

# Evaluating and Treating Comorbid Depression and Anxiety in Women

## *A systematic approach*

NICHOLAS GRECO, BA, and JOHN M. ZAJECKA, MD

The comorbidity of depression and anxiety is a clinically challenging issue not just for psychiatrists but for clinicians who work with patients in a variety of settings, including primary care. Compared with patients who have either depression or anxiety alone, patients who have symptoms of both<sup>1-7</sup>:

- ◆ Exhibit greater overall psychopathology.
- ◆ Are more frequently chronically ill.
- ◆ Have a higher statistical probability of suicide.
- ◆ Show greater social and occupational impairment.
- ◆ Have poorer prognoses.

Anxiety disorders and depressive disorders are common in women, but they tend to be underdiagnosed or approached as diagnoses of exclusion. The result may be unnecessary medical workups and delays in treatment. Furthermore, failure to establish the diagnosis of comorbid depression and anxiety promptly may result in increased morbidity and mortality (from either the comorbid depression and anxiety or a coexisting medical condition).<sup>8</sup>

This article will review the prevalence of comorbid depression and anxiety, explain how to obtain a diagnosis of depression and/or anxiety, and examine the particular anxiety disorders that often appear with depression. Management strategies will also be discussed.

*The authors are affiliated with the Woman's Board Depression Treatment and Research Center at Rush-Presbyterian-St. Luke's Medical Center in Chicago, Illinois. Mr. Greco is clinical research coordinator, and Dr. Zajacka is clinical director. Dr. Zajacka is also an associate professor of psychiatry at Rush-Presbyterian-St. Luke's Medical Center.*

**ABSTRACT:** Patients with comorbid depression and anxiety are more debilitated than are patients with either condition alone. Diagnosis can be established by gathering a thorough symptomatic history, obtaining a full reproductive history, performing a comprehensive mental-status examination, and including a full differential diagnosis. It is important to determine the type of anxiety disorder (eg, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder) because it will determine treatment. Patients may benefit from pharmacotherapy and cognitive behavioral therapy. (*Women Health Primary Care* 2000;3(5):349-360)

### **PREVALENCE**

**Anxiety disorders:** In epidemiologic studies, anxiety disorders are the most common psychiatric disorders.<sup>9</sup> The National Comorbidity Survey<sup>10</sup> showed that in this country, the chance of having an anxiety disorder was 24.9% over a lifetime and 17.2% over a 12-month period. Anxiety disorders include generalized anxiety disorder (GAD), panic disorder, obsessive-compulsive disorder (OCD), phobic disorders, and posttraumatic stress disorder.

Of the 27% to 48% of patients who present in the primary care setting with a psychiatric disorder, up to 50% do not receive a proper diagnosis.<sup>11-17</sup> Fifer et al<sup>18</sup> found that 33% of 6,307 primary care patients screened for psychiatric disorders met criteria for an anxiety disorder. Of positively screened cases, 56% had not been previously diagnosed.<sup>18</sup> Fifer et al<sup>18</sup> further analyzed 647 screen-positive patients and found that 52% met criteria for one or more anxiety disorders, and 28% met criteria for multiple diagnoses (the rate of comorbid anxiety and depression was especially high in this study).

**Depressive disorders:** In the National Comorbidity Survey,<sup>10</sup> the lifetime prevalence for depression was 17.1%; the 12-month prevalence was 10.3%. In primary care settings, depression can take many forms, including major depressive disorder and dysthymia. Any depressive disorder can coexist with anxiety.

**Comorbidity:** In epidemiologic studies conducted between 1972 and 1985, 21% to 91% of patients diagnosed with an anxiety disorder were also found to have a con-

## Mixed anxiety-depression

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*,<sup>25</sup> in conjunction with the International Classification of Diseases (10th edition), defines mixed anxiety-depressive disorder as a distinct clinical syndrome characterized by the equal presence of anxiety and depression that lasts for at least one month. Neither the anxiety symptoms nor the depressive symptoms meet the criteria for anxiety or depression. The prevalence of mixed anxiety-depressive disorder is between 1% and 10%.<sup>49</sup> Among primary care patients, prevalence may be as high as 4.1%.<sup>50</sup> The majority of primary care patients who present with vague complaints of anxiety and depression exhibit<sup>3,49</sup>:

- ◆ Many unexplained somatic symptoms, which leads to the overuse of medical services.
- ◆ Impaired social or occupational function.
- ◆ Chronic suffering that rarely remits without proper treatment.

A lack of controlled studies makes treatment of mixed anxiety-depressive disorder challenging. Use of any of the currently available antidepressants, all of which have demonstrated both anxiolytic and

antidepressant effects, is appropriate. Benzodiazepines alone are not first-line treatment because they may not effectively treat moderate-to-severe depression. We recommend administration of both an antidepressant and a benzodiazepine, as well as psychotherapy. The benzodiazepine can be used until the antidepressant begins to work; it may help in the early relief of anxiety. Nefazodone may provide early relief and eliminate the need for a benzodiazepine.

