available antidepressants.

DISCUSSION AND CONCLUSIONS

Epidemiologic studies reveal that the coexistence of depression and anxiety is a common occurrence that still presents treatment challenges, particularly because the

prognosis of patients with depression complicated by anxiety is worse than that of those with depression alone. In comorbid depression and anxiety, the treatment of choice is usually monotherapy with an antidepressant effective against both depression and anxiety. However, some antidepressants currently used can have early side effects of agitation and anxiety requiring the addition of an anxiolytic or sedative-hypnotic to manage treatment-emergent anxiety. Evidence from comparative clinical trials has shown that mirtazapine is an effective antidepressant that provides early relief of symptoms of anxiety. Moreover, the effect of mirtazapine on anxiety persists throughout the course of treatment. Since mirtazapine is effective against the symptoms of both depression and anxiety, polypharmacy is rarely needed, and it shows great promise as first-line treatment for the depressed patient with symptoms of anxiety.

Drug names: citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil).

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