Treating Comorbid Depression and Anxiety

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Depression and anxiety disorders are distinct illnesses that often coexist. Patients suffering from both disorders have more psychological, physical, and social impairment than do patients suffering from either illness alone. Mixed anxiety-depression is gaining recognition as a separate diagnosis and has been included in the *International Classification of Diseases,* 10th edition, and in the appendix of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition. Current treatment recommendations for comorbid depression and anxiety are based on clinical experience with the treatment of anxiety and depressive disorders when they occur independently. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective for simultaneously occurring anxiety and depression, but the side-effect profiles of the MAOIs and TCAs limit their use for this condition. Benzodiazepines are useful for the acute treatment of anxiety symptoms and buspirone for chronic generalized anxiety, but neither agent is effective for the long-term treatment of depression. The recently available antidepressants nefazodone and venlafaxine may also be useful for this patient population. When possible, psychotherapy should be used in conjunction with pharmacotherapy to improve treatment outcomes.

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Depression and anxiety have commonly been considered distinct illnesses that were treated exclusively with either antidepressants or anxiolytics, respectively. However, as clinical experience increased with diagnosing and treating these distinct disorders, the concepts of comorbid and mixed conditions began to emerge. It is not uncommon for a patient with a primary diagnosis of depression to experience significant symptoms of anxiety (Figure 1).[1] Similarly, many patients with a primary diagnosis of anxiety disorder also exhibit depressive symptomatology.

It is important to recognize the subtle differences between pure depression and pure anxiety, comorbid depression and anxiety, and the newly classified disorder, mixed anxiety-depression. There are several theoretical models that attempt to distinguish these disorders. Traditional theory classifies depression and anxiety as distinct entities that are clearly defined by separate diagnostic categories in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[2] In accord with the traditional theory, patients may be diagnosed with either one disorder or another, but not with both depression and anxiety disorder concomitantly. The comorbid theory suggests that although depression and anxiety disorder are distinct illnesses, both conditions may occur in the same patient at the same time. The final theory addresses the "subsyndromal" condition, in which symptoms of anxiety and depression do not meet the full diagnostic criteria for either disorder, but are chronic and stable enough to cause significant disability and to require treatment. At this time, the disorder classified as mixed anxiety-depression is only included as a provisional category in the DSM-IV (Table 1).[2] However, it is designated as a separate diagnostic category in the *International Classification of Diseases*, 10th edition.[3]

Successful treatment of a patient presenting with symptoms of depression and anxiety depends upon an accurate diagnosis of depression, anxiety disorder, comorbid depression and anxiety disorder, or mixed anxiety-depression. This article will focus on current treatment recommendations for comorbid depression and anxiety. Many drugs that are effective antidepressants will also alleviate symptoms of anxiety. Unfortunately, the opposite cannot be said about the effectiveness of anxiolytics for the treatment of depression. For example, benzodiazepines (BDZs) may appear to improve depressive symptoms acutely, but they are not effective for the long-

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term treatment of depression and may even cause depression.