Treatment with the benzodiazepine and the antidepressant should not be discontinued once the patient reports symptomatic improvement; it should be continued for 6 to 12 months. (In contrast, the acute treatment of comorbid depression and anxiety disorder may take as long as 12 weeks, and treatment may need to be continued for 6 to 12 months.) During this time, patients should be frequently assessed for the development of a full-syndrome anxiety-depressive disorder. Once remission is achieved, maintenance treatment should be continued for no less than six months. Some patients may require extended or even life-long treatment to prevent recurrence.

**Table 1. Common medical conditions associated with depressive symptoms\***

<p><b>Cancers<sup>†</sup></b> Central nervous system Lung Pancreatic</p> <p><b>Endocrine/metabolic disorders</b> Addison's disease Cushing's disease Diabetes mellitus Electrolyte abnormalities (eg, hypocalcemia, hyponatremia) Hyperparathyroidism/hypoparathyroidism Hyperthyroidism/hypothyroidism Menses/menopause Wilson's disease</p> <p><b>Infections</b> Acquired immunodeficiency syndrome Hepatitis (eg, amebic/viral) Infectious mononucleosis Tertiary syphilis Tuberculosis</p>	<p><b>Neurologic disorders</b> Alzheimer's disease Cerebrovascular accident Dementia Huntington's disease Migraine headaches Multiple sclerosis Narcolepsy Parkinson's disease Postconcussion (posttraumatic)   syndrome Seizure disorders (eg, epilepsy) Stroke</p> <p><b>Rheumatologic<sup>†</sup></b> Rheumatoid arthritis Systemic lupus erythematosus</p> <p><b>Other</b> Anemia Uremia Vitamin deficiency (eg, B<sub>12</sub>, C, thiamin)</p>
<p>* This table is not exhaustive. Rather, it illustrates the wide range of disorders that must be considered when a patient presents with depressive symptoms.</p> <p>† Including, but not limited to.</p>	

comitant major depressive disorder.<sup>19</sup> In the same reports, 33% to 85% of patients with a primary diagnosis of major depressive disorder also met criteria for an anxiety disorder, most often panic disorder.<sup>19</sup> Similar results were found by Clayton<sup>20</sup>: 66% of patients with panic disorder also had concomitant major depression, and 60% of depressed patients had some symptoms of anxiety (20% to 30% had distinct anxiety attacks). The more concomitant anxiety disorders are present, the greater the chance that depression will develop.<sup>21</sup> A good rule of thumb is: When you see anxiety, think depression. The overlapping of anxiety and depression symptoms tends to make comorbidity the rule rather than the exception in patients who present with anxiety disorder.<sup>21</sup>

An analysis of diagnoses based upon the structured clinical interview set forth in the revised third

edition of the *Diagnostic and Statistical Manual of Mental Disorders*<sup>22</sup> found that the ratio of women to men is 1:1 for anxiety and mood disorders in which there is no secondary axis I diagnosis.<sup>23</sup> However, the ratio of women to men is 2:1 for a comorbid disorder in which a mood or anxiety disorder is either the first or second diagnosis.<sup>23</sup> Thus, sex differences in comorbidity may be suggested.

Anxiety disorders and depressive disorders share symptoms such as dysphoria, sleep disturbance, appetite disturbance, impaired concentration, fatigue, irritability, and somatic complaints.

### DIAGNOSIS

Women not only experience depression more often than men do, but they also have higher rates of psychiatric and medical comorbidity, which makes diagnosis difficult.<sup>24</sup> Accurate diagnosis and treatment of women with comorbid depression and anxiety also can be com-

plicated by the physiologic changes that occur throughout a woman's life. Hormonal changes that occur with menstruation, pregnancy, childbirth, and menopause can be triggers for depressive episodes.<sup>24</sup> A woman may have had an undiagnosed first bout with depression after a birth or after a spontaneous or elective abortion.<sup>24</sup> Additionally, a woman's perceptions of the psychologic meaning of reproductive milestones can offer insight into her self-image.

In addition, women seem to be more vulnerable to thyroid disorders, migraines, fibrositis, polymyalgia rheumatica, and rheumatoid arthritis,<sup>24</sup> medical illnesses that may make depression and anxiety more difficult to diagnose. However, early awareness, assessment, and treatment of depression and/or anxiety can improve the prognosis of the medical disorder. Appropriate antidepressant and anxiolytic treatment can improve the symptoms of the medical condition and alleviate depression and anxiety.

### DIAGNOSTIC OBSTACLES

Patients may be reluctant to disclose anxious or depressive feelings and to accept the diagnosis of a psychiatric illness. They may feel embarrassed, afraid, and/or stigmatized by their symptoms. They may erroneously consider anxiety and depression a weakness of character or a normal reaction to life events, such as coping with a medical condition. Patients may be fearful that their clinician will dismiss feelings of anxiety and depression as "not a true medical problem." Or they may fear that their clinician will demand they seek psychiatric treatment.

Clinicians must be aware of their patients' concerns. When anxiety or depression is diagnosed or suspected, clinicians can reduce patients' fear and resistance by explaining that these are common, treatable medical conditions.

