Anxious Depression

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Depression and anxiety often coexist. When they co-occur, both anxiety and depression appear to be more severe. Increased morbidity, poorer acute and long-term outcome, increased suicide risk, and increased treatment resistance are associated with comorbid anxiety and depression. The term *anxious depression* has taken on newer meaning with the changes in the diagnostic system that allow for concurrent diagnosis of anxiety disorders and major depression. Attention to the subtype of both anxiety and depression could have significant effects on treatment choice by the clinician. The authors review some historical aspects of anxious depression and also highlight some of the advances in differential diagnosis and treatment of coexisting depression and anxiety.

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Mood and anxiety disorders constitute the 2 largest groups of mental disorders in the United States.[1] Mood disorders affect an estimated 19% of the general population, and anxiety disorders occur in approximately 17%. Anxiety and mood disorders are not only extremely common, but they coexist at some point in the majority of individuals who suffer from either anxiety or mood disorders. The association of anxiety and depression can take many different forms. For example, it could be an overlap of 2 distinct disorders that begin at the same time or at different times, depression with anxiety symptoms, anxiety with depressive symptoms, or as combined symptoms that are secondary to a medical or other psychiatric disorder. When they co-occur the prognosis for recovery from the acute episode—as well as the longer term prognosis—is affected adversely. The incidence of this comorbidity is high in the general population as well as in medically ill patients.[2,3] Breslau and Peterson[4] recently reported that anxiety disorders in women may be important determinants of risk for developing major depression. The risk for major depression is increased by preexisting anxiety disorders, and women are more likely than men to develop an anxiety disorder at an early age. They reported that the presence of more anxiety disorders in females accounted for 50% of the gender-related difference in lifetime major depression. It is estimated that up to one third of patients with current major depression have recurrent panic attacks.[5] 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.[6,7] In one study of 327 depressed patients, those who had high anxiety took twice as long to recover (26 weeks) from the index depressive episode as did those with low anxiety (13 weeks).[8]

The term *anxious depression* was initially used to describe individuals with prominent anxiety symptoms in the context of major depression. Overall, Zisook, and colleagues[9,10] described subtypes of depression based on a factor analysis of the Brief Psychiatric Rating Scale (BPRS) scores from depressed hospitalized veterans. They initially suggested that subtypes could be identified as "anxious," "hostile," and "retarded." These subtypes could be identified in a reliable fashion, and, as further support for the validity of this subtyping, they showed that there was a differential response to treatment among the subtypes.

Prior to DSM-III-R,[11] specific anxiety disorders such as panic disorder, social phobia, obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) were recognized as diagnostic entities. However, if these disorders co-occurred with major depression, diagnosis of a separate anxiety disorder was not permitted. In current diagnostic terms, the concept of anxious depression is not a DSM-IV category, but it is still clinically relevant. While many patients with major depression or dysthymia have additional, discrete anxiety disorders,[12] a residual category of patients have prominent anxiety symptoms that do not meet criteria for a DSM-IV diagnosis.[13] Additionally, a significant propor-

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Table 1. Anxious Depression: Diagnostic Evolution?

Historical Term	DSM-III-R/DSM-IV
Anxious depression	Major depression plus:
	Panic disorder
	Social phobia
	Generalized anxiety disorder
	Obsessive-compulsive disorder
	Posttraumatic stress disorder
	Mixed states:
	Mixed anxiety-depressive disorder

tion of the population suffers from subdiagnostic depressive and anxiety symptoms referred to in DSM-IV as mixed anxiety-depressive disorder (Table 1).

Important advances have been made in the pharmacologic treatment of mood disorders over the past several years. A number of medications that are effective tools for treating these disorders are now available. However, the clinician is frequently faced with a patient whose anxiety symptomatology is not responding satisfactorily to the standard treatment. A significant confounding factor in the effective treatment of anxiety disorders is the presence of a comorbid condition such as major depression. This review will highlight the differential diagnosis of depression with anxiety and give emphasis to the treatment implications of comorbid depressive symptomatology.

DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS FOR ANXIETY AND DEPRESSION

When a clinician evaluates a patient who has depression with prominent anxiety symptoms, several factors should be evaluated to establish the etiology of the anxiety and depressive symptoms. Firstly, the clinician should evaluate medical factors (especially in the elderly) that may be contributing to the clinical picture. These include concurrent psychotropic or other medication that could cause anxiety symptoms, sedative-hypnotic withdrawal, stimulant use/abuse, and other relevant factors. Since agitation associated with hypomania can present as anxiety, an important clinical consideration is to establish whether the patient has bipolar or nonbipolar (e.g., unipolar) depression, as treatment planning is likely to be considerably different if bipolar symptoms are or have been present. The natural history of the mood disturbance can inform the clinician regarding the response to treatments, duration, and severity of the episodes in the past, and whether there have been periods of complete remission or a more chronic course. The clinical features of the mood disturbance are important to consider. Determination of the pattern of the depression (e.g., endogenous or melancholic, atypical, nonendogenous, agitated, retarded) can have important clinical implications. For example, atypical depression, which is characterized by hypersomnia/hyperphagia, weight gain, reversed diurnal variation (worse in the evening), reactive mood, and heightened interpersonal sensitivity, is preferentially responsive to the monoamine oxidase inhibitors (MAOIs), and possibly selective serotonin reuptake inhibitors (SSRIs), than to the tricyclic antidepressants (TCAs).

In evaluation of anxiety symptoms, many of the same considerations regarding depression apply, such as a review of other causes for anxiety symptoms. Determination of the presence of a specific anxiety disorder is important and can have implications for choice of treatment also.[7] Even when subdiagnostic anxiety symptoms exist with major depression, targeting the coexisting anxiety syndrome may be important.

COEXISTING MAJOR DEPRESSION AND PANIC DISORDER

Major depression and panic disorder frequently coexist.[14] 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. Conversely, an average of one third (range, 21%–91%) of patients meeting criteria for panic disorder experience an episode of major depression at some time during their lives.[7]

Panic disorder and major depression may occur simultaneously, panic disorder may precede major depression, or vice versa. Studies indicate that approximately one third of patients experience panic disorder first, one third or more experience major depression first, and the remainder experience simultaneous onset of these disorders.

There are limited data evaluating the differences between primary (i.e., occurs temporally earlier) and secondary (i.e., occurs following the panic disorder) depression in patients with panic disorder. Several lines of evidence suggest 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. These comorbid patients have a longer period of illness, respond less positively to pharmacologic treatment, exhibit more psychological and psychosocial impairment, and have more anxiety and somatic concerns.

Treatment of coexisting panic disorder and major depression poses a considerable challenge to the clinician. Efficacy studies of pharmacotherapy in uncomplicated panic disorder have been completed with benzodiazepines, TCAs, MAOIs, and SSRIs. Overall, these agents provide the clinician with a wide range of safe and well-tolerated treatment options to achieve remission in panic symptoms. Although recent research suggested that benzodiazepine monotherapy may be effective in the treatment of coexisting panic disorder and depression, this issue remains controversial.[15] However, comparative data regarding the efficacy of different agents in the treatment of patients with panic disorder and concurrent depression are limited and rarely definitive.

