Overview of Antidepressants Currently Used to Treat Anxiety Disorders

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The syndromes of anxiety and depression may reflect separate disorders with overlapping symptoms. They also may be comorbid or reflect illnesses with similar underlying pathophysiology based upon a spectrum of central nervous system dysfunction. Antidepressants effectively treat both anxiety and comorbid anxiety-depression. Tertiary tricyclic antidepressant agents (TCAs) with dual serotonergic-noradrenergic effects, such as imipramine and amitriptyline, appear consistently effective across the anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) are particularly effective in panic disorder and obsessive-compulsive disorder. SSRIs are similar in efficacy to TCAs but are more tolerable and cause fewer serious adverse events. However, they are relatively slow to act, and efficacy data are limited in states such as generalized anxiety disorder. Newer antidepressants, such as mirtazapine, nefazodone, and venlafaxine XR, may provide some benefits across the broad spectrum of anxiety disorders with the safety and tolerability that are the hallmarks of third generation antidepressants.
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CONCEPTUAL MODELS LINKING ANXIETY AND DEPRESSION

Traditionally, our understanding of the relationship between anxiety and depression focused on the neurobiologic, clinical, and nosologic distinctiveness of these 2 disorders. However, the comorbidity hypothesis suggests that although anxiety and depression are distinct illnesses, they may appear simultaneously in a given patient. Accumulating evidence points to a continuum of disease,[1,2] in which anxiety and depression are considered different phenotypic expressions with a shared underlying neurochemical imbalance.[1,3] In this model, "pure" anxiety states, believed to result from excessive serotonergic activity, are at one end of the spectrum, and "pure" depressive states, believed to result from deficient serotonergic activity,[3] are at the opposite end. Situated in the middle is a newly defined category of mixed anxiety-depression, characterized by subsyndromal but chronic symptoms of both disorders.[2,4]

A growing body of evidence from epidemiologic, longitudinal, and family-history studies supports the theoretical model that links anxiety and depression. For example, as many as 95% of depressed patients also have symptoms of anxiety, nearly 75% of patients who are classified as having major depressive disorder (MDD) have moderate levels of worry, and 62% display moderate psychic anxiety.[5,6] Comorbidity of MDD and anxiety disorders is 58% in the United States.[7] In longitudinal changes, anxiety states such as generalized anxiety disorder (GAD) typically occur at an earlier age than MDD, and they usually precede the development of depressive states. Thus, some investigators have hypothesized that GAD may actually be prodromal for MDD.[8,9] A similar clustering of anxiety and depression has been elucidated in family studies of affected patients. Relatives of patients with comorbid anxiety and depression are twice as likely to have depression as are relatives of patients with depression alone, suggesting a familial component in the origin of these disorders.[10]

PHARMACOTHERAPEUTIC OPTIONS IN THE TREATMENT OF ANXIETY DISORDERS

Benzodiazepines and Azapirones

Standard treatment for anxiety has included treatment with benzodiazepines and azapirones. The benzodiazepines are effective, at least in the short term, in treating anxiety and panic, with a more rapid resolution of the somatic manifestations of anxiety.[11,12] However, with the possible exception of alprazolam, these agents as a class are not generally as effective as antidepressants when used alone.[13] Moreover, long-term treatment with benzodiazepines may lead to the development of major depression.[14]

As a class, the azapirones have shown equivocal results in treating anxiety either alone or in the presence of de-

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pression and generally have not been proven to be as effective in the treatment of depression alone.[3] Buspirone appears to be the most effective anxiolytic agent in this class; however, it does not appear to be effective for panic disorder.[15] The antidepressant effects of buspirone are generally noticeable only at the higher end of the dosage range (45–60 mg) and are limited by tolerability issues at these dosages.[2] The more appropriate role for this agent in depression may be to augment the effects of standard antidepressants.[16]

With these points in mind, the following sections review data on the anxiolytic effects of traditional antidepressants, including the tricyclic antidepressant agents (TCAs), monoamine oxidase inhibitors (MAOIs), and newer agents such as selective serotonin reuptake inhibitors (SSRIs), mirtazapine, nefazodone, and venlafaxine extended release (XR), to shed additional light on the relationship between anxiety and depression and on the differential responses of patient subgroups to these agents.