### NARROWING THE DIAGNOSIS

The diagnosis of anxiety, depression, or both is similar to the diag-

**Table 2. Substances and medications associated with depressive symptoms**

<p><b>Substance intoxication</b></p> <ul style="list-style-type: none"> <li>Alcohol</li> <li>Barbiturates</li> <li>Benzodiazepines</li> <li>Cannabis</li> <li>Opiates (eg, heroin, prescription pain medications)</li> </ul> <p><b>Substance withdrawal</b></p> <ul style="list-style-type: none"> <li>Amphetamines</li> <li>Cocaine</li> </ul> <p><b>Analgesic/anti-inflammatory agents</b></p> <ul style="list-style-type: none"> <li>Ibuprofen</li> <li>Indomethacin</li> <li>Nonsteroidal anti-inflammatory drugs</li> <li>Opiates</li> <li>Phenacetin</li> </ul> <p><b>Antibacterial/antifungal agents</b></p> <ul style="list-style-type: none"> <li>Ampicillin</li> <li>Cycloserine</li> <li>Ethionamide</li> <li>Griseofulvin</li> <li>Metronidazole</li> <li>Nalidixic acid</li> <li>Nitrofurantoin</li> <li>Trimethoprim</li> </ul>	<p><b>Antihypertensive/cardiac agents</b></p> <ul style="list-style-type: none"> <li><math>\alpha</math>-Methyldopa</li> <li><math>\beta</math>-Blockers (propranolol)</li> <li>Bethanidine</li> <li>Clonidine</li> <li>Digitalis</li> <li>Guanethidine</li> <li>Hydralazine</li> <li>Lidocaine</li> <li>Prazosin</li> <li>Procainamide</li> <li>Reserpine</li> </ul> <p><b>Antineoplastic agents</b></p> <ul style="list-style-type: none"> <li>Asparaginase</li> <li>Azathioprine</li> <li>6-Azauridine</li> <li>Bleomycin</li> <li>Vincristine</li> </ul> <p><b>Hormones/steroids</b></p> <ul style="list-style-type: none"> <li>Corticosteroids (including adrenocorticotrophic hormone)</li> <li>Danazol</li> <li>Oral contraceptives</li> <li>Prednisone</li> <li>Triamcinolone</li> </ul>	<p><b>Neurologic/psychiatric agents</b></p> <ul style="list-style-type: none"> <li>Amantadine</li> <li>Baclofen</li> <li>Bromocriptine</li> <li>Carbamazepine</li> <li>Levodopa</li> <li>Neuroleptics</li> <li>Phenytoin</li> <li>Sedatives/hypnotics (barbiturates, benzodiazepines, chloral hydrate)</li> </ul> <p><b>Miscellaneous</b></p> <ul style="list-style-type: none"> <li>Acetazolamide</li> <li>Choline</li> <li>Cimetidine</li> <li>Cyproheptadine</li> <li>Diphenoxylate</li> <li>Disulfiram</li> <li>Methysergide</li> <li>Stimulants (amphetamines, fenfluramine)</li> <li>Streptomycin</li> <li>Sulfamethoxazole</li> <li>Sulfonamides</li> <li>Tetracycline</li> </ul>
---	--	--

nosis of any other medical disorder. The diagnosis can be approached systematically (discussed below).

There are several possible diagnostic combinations. Diagnosis will depend on the kind, number, and duration of symptoms. Possible diagnoses include:

- ◆ A full syndromal anxiety disorder and a full syndromal depressive disorder.
- ◆ Coexistence of an anxiety disorder and a depressive disorder, with either or both of the disorders subsyndromal. (*Subsyndromal* refers to symptoms that do not meet diagnostic criteria in number or duration yet still cause significant disability.<sup>8</sup>)
- ◆ Comorbid disorders, including substance abuse.
- ◆ Somatic symptoms that may or may not be associated with a comorbid medical illness.

Major depressive disorder is the most prevalent comorbid disorder associated with anxiety. In the primary care setting, subsyndromal anxiety and/or depression are common (see “Mixed anxiety-depression” on page 350). Counter-intuitively, these subsyndromal conditions are associated with more severe impairment in psychosocial functioning than are conditions that meet full syndromal criteria.<sup>18</sup>

One of the most difficult diagnostic challenges when women present with anxiety and/or depression is to determine which somatic symptoms are caused by the anxiety and/or depression and which are caused by other medical conditions. Common somatic symptoms of anxiety and depression include fatigue, headaches, musculoskeletal pain, gastrointestinal symptoms, dizziness, chest pain, palpitations, breathlessness, and weight loss. Diagnoses that must be ruled out are irritable bowel syndrome (IBS), cardiovascular disease, chronic medical illness, acute medical illness, and arthritis. (While there is a strong association between IBS and anxiety,

**Table 3. Commonly used psychiatric instruments for diagnosis and follow-up**

<p><b>Anxiety</b>                  Beck Anxiety Inventory                  Covi Anxiety Scale (CAS)                  Hamilton Anxiety Scale (HAM-A)                  Primary Care Evaluation of Mental Disorders (PRIME-MD)                  Symptom-Driven Diagnostic System for Primary Care (SDDS-PC)                  Well-Being Life Chart                  Zung Self-Rating Anxiety Scale</p> <p><b>Depression</b>                  Beck Depression Inventory Primary Care                  Beck Depression Inventory (BDI)                  Hamilton Depression Scale (HAM-D)                  Montgomery-Asberg Depression Rating Scale (MADRS)                  Primary Care Evaluation of Mental Disorders (PRIME-MD)                  Raskin Depression Scale (RDS)                  Symptom-Driven Diagnostic System for Primary Care (SDDS-PC)                  Well-Being Life Chart                  Zung Self-Rating Depression Scale</p> <p><b>Mania</b>                  Mood Disorder Questionnaire (MDQ)                  Young Mania Rating Scale (YMRS)</p>
---

IBS is not a psychiatric condition.)