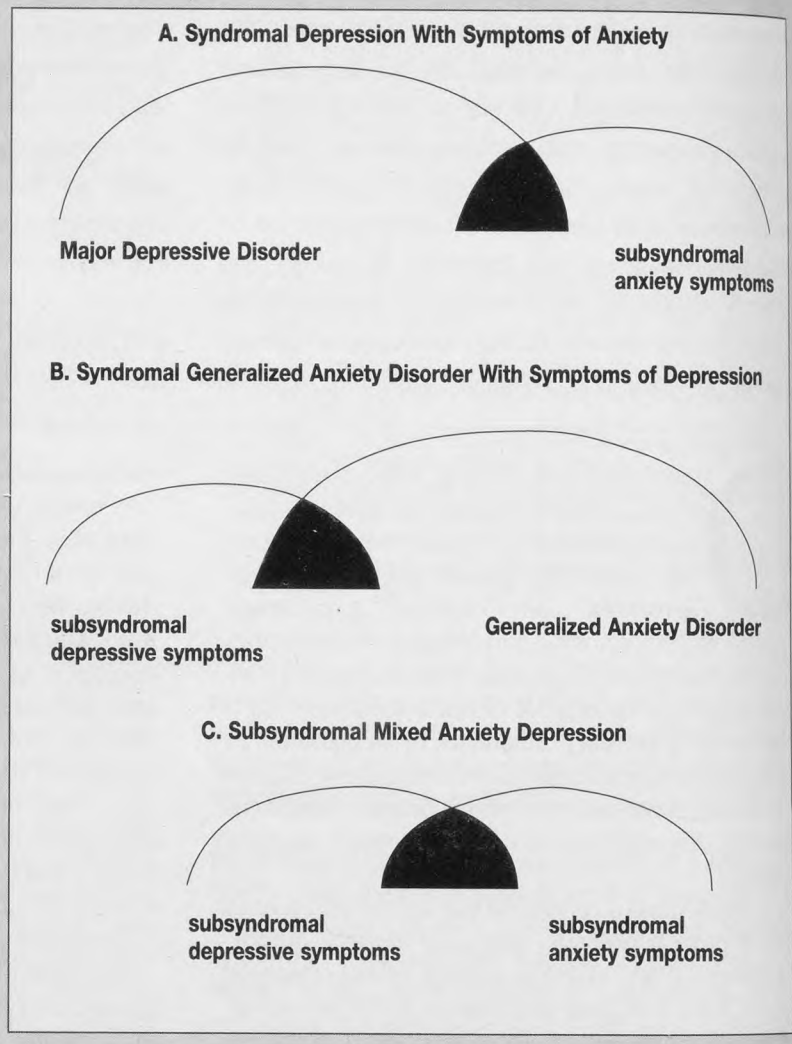
PREVALENCE

It is difficult to determine the true prevalence of comorbid depression and anxiety because there is no consensus about the specific diagnostic criteria for these concomitant conditions. Nevertheless, clinical experience suggests that symptoms of anxiety frequently complicate the course of a depressive episode. When major depression is the primary disorder, approximately 60% of patients will also experience moderate levels of anxiety and 20% to 25% will have severe anxiety.[4,5] Patients with depression also tend to have a high incidence of social phobia (15%) and a history of panic attacks (20% to 30%). It is estimated that as many as 10% of patients in the community setting have comorbid depression and anxiety.[6-9]

FIGURE 1

Theories on comorbid depression and anxiety.

Patients may have a major depressive disorder plus symptoms of anxiety not meeting the criteria for an anxiety disorder (A) or a generalized anxiety disorder with symptoms of depression not meeting the criteria for major depressive disorder (B) or subsyndromal mixed anxiety and depression (C). The subsyndromal concept includes patients with chronic, stable symptoms of anxiety and depression that do not reach the level of severity required to make a diagnosis of an anxiety or affective disorder. Reproduced from Stahl, 1993, with permission.[1]



RISK FACTORS

Unlike patients with depression alone or anxiety disorders alone, patients with comorbid depression and anxiety may exhibit reduced responsiveness to conventional therapies, a longer course of illness, and a poorer prognosis. Patients with comorbid depression and anxiety suffer more psychological and social impairment and have more anxiety and somatic complaints than do patients with either illness alone.[10-13] As a result, these patients utilize a disproportionate share of medical staff time in primary care settings.[14]

Suicide prevention is the first consideration in the treatment of major depression with anxiety because symptoms of severe psychic anxiety, panic attacks, and agitation are associated with higher suicide rates.[8,15,16] Lifetime rates of suicide attempts for pure major depression (7.9%) or pure panic (7%) occur at a similar frequency in the community, but the risk nearly triples when both depression and anxiety disorders are present (19.5%).[8] In studies evaluating patients hospitalized after an attempted suicide, 3% to 12% will commit suicide upon their release from the hospital.[17-19] Therefore, suicide attempts should be taken very seriously because many patients who fail in their first suicide attempt will often try again and succeed.

DIAGNOSIS

Considerable overlap exists between depression and anxiety disorders. It is not uncommon for depressed patients to also complain of anxiety symptoms, such as worry, fear, autonomic hyperactivity (eg, sweating), panic attacks, and obsessions and compulsions.[5] Other symptoms that can result from either depression or anxiety include physical restlessness, lack of concentration, insomnia, appetite changes, nonspecific cardiopulmonary or gastrointestinal complaints, irritability, lack of energy, and fatigue.