The available literature indicates that acute treatment outcome for individuals with comorbid panic disorder and major depression is usually poorer than for either alone. Grunhaus et al.[16] reported that following 3 weeks of treatment with imipramine, desipramine, or phenelzine, only 15% of hospitalized patients with panic disorder and major depression responded to treatment, compared with a 53% response rate in patients with major depression alone. In contrast, Lesser et al.[17] reported results from an 8-week, double-blind placebo-controlled study comparing the efficacy of alprazolam and placebo in outpatients with panic disorder. They found that subjects with a clinically predominant panic disorder and mild secondary nonmelancholic depressive symptoms responded well to alprazolam treatment, with good resolution of both depression and anxiety symptoms. However, it is noteworthy that this study excluded patients with "clinically predominant" major depression or an episode of depression that began before the onset of panic disorder. Maddock et al.[15] reported that outpatients with panic disorder and a history of recurrent depression exhibited greater symptom severity and poorer response to short-term treatment with the triazolobenzodiazepine adinazolam (sustained release) than patients with no history of major depression. More recently, Keller et al.[18] reported the results of a study specifically designed to evaluate the efficacy of alprazolam, imipramine, and placebo in patients with panic disorder and moderately severe current major depression. Patients with more severe depression than in the study by Lesser et al.[17] were included. Patients in all groups improved over the course of treatment; both alprazolam and imipramine were superior to placebo for anticipatory anxiety, phobia, and depression, but were not different in decreasing panic frequency or severity. The authors speculated that depression may reduce the antipanic effects of both medications. They reported that the presence of more severe depression was associated with generally less favorable treatment outcome compared with the presence of panic disorder and mild depressive symptoms. It appears that for the majority of patients with moderate depression coexisting with panic disorder, antidepressants are probably required; adjunctive benzodiazepine treatment may be helpful in controlling residual anxiety symptoms. Since active treatments and placebo treatments had similar effects on panic frequency, evaluation of the relative efficacy of these agents in patients with comorbid panic disorder and major depression was difficult. The efficacy of benzodiazepines for patients with severe major depression and panic disorder remains inadequately studied.

Recently, nefazodone, a phenylpiperazine compound chemically related to trazodone, has been evaluated in the treatment of 55 patients with coexisting major depression and panic disorder.[19] At 500 mg/day, nefazodone had significantly greater efficacy than imipramine at a dose of 250 mg/day or placebo in the treatment of patients with major depression and panic disorder. Additionally, nefazodone was better tolerated than imipramine.

Figiel et al.[20] evaluated the efficacy of electroconvulsive therapy (ECT) in the treatment of 8 patients with concurrent major depression and panic disorder. The authors found that following ECT (an average of 7.4 treatments), patients showed improvement in their depression and experienced no panic attacks beginning with the fourth ECT treatment.

Long-term, naturalistic follow-up studies strongly indicate that the long-term prognosis for patients with major depression and panic disorder is poorer than that for patients with major depression only. In a 2-year follow-up study of patients initially assessed in an index episode of major depression, Coryell et al.[21] reported that 74.1% with major depression alone had recovered, compared with 50% of patients with primary panic disorder and secondary major depression; work impairment was still evident in 67% of patients with panic disorder plus major depression versus 28% of patients with major depression alone. Patients with major depression and panic attacks had more depression, substance abuse, and impaired psychosocial adjustment at a 5-year follow-up compared with patients without coexisting anxiety. Noyes et al.[22] conducted a 3-year follow-up of patients with panic disorder both with and without current or past secondary, nonmelancholic major depression. They reported that the comorbid group had longer course of illness, more severe panic and phobic avoidance, and were less treatment responsive than were nondepressed subjects. Finally, recent data indicate that the prevalence of suicide attempts in patients with major depression and panic disorder is about twice that of patients with only 1 of the disorders; successful suicide within a year after hospitalization for depression was increased in those patients with concurrent panic attacks.[23] The clinician should keep in mind the increased risk for suicide in these comorbid patients, and choosing an agent which would be safe in overdose should be a part of the clinical assessment and treatment plan.

In summary, the optimal treatment for an individual with both major depression and panic disorder is not yet clear. Treatment choice must be guided by clinical judgment, side effects, and the wishes of the patient. It appears that patients with mild, nonmelancholic, secondary major depression and panic disorder exhibit similar or slightly lower response rates compared to those with panic only, while moderately to severely depressed patients with panic disorder respond significantly less well to treatment. It has been suggested that MAOIs may be superior to TCAs in the treatment of patients with comorbid depression and panic disorder, especially primary "atypical" depression with panic attacks.[6,24,25] Since the MAOIs require dietary restrictions, enthusiasm for using them as first-line treatment is limited. If the clinical situation allows for it, a trial of at least 2 other antidepressants (Table 2) with antipanic properties is probably preferable before initiating treat-