Patients with a serious medical illness normally experience some anxiety or depression. A common misconception is that it is “normal” to be depressed about acute, chronic, or terminal illness. However, it is not normal for the patient to have persistent symptoms of anxiety and depression associated with an acute, chronic, or even terminal illness.<sup>8</sup> When the patient’s quality of life is affected by depression and anxiety, symptoms need treatment. If left untreated, persistent anxiety and depression can worsen the medical condition. Appropriate diagnosis and treatment of anxiety and depression in a patient with a medical disorder can prevent worsening of symptoms and functioning.

**DIFFERENTIAL DIAGNOSIS**

Before a diagnosis of depression and/or anxiety can be made, clini-

cians must rule out medical illnesses, side effects of medications, substance abuse, bipolar disorder, and adjustment disorders.

*Medical illnesses* associated with depressive symptoms include anemia, hepatitis, and sclerosis (Table 1).

*Medications* that may produce depressive symptoms include corticosteroids and antihypertensives (Table 2). If a patient’s depressive symptoms may be related to medication, first determine if the medication can be changed. If the medication cannot be changed, the addition of an antidepressant is warranted.

*Substance abuse disorders* can be associated with anxiety and depressive symptoms (Table 2). Patients who use alcohol or marijuana are likely to have depressive symptoms. Those undergoing amphetamine or cocaine withdrawal are also likely to be depressed. A cycle may be established as patients with substance abuse disorders attempt to treat anxiety or depression with other substances, such as alcohol or other drugs (prescription or illicit). Thus, substance abuse patients with anxiety and depressive symptoms should be treated for such symptoms. Clinicians may need to treat the substance abuse and the depression and anxiety together.

*Bipolar disorder* must be ruled out in patients presenting with depressive symptoms. The use of an antidepressant alone in patients with bipolar disorder can induce a manic or hypomanic episode. The clinician should determine if an anxious or depressed patient has any history of mania or hypomania. The criteria for bipolar disorder are three or more of the following symptoms lasting for at least one week for a manic episode or at least four days for a hypomanic episode<sup>25</sup>:

- ◆ Inflated self-esteem or grandiosity.
- ◆ Decreased need for sleep.
- ◆ Greater talkativeness than usual or a pressure to keep talking.
- ◆ Flight of ideas or a feeling that

thoughts are racing.

- ◆ Distractibility.
- ◆ Increase in goal-directed activity or psychomotor agitation.
- ◆ Excessive involvement in pleasurable activities that have a high potential for unfortunate consequences (eg, unrestrained buying sprees, sexual indiscretions).

Symptoms of irritability and agitation can be common in mania or hypomania. Treatment of bipolar disorder includes mood stabilizers, such as lithium, valproate, or carbamazepine, administered with antidepressants. Other commonly used treatments include antipsychotics and anticonvulsants such as gabapentin, lamotrigine, and topiramate.

*Adjustment disorders* may also

cause depression and anxiety. The clinician should determine if a particular environmental stressor or life event has triggered symptoms. This disorder requires further study.

#### A SYSTEMATIC APPROACH

A patient interview and screening instruments can provide a systematic approach to the diagnosis of comorbid depression and anxiety. To establish the diagnosis:

- ◆ Gather a thorough history, often with collateral history from family members or a significant other. The history should include onset, persistence, precipitating events, and previous episodes. As depression may be familial, gathering a family history can be helpful.

- ◆ Obtain a full reproductive history. Ask if the patient has experienced rape or incest. If she has, a posttraumatic stress disorder may be the primary diagnosis; symptoms of depression may be secondary. In cases of posttraumatic stress disorder, the clinician should refer the patient to a mental health professional.

- ◆ Perform a comprehensive mental-status examination.

- ◆ Include a full differential diagnosis.

In *The Fifteen Minute Hour: Applied Psychotherapy for the Primary Care Physician*,<sup>26</sup> Stuart and Lieberman propose an interviewing technique to assess primary care patients for anxiety and depression. Their technique asks about psycho-

## Anxiety disorders

### GENERALIZED ANXIETY DISORDER AND DEPRESSION

Patients with generalized anxiety disorder (GAD) experience excessive anxiety and worry that impair social, occupational, or other important areas of functioning and that last for at least six months.<sup>25</sup> Although GAD is defined by the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders*<sup>22</sup> as an independent diagnosis, research shows it is almost nonexistent in isolation.<sup>51</sup> In one study of patients with GAD, only 26% did not have a comorbid psychiatric illness, and 42% had experienced at least one lifetime episode of major depressive disorder.<sup>52</sup> Similar results of comorbidity have been found in other studies: Between 54% and 79% of GAD patients had a current depressive, dysthymic, or other anxiety disorder.<sup>51,53</sup>

Additionally, patients with primary depression can show notable anxiety that may even predate the depression. A study of 200 patients with diagnosed major depressive disorder showed that 21% to 72% had moderate-to-severe comorbid anxiety symptoms of either psychic anxiety, somatic anxiety, or worry.<sup>31,53</sup>