Despite the similarities, there are factors that can assist in making an accurate diagnosis. Depressive disorders are distinguished from anxiety by the presence of a negative affect, feelings of hopelessness, apathy, emotional withdrawal, fatigue, and loss of interest or pleasure. Conversely, physiologic symptoms, such as motor tension and autonomic hyperactivity coupled with feelings of fear, agitation, and anxious mood, are more suggestive of anxiety than of depression (Table 2).[20-22] For example, panic disorder, a common anxiety disorder, is diagnosed by the occurrence of two or more unexpected panic attacks associated with at least 1 month of fear or worry about the consequences of the attack. Other anxiety disorders, such as generalized anxiety disorder and social phobia, are also characterized by excessive anxiety and worry. Another measure that can be used to distinguish depression from anxiety is the evaluation of sleep patterns. Depressed patients are more likely to complain of sleep disturbances due to early-morning awakening as opposed to patients with anxiety, who more often complain about having difficulty falling asleep. Diurnal mood variation (ie, improvement in mood as the day progresses) is also more indicative of depression than of anxiety.

An important aspect of diagnosing mood disturbances in the primary care setting is the realization that patients with comorbid depression and anxiety are more likely to present with general, medically unexplained, somatic complaints than with the classic symptoms of depression or anxiety. This nonspecific presentation of symptoms suggests the need for a more extensive workup because it is likely that a comorbid condition may be present. It is important to recognize that when depression is the primary disorder, the symptoms of anxiety are often subsyndromal and may not meet the diagnostic criteria for an anxiety disorder. Subsyndromal symptoms are of interest because under stress they may provoke the development of an overt anxiety or depressive disorder requiring additional treatment or hospitalization. Subsyndromal symptoms of anxiety should not be dismissed as insignificant because patients with these symptoms have a higher lifetime risk for developing a comorbid anxiety or depressive disorder. Therefore, their response to treatment should be closely monitored.

DRUG THERAPY

The recommended treatment approach for patients with comorbid depression and anxiety is to focus on treating the depressive component because it is associated with more serious morbidity and mortality.[22] Initiating therapy with an antidepressant is beneficial because most antidepressants are also effective for anxiety symptoms[23-27] as opposed to the BDZs, which are ineffective in alleviating depressive symptoms.[28] Further support for using antidepressants as monotherapy in this patient population is provided by clinical experience. Many primary care physicians have observed that as the overall depressive symptoms improve, the anxiety symptoms will resolve spontaneously and not require specific treatment. Therapeutic choices in the treatment of depression in the patient with comorbid anxiety include the tricyclic antidepressants (TCAs), the selective serotonin reuptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). Other recent introductions to the antidepressant armamentarium (eg, nefazodone, venlafaxine) may also be effective for this patient population.

Tricyclic Antidepressants

Some clinicians favor the use of TCAs because their sedative properties are useful for the anxious component of the patient's disorder. However, this may not be of clinical benefit to some patients who become overly sedated with TCAs. In addition, other side effects of TCA therapy (eg, dry mouth, constipation, blurred vision, weight gain, and sexual dysfunction) do not decrease in severity with continued therapy and are usually enough of a problem to prevent patients from completing a full course of therapy or from receiving full therapeutic doses. The secondary amines (eg, nortriptyline and desipramine) are better tolerated than are the tertiary amines (eg, imipramine or amitriptyline) because they cause fewer anticholinergic side effects and less orthostat-

TABLE 1

Research Criteria for Mixed Anxiety-Depression

Persistent or recurrent dysphoric mood lasting at least 1 month

Four (or more) of the following symptoms present during the same period:

- Difficulty concentrating or "mind going blank"
- Sleep disturbance (eg, difficulty falling or staying asleep or restless, unsatisfying sleep)
- Fatigue or low energy
- Irritability
- Worry
- Being easily moved to tears
- Hypervigilance
- Anticipating the worst
- Hopelessness (eg, pervasive pessimism about the future)
- Low self-esteem or feelings of worthlessness
- Clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse or a medication) or a general medical condition

All of the following:

- Criteria have never been met for Major Depressive Disorder, Dysthymic Disorder, Panic Disorder, or Generalized Anxiety Disorder
- Criteria are not currently met for any other Anxiety or Mood Disorder (including an Anxiety or Mood Disorder, In Partial Remission)
- The symptoms are not better accounted for by any other mental disorder

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ic hypotension and sedation. Nevertheless, because other agents are available that have more favorable side-effect profiles (eg, SSRIs), TCAs should only be used after other therapeutic options have failed.