Table 2. Efficacy of Pharmacologic Agents for Coexisting Depression and Anxiety*

Agent	Panic Disorder	Social Phobia	Generalized Anxiety Disorder	Mixed Anxiety-Depression	Posttraumatic Stress Disorder	Major Depression
Antidepressants						
MAOIs	++++	++++	+/?	+/?	+	++++
SSRIs	+++	+++	+	+/?	++	++++
TCAs	++++	0	++	+/?	+	++++
Anxiolytics						
Benzodiazepines	++++	+++	++++	+/?	–	0
Buspirone	0	–	++++	++/?	+	++
Novel antidepressants						
Bupropion	0	+	?	?	?	++++
Mirtazapine	+/?	+/?	+	+	+/?	++++
Nefazodone	+	?	+	+/?	?	++++
Trazodone	0	?	++	+/?	?	++++
Venlafaxine	+	++	+	+/?	?	++++

*Adapted from reference 26, with permission.
Abbreviations: MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.
Symbols: 0 = not effective; + = limited data; ++ = limited controlled data; +++ = clearly effective; ++++ = superior efficacy; +/? = possibly effective, not studied; ? = has not been studied; – = not applicable.

ment with MAOIs. The efficacy of the available SSRIs (fluoxetine, paroxetine, sertraline, and fluvoxamine) in the acute treatment and long-term maintenance of patients with major depression has been documented in several research trials.[27] The SSRIs have also been used successfully in the treatment of uncomplicated panic disorder and are increasingly used as the first-line treatment for panic disorder.[28] It is plausible, therefore, that these agents may be useful in the treatment of panic disorder with comorbid depression. However, no systematic evaluation of patients with panic disorder and depression has yet been reported. We favor the use of these agents, especially in cases in which other antidepressants are not well tolerated.

COEXISTING MAJOR DEPRESSION AND SOCIAL PHOBIA

Social phobia is a disorder characterized by fear and avoidance of situations in which an individual may be scrutinized by others and fears that he or she will be embarrassed or humiliated.[11] Social phobia is the third most common lifetime mental disorder in the general U.S. population (13.1%), following major depression (17.1%) and alcohol dependence (14.1%).[1] Major depression is frequently associated with social phobia, and conversely, social phobia is often complicated by major depression.[7] From a differential diagnostic perspective, it is important to discriminate social phobia from the social withdrawal associated with depressive illness.[29]

Treatment of patients with social phobia is particularly important because of the significant impairment in functioning, social isolation, and depression that accompany it.[30] Clinical trials and case reports have documented the efficacy of medication treatment for social phobia.[26] Efficacy of pharmacotherapy for social phobia has been shown for MAOIs, benzodiazepines, and, more recently, for the SSRIs in the treatment of social phobia.[31] Although social phobia is a discrete disorder, individuals with social phobia are at high risk for additional disorders, including major depression. Schneier et al.[32] studied social phobia in 4 U.S. community samples from the Epidemiologic Catchment Area (ECA) study and reported substantial comorbidity of social phobia with other anxiety disorders and major depression. Major depression and dysthymia occurred in 29% of subjects with social phobia. In 71% of social phobics with comorbid major depression, the depression developed after the onset of social anxiety. These data indicate that clinicians must have a high index of suspicion for the presence of a depressive disorder in patients presenting with social phobia.

As mentioned, comorbidity of major depression with social phobia is often associated with more severe psychopathology, increased impairment in functioning, and an increased rate of suicide attempts. Despite the high prevalence and clinical significance of comorbid presentation of social phobia and major depression, empirical data regarding treatment are lacking. Until more information regarding treatment is available, treatment choice must necessarily be guided by identifying all disorders present (e.g., social phobia, depression, panic disorder, others) and treating with an agent (or more than 1) that should be effective in treating all of them.