### PANIC DISORDER AND DEPRESSION

Patients with panic disorder experience recurrent, unexpected panic attacks, which are discrete periods of intense fear or discomfort that may include chest pain, nausea, and chills.<sup>25</sup> Almost 70% of pa-

tients with panic disorder have either a past or present history of depression. Half the time a depressive episode will precede the onset of panic attacks, and half the time it will follow. The longer the history of panic disorder, the greater the likelihood the patient will have comorbid secondary depression.<sup>54-57</sup> Panic attacks are seen in 30% of depressed patients.<sup>4</sup>

### OBSESSIVE-COMPULSIVE DISORDER AND DEPRESSION

Patients with obsessive-compulsive disorder (OCD) experience recurrent and persistent thoughts, impulses, or images that cause marked anxiety or distress.<sup>25</sup> Current comorbid depression is seen in 31.7% of OCD patients; 66% of OCD patients have experienced major depression.<sup>58</sup> Additionally, 85% have suffered secondary depression resulting from chronic OCD, and 15% of patients with OCD have depression as their primary diagnosis.<sup>59,60</sup>

### SOCIAL PHOBIA AND DEPRESSION

Patients with social phobia fear social performance situations in which they may be exposed to unfamiliar people or to possible scrutiny by others. Exposure to such a situation almost invariably provokes anxiety.<sup>25</sup> Between 35% and 70% of patients with social phobia also experience depression.<sup>61,62</sup> The social phobia often manifests before the depression does.<sup>61,62</sup>

**Table 4. DSM-IV diagnostic criteria for major depressive episode**

- A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition or to mood-incongruent delusions or hallucinations.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). Note: In children and adolescents, can be irritable mood.
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
  3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
  4. Insomnia or hypersomnia nearly every day.
  5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  6. Fatigue or loss of energy nearly every day.
  7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms do not meet criteria for a mixed episode.
- C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
- E. The symptoms are not better accounted for by bereavement (ie, after the loss of a loved one, the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation).

*DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. 1994.<sup>25</sup>

social issues in a brief, sequential, logical approach. It allows clinicians to gather and record information in a typical medical model format.

#### SCREENING INSTRUMENTS

The use of systemized instruments can aid in the routine screening and follow-up of depression and anxiety disorders. Systemized psychiatric screening instruments (Table 3) are an easy, affordable, time-efficient aid to the diagnosis of comorbid depression and anxiety disorders in women. Follow-up instruments

should be routinely administered to patients with diagnosed depression and anxiety disorders.

With these instruments, clinicians can consistently and systematically assess symptoms of anxiety and depression. These instruments may also bring to consideration issues that patients and clinicians may not spontaneously discuss, and they can improve communication between patients and clinicians. The use of screening instruments can possibly decrease the need to run costly and unneeded medical

workups. (Although they can be helpful, screening instruments are not a substitute for good clinical judgment.) If the screening instrument suggests depression and/or anxiety but the diagnosis is still in doubt, the clinician should consult with a psychiatrist or refer the patient to a mental health professional.

#### DIAGNOSTIC CRITERIA

The diagnosis of comorbid depression and anxiety is contingent upon the existence of:

- ◆ Major depression or dysthymia (Tables 4 through 6).
- ◆ One of the distinct anxiety disorders (see “Anxiety disorders,” page 355).

#### TREATMENT

Treatment of concomitant depression and anxiety will be dictated by the type of anxiety disorder.

#### GAD AND DEPRESSION

Patients with comorbid GAD and depression are treated primarily with antidepressants and, possibly, with adjunctive anxiolytics.

The selective serotonin reuptake inhibitors (SSRIs) and venlafaxine are quite effective, and their low side effects make them a good first-line choice in primary care. Nefazodone may be promising for GAD as well.

Although any of the older antidepressants can be used, the monoamine oxidase inhibitors (MAOIs) are more effective than the tricyclic antidepressants (TCAs) in treating patients with atypical depression—that associated with significant anxiety, hypersomnia, hyperphagia, reversed diurnal variation, and extreme mood reactivity.<sup>27-30</sup> TCAs can be used in patients who have not adequately responded to SSRIs and MAOIs.

In patients with GAD, antidepressants often must be combined with an anxiolytic agent.<sup>21</sup> Benzodiazepines are often briefly used for early relief of anxiety. They are gradually stopped once the antide-

pressant takes full effect. Alternative anxiolytic agents include:

- ◆ Sedating neuroleptics,<sup>31</sup> which can also aid in delusional depressions.
- ◆ Divalproex sodium,<sup>32</sup> which can be useful in bipolar states.<sup>33</sup>
- ◆ Antihypertensives, such as clonidine or  $\beta$ -blockers.
- ◆ Antihistamines.

Psychotherapy can be useful in combination with pharmacotherapy. If a patient does not respond to treatment, potentiation strategies include the addition of lithium, a thyroid supplement, or stimulants.