Another concern with TCA therapy in patients with anxiety symptoms is the potential for TCAs to induce akathisia, jitteriness, and other anxiety symptoms.[23,29,30] This has primarily been reported in depressed patients with panic attacks and may be avoided by starting therapy with low doses (eg, 10 mg imipramine/day). The potential for TCAs to be fatal in an overdose situation should also be taken into consideration when prescribing these agents to patients with suicidal tendencies or thoughts.[31] As little as a week's worth of drug (1500 mg of amitriptyline or imipramine) can result in toxic or lethal doses.[32] Coupled with the fact that the TCAs are one of the most common causes of death by deliberately ingested toxic overdose,[33] it would seem prudent that alternatives to TCAs be used in suicidal patients.

Selective Serotonin Reuptake Inhibitors

The SSRIs are effective treatments for depression, including depression that is associated with comorbid anxiety, eating disorders, panic disorder, social phobia, obsessive-compulsive disorder, and agoraphobia.[34,35] The SSRIs are preferred over the TCAs and MAOIs because they are better tolerated and safer when taken in an overdose situation. As a class, the common side effects of SSRIs (eg, nausea, insomnia, headache, and sexual dysfunction) are mild and transient.[32,36] Still, SSRI-induced sexual dysfunction may persist in some patients. Interestingly, the rate at which sexual side effects develop in clinical practice is higher than what is reported in the manufacturers' literature.[37,38]

Clinical experience with the SSRIs has shed light on the differences between these agents. For example, jitteriness, nervousness, and anxiety have been reported with fluoxetine therapy.[39-41] To alleviate this treatment-emergent side effect, a short course of a concomitant BDZ (eg, alprazolam 0.5 mg 3 times a day),[39] β blocker (eg, propranolol 10 to 20 mg 2 or 3 times a day),[42,43] or trazodone (50 mg at bedtime) may be prescribed. Paroxetine usually does not exacerbate or cause treatment-emergent anxiety,[27] and one double-blind, comparative study of fluoxetine and paroxetine showed an earlier onset of anxiety reduction in depressed patients treated with paroxetine ($P = .01$).[44] Paroxetine has very weak muscarinic effects compared to the TCAs, but constipation, somnolence, and dry mouth may develop more frequently with paroxetine relative to the other SSRIs. A higher incidence of diarrhea and loose stools appears to be associated with sertraline.[36,45]

The potential for drug interactions is another distinguishing factor between the SSRIs. All of the SSRIs, including fluvoxamine, an SSRI indicated for the treatment of obsessive-compulsive disorder in the United States but widely used as an antidepressant in Europe, fluoxetine, sertraline, and paroxetine, have been shown to inhibit cytochrome P450 3A4 in vitro. Fluvoxamine and norfluoxetine, the active metabolite of fluoxetine, inhibit cytochrome P450 3A4 to a greater extent than do sertraline, paroxetine, or fluoxetine, listed here in decreasing

order of potency. Understanding the degree by which the different SSRIs inhibit this enzyme can guide the clinician in prescribing SSRIs with drugs metabolized by cytochrome P450 3A4. Concomitant therapy with alprazolam or triazolam and an SSRI, particularly fluvoxamine, may increase plasma concentrations of the BDZs, resulting in enhanced sedation, impaired cognition, and hangover effects.[46] Inhibition of cytochrome P450 3A4 has also been implicated as the mechanism responsible for fatal arrhythmias during concomitant therapy with terfenadine or astemizole.[47] As a result, simultaneously prescribing fluvoxamine with these antihistamines is contraindicated.[48]

Other drug-metabolizing enzymes that are important in mediating significant drug-drug interactions involve cytochrome P450 2D6, 2C, and 1A2. Paroxetine, fluoxetine, and sertraline are listed according to their relative ability to inhibit cytochrome P450 2D6.[49] This isozyme is responsible for the metabolism of TCAs, antipsychotics, type IC antiarrhythmics, and other drugs. As a result, TCA plasma concentrations may increase if TCAs are coadministered with the SSRIs.[50-58] However, patients requiring combination therapy with a TCA and an SSRI are rarely managed in primary care; therefore, this drug interaction is seldom observed in this clinical setting.[59]

Monoamine Oxidase Inhibitors

The MAOIs are as effective as other antidepressants, but their use is limited by their generally intolerable side-effect profile and their potential for life-threatening drug and food interactions. Nevertheless, MAOIs may be a reasonable treatment option in patients with comorbid depression and anxiety because they are effective for depression and some anxiety disorders (eg, panic disorder,[60] social phobia,[61] and posttraumatic stress disorder[62]). In addition, MAOIs have been shown to have superior efficacy compared with the TCAs in patients with atypical depression,[63-66] a condition that is characterized by prominent anxiety symptoms. Although MAOIs may be appropriate for some disorders, the decision to initiate therapy requires an individualized risk-benefit assessment. Because patients being considered for MAOI therapy usually have a more complicated disease course, these individuals are often referred to psychiatrists for assessment and management.