TCAs and MAOIs

TCAs have been studied extensively in a wide range of anxiety disorders, including panic disorder,[17] GAD,[3] and obsessive-compulsive disorder (OCD).[18] Although these agents exhibit a wide spectrum of pharmacologic effects, it appears that the tertiary amine TCAs (imipramine and amitriptyline) with noradrenergic and serotonergic effects provide a more predictable response in the treatment of anxiety. Clomipramine, which is a potent serotonin-selective TCA (although its metabolite inhibits norepinephrine reuptake), stands out in terms of efficacy only in the treatment of OCD.[19,20] TCAs appear to be at least equivalent to the benzodiazepines in the short term and more effective in the long term, with particular effectiveness in reducing the psychic symptoms associated with anxiety.[12,21] However, data on the use of TCAs in GAD are generally from older studies and limited to patients who met outdated diagnostic criteria for GAD.

Despite the anxiolytic efficacy of TCAs, therapy with these agents is compromised by their association with serious adverse effects and a high incidence of intolerably annoying side effects.[18] TCAs are associated with anticholinergic side effects that limit patient acceptability; additionally, these agents may produce substantial weight gain and activation symptoms that may initially worsen symptoms of anxiety.[22] Another important concern with TCA therapy is the potential for fatal overdose with relatively small supplies of drug.

MAOIs are often used for the treatment of more severe forms of MDD, atypical depression, and TCA treatment–resistant depression, in which they have shown good efficacy. Studies in depression have found positive effects on the symptoms of anxiety associated with these disorders; however, the use of MAOIs is limited by their generally intolerable side effects and their potential for adverse drug interactions.[23–26] At least one study has shown MAOIs to be more effective than TCAs in treating patients with atypical depression who also suffer from panic attacks.[25] In another study, the MAOI moclobemide was as effective as fluoxetine in the treatment of panic disorder.[27]

Weight gain, orthostatic dizziness, and hyposomnia are well-characterized side effects of MAOI treatment. In addition, patients receiving MAOIs must follow a tyramine-restricted diet to prevent the occurrence of hypertensive crisis.[18]

SSRIs

It has been suggested that SSRIs will continue to play a significant role in treating certain anxiety disorders. Numerous placebo-controlled studies have demonstrated the efficacy of these agents in related anxiety disorders, such as OCD, panic disorder, and social phobia.[17,18,28–32] The mechanism of action of these agents is believed to involve their selective increase in the availability of serotonin.[33] From a neuropharmacologic perspective, SSRIs may be uniquely suited for the treatment of OCD, with significant treatment effects seen in large numbers of patients in studies of fluoxetine, fluvoxamine, sertraline, and paroxetine.[18] A meta-analysis has suggested that clomipramine may be more potent than the SSRIs in patients with OCD,[34] but with a less favorable side effect profile.

The effect of SSRIs in the treatment of GAD is only now being explored. In one comparator-controlled trial of patients meeting current diagnostic criteria for GAD, Rocca and colleagues[11] found paroxetine to be more effective than the benzodiazepine 2'-chlordesmethyldiazepam by treatment week 4 and equivalent to imipramine. Like the TCAs, the SSRI preferentially improved psychic symptoms of anxiety, whereas the benzodiazepine was more effective at resolving somatic manifestations.[11] The usefulness of SSRIs in GAD may be somewhat limited by their potential to cause activating symptoms, particularly if the initial dosage is too high, and by their relatively slow onset of action.[18]

Overall, the SSRIs have more favorable adverse effect profiles than older antidepressants. Aside from the "jitteriness" reaction that is common with SSRIs, these agents lack the anticholinergic effects of TCAs and are considerably safer in overdosage. However, treatment with SSRIs is not free of adverse effects. These agents are commonly associated with sleep disturbances and gastrointestinal side effects such as diarrhea and nausea.[18] Sexual dysfunction (such as loss of interest in sex or problems with physiologic arousal) are of considerable concern with SSRIs[35] and may require a dosage adjustment or a switch to a different agent.

Miscellaneous Agents

Mirtazapine. Mirtazapine is a newer antidepressant that has noradrenergic and enhanced serotonergic effects.

Its primary mechanism of action appears to be antagonism of presynaptic α_2-adrenoceptors and heteroreceptors.[36] Overall, mirtazapine increases both norepinephrine and serotonin neurotransmission with no effect on the reuptake of these neurotransmitters. No specific studies on mirtazapine in GAD or other related anxiety states have been reported. In one small placebo-controlled study of outpatients with a variety of primary diagnoses of anxiety, mirtazapine at dosages of 15 to 25 mg/day significantly improved overall anxiety symptoms, psychic anxiety on the Hamilton Rating Scale for Anxiety, and global functioning.[37] A meta-analysis of 8 double-blind, controlled trials in patients with MDD also has suggested that mirtazapine is effective at reducing anxiety-related items of the Hamilton Rating Scale for Depression.[38]