#### PANIC DISORDER AND DEPRESSION

In research studies, antidepressants have effectively treated panic disorder. First-line treatment should be with an SSRI. Imipramine,<sup>34</sup> clomipramine,<sup>34</sup> MAOIs,<sup>34</sup> and SSRIs<sup>35</sup> are all treatment options for patients with comorbid panic disorder and depression. (The American Psychiatric Association recommends that MAOIs be reserved for patients who do not respond to other treatment options.) Regardless of the antidepressant chosen, pharmacotherapy must be initiated gradually, possibly by using lower-than-usual starting doses and gently titrating upward to avoid the side effects occasionally experienced by patients with panic disorder.

Other treatments often used in conjunction with antidepressants include benzodiazepines,<sup>36</sup> divalproex sodium,<sup>32,37</sup> and cognitive behavioral therapy (CBT).<sup>38</sup> Benzodiazepine treatment can be quite helpful when acute, rapid relief of panic attacks is needed or before antidepressant effects have become evident. The benzodiazepine may be gradually discontinued once the antidepressant begins to work.

#### OCD AND DEPRESSION

A number of antidepressants can effectively treat OCD, including the SSRIs.<sup>39-41</sup> Because the agents treat both depression and OCD, monotherapy with or without behavioral

**Table 5. DSM-IV diagnostic criteria for major depressive disorder, recurrent**

- A. Presence of two or more major depressive episodes (see Table 4). Note: To be considered separate episodes, there must be an interval of at least two consecutive months in which criteria are not met for a major depressive episode.
- B. The major depressive episodes are not better accounted for by a schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
- C. There has never been a manic episode, a mixed episode, or a hypomanic episode. Note: This exclusion does not apply if all of the maniclike, mixed-like, or hypomaniclike episodes are substance- or treatment-induced or are due to the direct physiologic effects of a general medical condition.

*DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. 1994.<sup>25</sup>

**Table 6. DSM-IV diagnostic criteria for dysthymic disorder**

- A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years. Note: In children and adolescents, mood can be irritable and duration must be at least one year.
- B. Presence, while depressed, of two (or more) of the following:
  1. Poor appetite or overeating.
  2. Insomnia or hypersomnia.
  3. Low energy or fatigue.
  4. Low self-esteem.
  5. Poor concentration or difficulty making decisions.
  6. Feelings of hopelessness.
- C. During the two-year period (one year for children and adolescents) of the disturbance, the person has never been without the symptoms in Criteria A and B for more than two months at a time.
- D. No major depressive episode (see Table 4) has been present during the first two years of the disturbance (one year for children and adolescents); ie, the disturbance is not better accounted for by chronic major depressive disorder, or major depressive disorder in partial remission. Note: There may have been a previous major depressive episode provided there was a full remission (no significant signs or symptoms for two months) before development of the dysthymic disorder. In addition, after the initial two years (one year in children and adolescents) of dysthymic disorder, there may be superimposed episodes of major depressive disorder, in which case both diagnoses may be given when the criteria are met for a major depressive episode.
- E. There has never been a manic episode, a mixed episode, or a hypomanic episode, and criteria have never been met for cyclothymic disorder.
- F. The disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as schizophrenia or delusional disorder.
- G. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).
- H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Early onset: If onset occurs before age 21.

Late onset: If onset occurs at age 21 or after.

*DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. 1994.<sup>25</sup>

therapy may be sufficient.

Medication should be given at an appropriate dosage for an ample amount of time. Unlike depression, which may remit in four to six weeks, OCD can require 12 weeks of treatment at doses higher than those recommended for depression. To increase the response to monotherapy, potentiation strategies include the introduction of buspirone, neuroleptics, TCAs, trazodone, lithium, or benzodiazepines.<sup>42,43</sup> If treatment with an SSRI improves symptoms of OCD but not those of depression, options include changing to a different SSRI or adding a low-dose noradrenergic antidepressant, such as desipramine (of which blood levels must be frequently monitored).<sup>43</sup> Finally, electroconvulsive therapy<sup>43</sup> or psychosurgery<sup>42</sup> may be an option when other treatments fail.

#### SOCIAL PHOBIA AND DEPRESSION

Like the other comorbid depression and anxiety disorders, social phobia with depression is treated with antidepressants. First-line treatment should be with an SSRI<sup>44</sup> because they have few adverse reactions. MAOIs treat social phobia more effectively than do TCAs.<sup>45</sup> Buspirone<sup>46</sup> is also effective. In patients in whom monotherapy is ineffective, benzodiazepines<sup>47</sup> and  $\beta$ -blockers<sup>47,48</sup> may be helpful additions. As with the other anxiety disorders, treatment of social phobias may include CBT, which can be used to address significant misinterpretations and cognitive distortions.<sup>38</sup> For intermittent phobias (eg, public speaking), the clinician should consider the use of  $\beta$ -blockers or benzodiazepines as needed. 🌿

#### REFERENCES

1. Alnaes R, Torgersen S. DSM-III personality disorders among patients with major depression, anxiety disorders, and mixed conditions. *J Nerv Ment Dis.* 1990;178:693-698.
2. Liebowitz MR, Hollander E, Schneier F, et al. Anxiety and depression: discrete diagnostic entities? *J Clin Psychopharmacol.* 1990;10(3 suppl):61S-66S.