Based on the information currently available, patients with comorbid major depression and social phobia should probably receive antidepressant treatment. For patients suffering from comorbid atypical depression, MAOIs may be the optimal treatment. The SSRIs have been established as effective for patients with major depression,[27] and, like the MAOIs, also appear to be more effective than the TCAs for patients with atypical depression.[33] As noted above, there is also growing evidence that SSRIs are beneficial in the treatment of social phobia. Thus, these agents may also have a therapeutic role in patients with coexisting major depression and social phobia. Because of the inconvenience associated with MAOI treatment, a trial with 1 or more SSRIs is a reasonable first treatment for major depression coexisting with social phobia. If the SSRI is ineffective or not tolerated, after a washout of 2 weeks (or 5 weeks for fluoxetine), an MAOI such as phenelzine or tranylcypromine may be used. Addition of a high-potency benzodiazepines may be considered, if necessary.

TCAs have not been studied in a controlled fashion in comorbid depression and social phobia. In our experience,

a TCA such as imipramine is ineffective for patients with social phobia.[34] For some patients, additional cognitive-behavioral therapy may be required to optimally control social anxiety.

In summary, some antidepressant agents are clearly effective for social phobia (see Table 2). The benzodiazepines are effective in the treatment of social phobia, but are not consistently effective antidepressants. Because social phobia is a chronic, often unremitting condition, long-term treatment may be necessary. As noted, social phobia is frequently associated with depression. The presence of major depression with social phobia can complicate treatment and negatively affect outcome. Despite the lack of data on the comorbid condition, the MAOIs and SSRIs should be considered currently as reasonable first-line treatments for patients with coexisting major depression and social phobia. The addition of other agents (e.g., adjunctive benzodiazepines) and/or cognitive-behavioral therapy could further enhance response. The need for maintenance treatment to prevent relapse may be indicated.

Remaining questions, including the relative efficacy of different treatments, relapse after discontinuation of medication, or cognitive-behavioral therapy, and indications for long-term treatment await further study.

COEXISTING MAJOR DEPRESSION AND OBSESSIVE-COMPULSIVE DISORDER

A relatively small subgroup of patients presenting with major depression also have OCD, but there is a strong association of OCD with depression. Rasmussen et al.[35] observed that 80% of a 44 OCD patient sample had a lifetime history of major depression; 30% met criteria for major depression at the time of evaluation. Using data from 7 national community surveys (including the United States), Weissman et al.[36] reported that subjects with OCD were at substantial risk for comorbid lifetime major depression (range, 12.4%–60.3%).

A few studies have examined pharmacologic treatment for OCD with coexisting depressive symptoms or major depression. Katz and Deveaugh-Geiss[37] analyzed the data from 2 placebo-controlled, multicenter trials of clomipramine in the treatment of patients with OCD. They observed that patients with major depression or depressive symptoms experienced improvement on OCD ratings that was comparable to improvement in those without depression after clomipramine treatment. Since patients with severe current major depression or any prior major depression were excluded from this study, it is not possible to draw conclusions about the efficacy of clomipramine in severely depressed OCD patients.

The SSRIs are effective in the treatment of both depression and OCD.[26] The first systematic study of comorbid major depression and OCD was recently reported by Hoehn-Saric et al.[38] In that study, which compared the SSRI sertraline, the TCA desipramine, and placebo, the SSRI was superior to desipramine and placebo in alleviating both depression and OCD. Thus, the SSRIs appear to be superior in alleviating concurrent depressive and OCD symptoms; other antiobsessionals have not yet been studied in a rigorous fashion. The clinical relevance of comorbid major depression and OCD was noted by Hollander et al.,[39] who reported unexpected exacerbation of depressive symptoms in 6 of 10 patients during a rapid dose increase (20 mg every 2 days to 60–80 mg/day) of fluoxetine. Eight of these patients showed further improvement in depressive symptoms with the addition of nortriptyline, desipramine, or imipramine to fluoxetine. The authors concluded that perhaps both noradrenergic and serotonergic effects may be required for optimal response to pharmacotherapy in some patients.