Although preliminary evidence suggests some potential for mirtazapine in the treatment of anxiety disorders, the adverse events associated with this agent are somewhat limiting. For example, mirtazapine has a high affinity for histamine H_1 receptors and is sedating.[36] Common side effects include sedation, which may diminish somewhat with continued therapy; increased appetite; dry mouth; and weight gain.[36] However, when compared with SSRIs, mirtazapine appears to be associated with a lower incidence of nausea, sleep disturbances, and sexual dysfunction.[36]

Nefazodone. Nefazodone possesses both serotonin (at a somewhat lower level than the SSRIs) and norepinephrine reuptake activity, although its strongest action is antagonism of the serotonin–type 2A receptor.[39,40] There is a low incidence of insomnia and sexual dysfunction reported with nefazodone.[39] Nefazodone has been studied in patients with MDD and associated anxiety with good results. At dosages of 100 to 600 mg/day, nefazodone significantly reduced scores on anxiety-specific rating scales and on depression-specific psychic anxiety and agitation subscales. It also was associated with improvements in patient-rated symptoms of anxiety, including those in patients with comorbid panic disorder.[41,42] One small open-label trial has also reported on the effects of nefazodone in patients who met current diagnostic criteria for GAD.[43] This preliminary study showed that nefazodone improved symptoms of GAD.

Adverse effects associated with nefazodone therapy include somnolence, dry mouth, nausea, dizziness, constipation, and asthenia. These effects are generally mild to moderate and rarely lead to discontinuation of treatment.[39] In general, nefazodone is better tolerated than the second generation antidepressant trazodone, to which it is structurally similar.

Venlafaxine XR

Venlafaxine XR is a newer antidepressant that increases both norepinephrine and serotonin as a function of reuptake inhibition.[44] This agent has shown considerable efficacy in alleviating anxiety in patients with depression in a randomized, placebo-controlled, clinical trial.[45] Recently, 5 pivotal, placebo-controlled trials with rigorous criteria for GAD have demonstrated overall statistical and clinical superiority of venlafaxine XR compared with placebo (data on file, Wyeth-Ayerst, Philadelphia, Pa., 1998).[46–49] Of particular note is the suggestion of a relatively fast onset of action with venlafaxine XR, especially at higher doses, and evidence of its efficacy in resolving equally well both the psychic and somatic manifestations of anxiety.[50,51]

Table 1. Effect of Antidepressants on Depression, Anxiety, and Mixed Anxiety-Depression[a]

Drug	Major Depression	Panic Disorder	Generalized Anxiety Disorder	Mixed Anxiety-Depression
Tricyclics[b]	+++[c]	+++	+++	++
SSRIs	+++	+++	+++	++
Mirtazapine	++	0	0	+
Nefazodone	++	+	+	++
Venlafaxine XR	+++	++	+++	++

[a]Adapted with permission from Goldberg.[4]
[b]Studies of tricyclics in GAD have been conducted predominantly with previously defined and currently outdated diagnostic criteria.
[c]Efficacy is indicated as follows: +++ = proven; ++ = strong evidence; + = some evidence; 0 = inconclusive.

DISCUSSION

The possible common underlying neurobiochemistry of anxiety and depression may explain the rationale for using antidepressants in the treatment of anxiety disorders. The available anxiolytic agents are typically not effective in the management of anxiety that exists comorbidly with depression. The current database on the wide array of antidepressants suggests that these agents are important in the treatment of both "pure" anxiety disorders and those associated with depression (Table 1).[4] Although the data are most extensive for the TCAs and MAOIs, treatment with these agents is substantially limited because of their adverse event profiles and risk in overdosage. Several therapeutic agents have been proven effective (see Table 1); however, they may vary considerably in potency and specificity of symptoms for the conditions they are effective in treating. Although the SSRIs appear to be effective in panic disorder, OCD, and social phobia, significant data on their effects in GAD are currently lacking.

Perhaps agents that are not limited to action at serotonin receptor sites (i.e., those with dual noradrenergic and serotonergic action, such as mirtazapine, nefazodone, and venlafaxine XR) may play an important role in the treatment of anxiety disorders. Benefits of newer agents that have dual mechanisms of action have been established for treatment of depression and symptoms of anxiety associated with depression.[39,45] Because of the frequent comorbidity of depression and anxiety disorders, the use of

monotherapy with an antidepressant in patients with a comorbid diagnosis may enhance compliance and reduce risk of drug-drug interactions. Moreover, antidepressant therapy can facilitate treatment in patients with mixed symptoms when a primary diagnosis of depression or anxiety is difficult to distinguish.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), buspirone (BuSpar), clomipramine (Anafranil and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine XR (Effexor XR).

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