3. Katon W, Roy-Byrne PP. Mixed anxiety and depression. *J Abnorm Psychol.* 1991;100:337-345.
4. Clayton PJ. The comorbidity factor: establishing the primary diagnosis in patients with mixed symptoms of anxiety and depression. *J Clin Psychiatry.* 1990;51(suppl):35-39.
5. Stein MB, Shea CA, Uhde TW. Social phobic symptoms in patients with panic disorder: practical and theoretical implications. *Am J Psychiatry.* 1989;146:235-238.
6. Rudd MD, Dahm PF, Rajab MH. Diagnostic comorbidity in persons with suicidal ideation and behavior. *Am J Psychiatry.* 1993;150:928-934.
7. Wittchen HU, Essau CA, Krieg JC. Anxiety disorders: similarities and differences of comorbidity in treated and untreated groups. *Br J Psychiatry Suppl.* September 1991:23-33.
8. Zajecka J. Importance of establishing the diagnosis of persistent anxiety. *J Clin Psychiatry.* 1997;58(suppl 3):9-15.
9. Regier DA, Narrow WE, Rae DS, et al. The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. *Arch Gen Psychiatry.* 1993;50:85-94.
10. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994;51:8-19.
11. Ormel J, Koeter MW, van den Brink W, van de Willige G. Recognition, management, and course of anxiety and depression in general practice. *Arch Gen Psychiatry.* 1991;48:700-706.
12. Kessler LG, Cleary PD, Burke JD Jr. Psychiatric disorders in primary care. Results of a follow-up study. *Arch Gen Psychiatry.* 1985;42:583-587.
13. Klerman GL, Budman S, Berwick D, et

## Comorbid Depression and Anxiety in Women

### PRIMARY POINTS

The more concomitant anxiety disorders present, the greater the chance that depression will develop. A good rule of thumb is: When you see anxiety, think depression.

Major depression is the most prevalent comorbid disorder associated with anxiety. The comorbidity of anxiety and depression can present in various ways: both or either condition may be subsyndromal. In the primary care setting, subsyndromal anxiety and/or depression are common.

One of the most difficult challenges when women present with anxiety and/or depression is to determine which somatic symptoms are caused by the anxiety and/or depression and which are caused by other medical conditions.

Before a diagnosis of depression and/or anxiety can be made, clinicians must rule out medical, substance abuse, bipolar, and adjustment disorders.

A patient interview and screening instruments can provide a systematic approach to the diagnosis of comorbid depression and anxiety in women.