Lithium augmentation has been reported to benefit OCD patients with depressive symptoms. In 2 studies evaluating the efficacy of lithium augmentation in patients with OCD, some patients showed improvement in depression ratings but not in obsessive-compulsive symptoms following the addition of lithium.[40]

Limited data regarding the use of ECT in the treatment of patients with OCD and OCD with depression are available. ECT should be considered in patients with severe major depression and comorbid OCD who have been unresponsive to other treatments.

Several strategies for the treatment of comorbid OCD and depression have been suggested.[41] Following an adequate therapeutic trial with at least 2 antiobsessional agents, augmentation strategies (SSRI + TCAs such as desipramine or imipramine, SSRI + lithium, clomipramine + lithium or SSRI) should be completed. Use of TCAs combined with SSRIs should be conducted cautiously, as SSRIs may interfere with TCA metabolism and increase blood TCA levels. Combined use of SSRIs has also been utilized in the treatment of unresponsive OCD patients.[40] Since controlled data are lacking, we recommend combining clomipramine with SSRIs only if side effects prevent dose escalation of clomipramine to 250 mg/day. Since clomipramine has some potential for lowering seizure threshold, it is advisable to monitor plasma clomipramine levels before and after the addition of SSRIs to assure that clomipramine levels do not rise to extremely high levels. The addition of lithium may also be helpful in some mood disordered refractory patients. Intensive behavioral therapy in conjunction with pharmacotherapy may also be useful in the treatment of comorbid depression and OCD; depressed mood may limit patient motivation to participate fully in cognitive-behavioral therapy.

COEXISTING MAJOR DEPRESSION AND POSTTRAUMATIC STRESS DISORDER

An important variable that requires consideration during the treatment of patients with PTSD is the presence of co-

morbidity with another Axis I or Axis II disorder. Davidson et al.[42] evaluated lifetime diagnoses of 44 World War II and Vietnam veterans and found that 59% met lifetime criteria for major depression, 59% for alcoholism, 47% for GAD, and 30% for panic disorder. The authors also reported that alcoholism, PTSD, GAD, panic disorder, and depression represented, on average, the sequence of illness onset. Similarly, major depression and panic disorder were also found to be the most delayed in onset compared with PTSD in 60 veterans of Vietnam, World War II, and Korea reported in a study by Mellman et al.[43] These observations suggest that panic and depression may represent secondary complications, manifestations of illness progression, or both.

Despite high rates of depression in PTSD patients, antidepressants and psychotherapeutic techniques targeted at reducing depressive symptoms were less effective in depressed patients with PTSD than in patients with depression alone.[44] For example, Davidson et al.[45] reported results from a study investigating the predictors of response to pharmacotherapy in PTSD. They observed that treatment response to amitriptyline was related to lower baseline levels of depression, neuroticism, combat intensity, anxious mood, impaired concentration, somatic symptoms, feelings of guilt, and high degree of trauma avoidance.

Based on clinical neuroendocrine challenge response differences between patients with major depression with and without PTSD, Southwick et al.[44] suggested that depressive symptoms in PTSD may not simply be a manifestation of a concurrent major depressive episode, but rather may reflect either secondary or "nontypical" depressions. Since etiology of comorbid depression accompanying PTSD may differ significantly from the primary major depression, patients with PTSD probably require different, individualized treatment interventions.

COEXISTING MAJOR DEPRESSION AND GENERALIZED ANXIETY DISORDER

The hierarchical rules used in DSM-III that obscured the independence of generalized anxiety disorder (GAD) from mood disorders were dropped. As a result of these shifting diagnostic criteria, our knowledge of the clinical relevance of coexisting major depression and GAD is unfortunately limited. Sanderson et al.[12] reported that over half of a sample of approximately 100 patients presenting for treatment for major depression or for dysthymia also had anxiety disorders; approximately 20% of each group had GAD. We evaluated 109 patients with GAD and found that 42% had experienced at least 1 major depressive episode during their lifetime, with the first episode typically beginning shortly after the onset of GAD.[46]