Newer Agents

Recent introductions to the antidepressant armamentarium include venlafaxine and nefazodone. Each possesses a unique mechanism of action. Venlafaxine selectively inhibits serotonin and norepinephrine reuptake. In addition to having activity at these receptors, nefazodone also inhibits the 5-HT_2 receptor. Both agents are effective in the treatment of depression. Similar to the SSRIs, available clinical data suggest that nefazodone does not have the tendency to increase anxiety, agitation, or insomnia.[25] Therefore, nefazodone may also be considered a treatment alternative for simultaneously occurring depression and anxiety. Nefazodone may also be an option for patients with sexual dysfunction related to other antidepressants.

One drawback to therapy with these agents is that they must be dosed 2 or 3 times daily due to their short half-lives. Elevated blood pressure has also been noted with higher doses of venlafaxine. Nefazodone inhibits the cytochrome P450 3A4 enzyme and can potentially increase drug-plasma concentrations of BDZs such as triazolam, alprazolam, or midazolam. Potent inhibition of cytochrome P450 3A4 by nefazodone is also the reason why this agent is contraindicated for use with terfenadine or astemizole.

OTHER TREATMENT OPTIONS

Benzodiazepines

The BDZs are useful in relieving symptoms of insomnia, agitation, and anxiety, but they have no effect on other core symptoms of depression.[20] Therefore, treatment of comorbid anxiety and depression with BDZs alone would worsen the long-term prognosis because the depressive component would continue to go untreated.[28] Antidepressant monotherapy is effective for treating most cases of comorbid depression and anxiety, but combination therapy with BDZs may be required when an immediate relief to the anxiety symptoms is necessary.[67] For example, patients with severe anxiety or who manifest risk factors for suicide may not be able to wait the 3 to 6 weeks for an antidepressant to reach its peak efficacy. Alleviating the anxiety symptoms early in the disease course may also promote long-term compliance with antidepressant therapy. Once the anxiety symptoms are controlled and the antidepressant becomes fully effective, BDZ therapy no longer becomes necessary and should be discontinued. A short treat-

ment period with BDZs will also prevent the development of physical and psychological dependence and minimize sedation. When stopping BDZ therapy, doses should be slowly tapered in order to prevent rebound anxiety or a withdrawal syndrome.

TABLE 2

Distinguishing Depression from Anxiety

Factor	Depression	Anxiety
Predominant mood	Low, anhedonia, loss of self-esteem, guilt, hopelessness	Fearful, excessive anxiety and worry often with irritability
Suicidal tendencies	Common	Not normally a characteristic
Sleep patterns	Terminal insomnia, diurnal variation,hypersomnia	Reverse diurnal variation, trouble falling asleep or staying asleep (awakens tense but better later)
Psychomotor signs	Agitation, slowing of speech and response	No slowing, calm appearance or restlessness, feeling keyed up, exaggerated startle response fidgety
Age at onset	Tends to be older	Often younger
Concentration	Diminished ability to think or concentrate	Difficulty concentrating or "mind going blank" because of anxiety
Response to exercise	Improvement of disorder with exercise	Exercise can induce an attack
Psychosocial contact	Loss of interest in family and friends	Often normal psychosocial contacts

Based on data from Keller and Hanks[20]; McGlynn and Metcalf[21]; and Preskorn and Fast.[22]

BUSPIRONE

The anxiolytic properties of buspirone are most effective in the treatment of chronic generalized anxiety.[68] Because it has partial agonist activity at serotonin 5-HT_{1A} receptors,[69] buspirone has been shown to have some activity in the treatment of depression. However, doses that were found to be effective for depression were generally higher (45 to 60 mg) than the dose used for generalized anxiety disorder (30 mg).[70,71] These higher doses may not be feasible for the treatment of depression because many patients already have difficulty tolerating the side effects of buspirone (eg, dizziness, headache, and nausea) at the lower doses. Because there is still a lack of evidence demonstrating the efficacy of buspirone in the treatment of depression, it is currently not recommended for the treatment of depression associated with anxiety.[72]