- al. Efficacy of a brief psychosocial intervention for symptoms of stress and distress among patients in primary care. *Med Care*. 1987;25:1078-1088.
14. Zung WW, Magill M, Moore JT, George DT. Recognition and treatment of depression in a family medicine practice. *J Clin Psychiatry*. 1983;44:3-6.
  15. Good MJ, Good BJ, Cleary PD. Do patient attitudes influence physician recognition of psychosocial problems in primary care? *J Fam Pract*. 1987;25:53-59.
  16. Magruder-Habib K, Zung WW, Feussner JR. Improving physicians' recognition and treatment of depression in general medical care. Results from a randomized clinical trial. *Med Care*. 1990;28:239-250.
  17. Shapiro S, Skinner EA, Kessler LG, et al. Utilization of health and mental health services. Three Epidemiologic Catchment Area sites. *Arch Gen Psychiatry*. 1984;41:971-978.
  18. Fifer SK, Mathias SD, Patrick DL, et al. Untreated anxiety among adult primary care patients in a Health Maintenance Organization. *Arch Gen Psychiatry*. 1994;51:740-750.
  19. Wetzler S, Katz MM. Problems with the differentiation of anxiety and depression. *J Psychiatr Res*. 1989;23:1-12.
  20. Clayton PJ. Anxious depression: a reemerging subtype of depression. In: Racagni G, Smeraldi E, eds. *Anxious Depression: Assessment and Treatment*. New York, NY: Raven Press; 1987:1-6.
  21. Zajecka JM, Ross JS. Management of comorbid anxiety and depression. *J Clin Psychiatry*. 1995;56(suppl 2):10-13.
  22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, rev. Washington, DC: American Psychiatric Association; 1987.
  23. Ochoa L, Beck AT, Steer RA. Gender differences in comorbid anxiety and mood disorders. *Am J Psychiatry*. 1992;149:1409-1410.
  24. Pajer K. New strategies in the treatment of depression in women. *J Clin Psychiatry*. 1995;56(suppl 2):30-37.
  25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
  26. Stuart MR, Lieberman JA. *The Fifteen Minute Hour: Applied Psychotherapy for the Primary Care Physician*. 2nd ed. Westport, Conn: Praeger Publications; 1993.
  27. Quitkin FM, Stewart JW, McGrath PJ, et al. Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. *Am J Psychiatry*. 1988;145:306-311.
  28. Quitkin FM, McGrath PJ, Stewart JW, et al. Phenelzine and imipramine in mood reactive depressives. Further delineation of the syndrome of atypical depression. *Arch Gen Psychiatry*. 1989;46:787-793.
  29. Quitkin FM, McGrath PJ, Stewart JW, et al. Atypical depression, panic attacks, and response to imipramine and phenelzine. A replication. *Arch Gen Psychiatry*. 1990;47:935-941.
  30. Quitkin FM, Harrison W, Stewart JW, et al. Response to phenelzine and imipramine in placebo nonresponders with atypical depression. A new application of the crossover design. *Arch Gen Psychiatry*. 1991;48:319-323.
  31. Rickels K, Schweizer E. The treatment of generalized anxiety disorder in patients with depressive symptomatology. *J Clin Psychiatry*. 1993;54(suppl):20-23.
  32. Primeau F, Fontaine R, Beauclair L. Valproic acid and panic disorder. *Can J Psychiatry*. 1990;35:248-250.
  33. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA*. 1994;271:918-924.
  34. Ballenger JC. Pharmacotherapy of the panic disorders. *J Clin Psychiatry*. 1986;47(suppl):27-32.
  35. Schneier FR, Liebowitz MR, Davies SO, et al. Fluoxetine in panic disorder. *J Clin Psychopharmacol*. 1990;10:119-121.
  36. Pollack MH, Rosenbaum JF. Benzodiazepines in panic-related disorders. *J Anxiety Disord*. 1988;2:95-107.
  37. Zajecka JM, Fanelli J, Ross JS, et al. Valproic acid in the treatment of panic disorder. Poster presented at: New Clinical Drug Evaluation Unit Meeting; 1994; Marco Island, Fla.
  38. Barlow DH. *Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic*. New York, NY: Guilford Press; 1988:425-427.
  39. DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive compulsive disorder with clomipramine. *Psychiatr Ann*. 1989;19:97-101.
  40. Fontaine R, Chouinard G. Fluoxetine in the long-term maintenance treatment of obsessive compulsive disorder. *Psychiatr Ann*. 1989;19:88-91.
  41. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder. A double-blind comparison with placebo. *Arch Gen Psychiatry*. 1989;46:36-44.
  42. Zetin M, Kramer MA. Obsessive-compulsive disorder. *Hosp Community Psychiatry*. 1992;43:689-699.
  43. Goodman WK, McDougle CJ, Price LH. Pharmacotherapy of obsessive compulsive disorder. *J Clin Psychiatry*. 1992;53(suppl):29-37.
  44. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. *J Clin Psychiatry*. 1993;54:27-32.
  45. Liebowitz MR, Campeas R, Levin A, et al. Pharmacotherapy of social phobia. A condition distinct from panic attacks. *Psychosomatics*. 1987;28:305-308.
  46. Schneier FR, Saoud JB, Campeas R, et al. Buspirone in social phobia. *J Clin Psychopharmacol*. 1993;13:251-256.
  47. James IM, Griffith DN, Pearson RM, Newbury P. Effect of oxprenolol on stage-fright in musicians. *Lancet*. 1977;2:952-954.
  48. Hartley LR, Ungapen S, Davie I, Spencer DJ. The effect of beta adrenergic blocking drugs on speakers' performance and memory. *Br J Psychiatry*. 1983;142:512-517.
  49. Wittchen HU, Essau CA. Comorbidity and mixed anxiety-depressive disorders: is there epidemiologic evidence? *J Clin Psychiatry*. 1993;54(suppl):9-15.
  50. Barrett JE, Barrett JA, Oxman TE, Gerber PD. The prevalence of psychiatric disorders in a primary care practice. *Arch Gen Psychiatry*. 1988;45:1100-1106.
  51. Massion AO, Warshaw MG, Keller MB. Quality of life and psychiatric morbidity in panic disorder and generalized anxiety disorder. *Am J Psychiatry*. 1993;150:600-607.
  52. Brawman-Mintzer O, Lydiard RB, Emmanuel N, et al. Psychiatric comorbidity in patients with generalized anxiety disorder. *Am J Psychiatry*. 1993;150:1216-1218.
  53. Fawcett J, Kravitz HM. Anxiety syndromes and their relationship to depressive illness. *J Clin Psychiatry*. 1983;44(8 pt 2):8-11.
  54. Breier A, Charney DS, Heninger GR. Major depression in patients with agoraphobia and panic disorder. *Arch Gen Psychiatry*. 1984;41:1129-1135.
  55. Breier A, Charney DS, Heninger GR. Agoraphobia with panic attacks. Development, diagnostic stability, and course of illness. *Arch Gen Psychiatry*. 1986;43:1029-1036.
  56. Stein MB, Uhde TW. Panic disorder and major depression. A tale of two syndromes. *Psychiatr Clin North Am*. 1988;11:441-461.
  57. Lesser IM, Rubin RT, Pecknold JC, et al. Secondary depression in panic disorder and agoraphobia. I. Frequency, severity, and response to treatment. *Arch Gen Psychiatry*. 1988;45:437-443.
  58. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45:1094-1099.
  59. Rasmussen SA, Eisen JL. The epidemiology and differential diagnosis of obsessive compulsive disorder. *J Clin Psychiatry*. 1992;53(suppl):4-10.
  60. Rasmussen SA, Eisen JL. Clinical and epidemiologic findings of significance to neuropharmacologic trials in OCD. *Psychopharmacol Bull*. 1988;24:466-470.
  61. Stein MB, Tancer ME, Gelernter CS, et al. Major depression in patients with social phobia. *Am J Psychiatry*. 1990;147:637-639.
  62. Van Ameringen M, Mancini C, Styan G, Donison D. Relationship of social phobia with other psychiatric illness. *J Affect Disord*. 1991;21:93-99.