Benzodiazepines have traditionally been the treatment of choice in patients with GAD. However, coexisting depression and GAD raise questions regarding monotherapy with benzodiazepines in this patient subgroup. For example, Rickels et al.[47] observed that the presence of concomitant depression in GAD patients was associated with poor response to diazepam treatment. There is some evidence in the literature suggesting that the triazolobenzodiazepine alprazolam may have specific antidepressant properties.[48] Whether it is optimally effective in treating anxious patients with moderate-to-severe depression remains unclear. Recent evidence that the TCAs are effective in the treatment of GAD accompanied by high levels of depression provides a useful clinical alternative.[47] The antidepressant effect of azapirones in the treatment of GAD with coexisting major depression has not been studied directly. Rickels and Schweizer[48] reviewed previous GAD treatment studies and found a significant improvement in depressive symptomatology during the course of anxiolytic treatment with buspirone. It appears that buspirone may be a useful anxiolytic for patients with coexisting depressive symptoms. Controlled studies of coexisting GAD and depression are required in order to confirm these indirect observations. Based on these data and our clinical experience, it appears that the TCAs or buspirone may have a useful role in the treatment of GAD with prominent depressive symptomatology, particularly for patients for whom benzodiazepine treatment does not ameliorate depressive symptoms. SSRIs have not been studied, but clinical experience suggests that anxious depressed patients respond well to the SSRIs. Mirtazapine, a newly released antidepressant, also appears to ameliorate depression-related anxiety or GAD associated with major depression.[49,50] At this point, prior treatment response, patient preference, and side effect profiles should be considered in the treatment decision process.

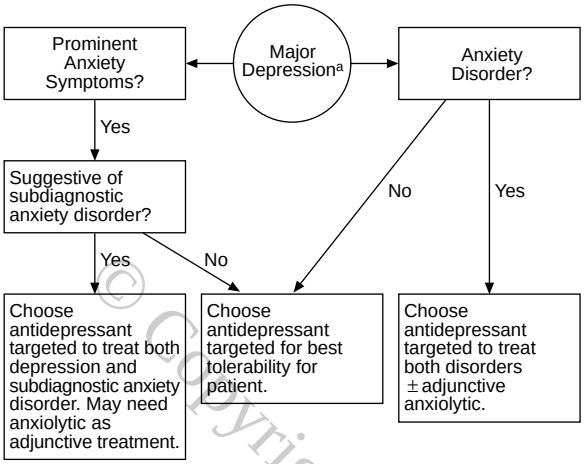
MIXED ANXIETY-DEPRESSION

The presentation of patients with mixed symptoms of anxiety and depression is common in general medicine.[51] It is estimated as the third most common ambulatory diagnosis in primary care practice.[52] Little is known about the treatment of this group of patients, but it probably most closely corresponds with the major depression-GAD group discussed above. The impairment and health care utilization associated with untreated mixed anxiety-depression is significant, and recognition and treatment of these patients are important.[53] Until more is learned about the treatment of these patients, targeting the more prominent component for treatment and careful monitoring are suggested (Figure 1).

CONCLUSIONS AND SUMMARY

The concomitant existence of both mood disorders and anxiety has only recently been routinely assessed. It is now

Figure 1. Treatment Strategies for Anxiety and Depression



[a]Same general strategy can be used with subdiagnostic depression instead of major depression.

clear that the presence of comorbid depression and anxiety can affect the course and treatment outcome. This review highlighted recent advances in the pharmacologic treatment of depression in the significant subgroup of anxious depression. Anxious depression as a diagnostic category does not exist in the DSM-IV; however, more study is needed to identify whether there is a residual category of patients with major depression with problematic anxiety symptoms. As was suggested over 30 years ago by Overall et al.,[9] identification of coexisting anxiety is extremely important and may determine treatment choice. We now know that the type of anxiety detected may affect treatment planning (see Table 1). The need for controlled studies comparing different agents that specifically include patients with coexisting anxiety and mood disorders is clear. Considerable progress has been made in recent years in our ability to offer help to these patients, although issues of comparative efficacy, treatment resistance, length of treatment, and relapse prevention remain areas requiring further investigation.

Drug names: adinazolam (Deracyn), alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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