PSYCHOTHERAPY

Psychotherapy has been used effectively either as an alternative or in conjunction with antidepressants for comorbid anxiety and moderate depression.[73] Although it is associated with a lower response rate when used alone, it is worthwhile to consider for those who refuse medication, for those who cannot tolerate medication side effects, for those whose depressive symptoms are refractory to pharmacotherapy, or for those in whom antidepressant therapy is contraindicated.[20] Unfortunately, a clinical response from psychotherapy may not become apparent until after 12 months of treatment, and the response rate is lower than that observed with pharmacotherapy. Because of these drawbacks, psychotherapy should be used as adjunctive treatment to pharmacotherapy rather than as a primary treatment whenever possible.

CONCLUSIONS

Epidemiologic data about the frequency, risk factors, course, and outcome of comorbid depression and anxiety are difficult to confirm. Therefore, the interrelationships between these disorders and the response to treatment are important areas of clinical research. Further study is needed to determine

whether depression associated with anxiety responds differently to specific antidepressants. However, it is clinically apparent that if untreated, depression with comorbid anxiety causes a high level of impaired family, social, and occupational function[11-13] and is associated with a high incidence of suicide.[8]

Comorbid anxiety and depression requires aggressive management because the rates of noncompliance and premature termination of therapy will be substantial if anxiety symptoms are not controlled early. Patients should receive full antidepressant doses combined with psychotherapy for at least 6 to 8 weeks. Short-term, adjunctive therapy with low doses of a sedating antidepressant (eg, trazodone or doxepin) or BDZ may be necessary for those who are highly anxious, who are suicidal, or who have problems sleeping. Long-term use of a BDZ can be associated with dependence and difficulty in discontinuing therapy. Thus, these agents should be slowly discontinued as soon as the anxiety symptoms are controlled.

Preliminary data suggest that the SSRIs are effective for the treatment of comorbid depression and anxiety. Although other classes of antidepressants have demonstrated efficacy for these concomitant disorders (eg, TCAs and MAOIs), there are drawbacks associated with these therapies. These include difficult-to-tolerate side effects, the need for multiple daily dosing, and the risk of death when taken in an overdose situation.

The SSRIs are the drugs of choice for treating this patient population because side effects are better tolerated and decrease with continued treatment. However, fluoxetine may need to be avoided in some patients because it could exacerbate symptoms of anxiety. A notable advantage associated with the SSRIs is that they are safer when taken in an overdose situation; this is an important consideration in a patient population associated with a high incidence of suicide. Also, SSRIs facilitate compliance because they can be given on a once-daily basis and, in many cases, can be used as monotherapy.

Patients with depression and anxiety frequently present to their primary physician with somatic complaints rather than with classic symptoms. It is not surprising, therefore, that anxiety and depression may go unrecognized in this setting.[74,75] The family physician plays a central role in the initial screening and diagnosis of these simultaneously occurring conditions. Early intervention and aggressive treatment will prevent development of a more severe and disabling depressive episode. In addition, increased recognition and appropriate treatment of comorbid depression and anxiety will reduce the significant morbidity and mortality related to these concomitant conditions.

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DISCUSSION

Dr De Wester: What impact do you think family physicians have on improving the outcome of comorbid depression and anxiety?

Dr Kuzel: By recognizing this disorder early, we can prevent many long-term problems. This is best illustrated when we look through patient charts that document an extensive history of medical problems. When you go back and look at your first note, you think to yourself: "Had I recognized this disorder early when this patient first came to see me at age 18 for college anxiety and depression accompanied by abdominal pain, discomfort, and somatic complaints, then maybe I would not be dealing now with a chronic pain patient who is overweight, who smokes, who is hypertensive, who is not compliant, and who has had 17 procedures and 4 or 5 operations."

Dr Richardson: I think the main reason we failed to recognize the impact of anxiety symptoms on depression in the past was because we were basing our decisions on diagnostic criteria for pure disorders. If patients did not meet the criteria for an anxiety disorder, we did not consider the symptoms to be significant and, therefore, felt there was no need to treat them. Now, the subsyndromal concept of mixed anxiety and depression is becoming more popular, and it is recommended that diagnostic criteria be used to guide the family physician in making a diagnosis.