Approximately one-half of all Americans will meet the criteria for a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) disorder at some point in time in their lives.1 Anxiety disorders are the most common psychiatric disorders—diagnosed alone or with other psychiatric diagnoses. Approximately 1 in 4 individuals in the United States report a lifetime history of at least one anxiety disorder. The annual cost of anxiety disorders is estimated in billions of dollars; direct costs include missed days at work while indirect costs include the negative effects on a person's quality of life.2,3 In general, anxiety disorders occur more frequently in women than in men,1 are prevalent worldwide, and are not culture-bound.4

Fifty-eight percent of patients with a depressive illness also have an anxiety disorder.5 Research suggests that the presence of anxiety disorders poses a significant risk for developing a major depressive disorder; therefore, early identification and treatment of anxiety may prevent subsequent development of depression with comorbid anxiety.5 In addition, recent guidelines recommend that clinicians be particularly attentive to patients at risk for depression, such as those with a chronic illness, a family or personal history of depression, or who have experienced recent losses. Patients are also at risk who have a sleep disorder, suffer chronic pain, demonstrate multiple unexplained somatic complaints, or have some current symptoms of depression.6,7

Only one-third of Americans with mental illness receive proper treatment, and most receive their care in primary care settings. Clinical myth persists that anxiety and depression are “caused” by general medical conditions.8 The stress-diathesis model demonstrates that vulnerability preexists for some patients and that under stressful conditions, such as chronic or protracted acute illnesses, anxiety and depression may express themselves.9

The consensus is that patients with anxiety and depressive disorders are underecognized, undertreated, and misdiagnosed.4,5,10 Cross-sectional or snapshot assessments common in primary care do not recognize the longitudinal nature of these disorders.10 In primary care, mixed anxiety and depression are rarely diagnosed due to fluctuating course and presentation of symptoms.10,11 Because of other comorbid illnesses, patients have other somatic symptoms contributing to the diagnostic dilemma.8,11,12

Symptoms of Anxiety and Depression

Many symptoms of chronic anxiety are shared with depression,13 making accurate diagnosis difficult (see Table: “Symptoms of Anxiety and Depression”). Untreated anxiety and comorbid depression lead to increased severity and chronicity of symptoms, social and vocational impairment, increased alcohol and substance abuse, increased risk of suicide, and a poorer response to acute and long-term treatment regardless of setting.14 There is also a greater chance for treatment discontinuation or nonadherence, especially in patients who are new to antidepressant therapy.15

When anxiety is the predominant presenting condition, patients present with fear and nonspecific worry not associated with a particular issue or event, often accompanied by repetitive, intrusive, and inappropriate thoughts or actions. When depression is the predominant presenting condition, there is depressed mood and significant absence of a positive affect accompanied by anhedonia, hopelessness, and irritability. Anxiety more often has physiologic symptoms with motor tension and autonomic hyperactivity, such as repetitive foot movements, sweating palms, increased pulse, and dry mouth. Both symptoms of anxiety and depression may occur in the diagnostic category of mixed anxiety and depression without meeting the full diagnostic criteria for either depression or anxiety.11 They should both be treated
Anxiety and Depression

Differentiating anxiety symptoms associated with medical conditions from those caused by anxiety disorders can be difficult. Features of anxiety associated with medical conditions include onset of symptoms after 35 years of age and the absence of personal or family history of an anxiety disorder, childhood history of significant anxiety, significant life events generating anxiety symptoms, and avoidance behavior.

Anxiety is an ubiquitous symptom of a number of medical conditions such as hyperthyroidism, pheochromocytoma, hypoglycemia, as well as Cushing’s syndrome, cardiovascular disorders, respiratory disorders, metabolic disorders, and neurologic diseases. Medical conditions associated with depression include hypothyroidism and chronic illnesses such as cardiovascular disease and diabetes. Physical symptoms common in depression include fatigue, headache, dizziness or fainting, feeling of weakness in parts of the body, muscle or joint aches and pains, and abdominal or chest pains.

In addition, persons with anxiety associated with a medical condition often have a poor response to the initiated psychiatric treatment. These features should alert the nurse practitioner to explore nonpsychiatric explanations of the anxiety symptoms.

Anxiety and depressive symptoms are also associated with prescribed and over-the-counter medications, some beverages, foods, supplements, and other substances used and/or abused. Even appropriately prescribed beta adrenergics, anticholinergics, selective serotonin reuptake inhibitors (SSRIs), and corticosteroids are associated with symptoms of anxiety and depression.

Susman urged caution in waiting to treat symptoms of anxiety and depression until medical conditions are ruled out by means of expensive workups. He recommended that if the criteria for depression or anxiety disorder are met, the clinician should focus on those symptoms while using one’s clinical expertise in the differential diagnosis. The message is to presumptively treat anxiety and depression in the early phases of presentation to avoid harm by delaying patient relief of symptoms.

Screening and Diagnosing

Kramer recommended screening patients for depression if they present at three or more visits with symptoms of recurrent headache, low back pain, generalized pain, insomnia or fatigue, or chronic gastrointestinal (GI) symptoms such as bloating and gas. The following two screening questions for depression are recommended: Over the past 2 weeks have you felt down, depressed, or hopeless? Over the past 2 weeks have you felt little interest in pleasure in doing things?

For a positive response to either question, a validated depression instrument such as the Patient Health Questionnaire (PHQ-9) or the Quick Inventory of Depressive Symptomatology (QIDS-SR) is recommended for confirmatory testing, which can be completed in the waiting room prior to the primary care visit.

Patients who have any risk factors should be followed-up with an interview to assess symptoms (see Table: “Risk Factors of Anxiety and Depression”). Recurrent screenings should be done on those with histories of depression, unexplained somatic symptoms (GI complaints, fatigue), and comorbid conditions such as panic disorder (PD), generalized anxiety...
Anxiety and Depression

Disorders (GAD), substance abuse, or chronic pain. After treatment is initiated, frequent reevaluation of symptoms using validated instruments should be done to monitor, document treatment progress, and assist in treatment decisions.

Instruments to measure depression and anxiety can be downloaded from the Internet. Selected instruments can be distributed at check in, completed in the waiting room, and scored prior to bringing the patient into the examining room. The instruments should be periodically readministered to document patient progress toward remission.

Patients with anxiety and depression should be assessed for suicide risk. In 2003, suicide was the 10th leading cause of death in the United States. One of every seven patients with recurrent depression commits suicide, and 70% of persons who attempt suicide have been seen in a primary care setting within 6 weeks prior to the suicide attempt. The risk of suicide attempts increases with any anxiety disorder. Comorbid anxiety with depression substantially increases the risk of suicide and the presence of anxiety increases the difficulty of achieving medication treatment responses and remission.

When assessing patients for depression, bipolar depression must be ruled out prior to starting medication therapy. For patients presenting with depressive symptoms, consider the diagnosis of major depression as one of exclusions because all depressions are not unipolar. Ask the patient if there is any history of mania, such as talkative or pressured speech, decreased need for sleep, inflated self-esteem or grandiosity, easily distracted, increased involvement in goal-directed activities, and excessive involvement in pleasurable activities. In addition, ask about history of “mood movement” and hypomania that is indicative of a Bipolar II Disorder. Ask about histories of “antidepressant misadventures” with unusually quick, energized responses in just a few days to medication, suggesting risk of treatment-emergent hypomania. To distinguish, look for symptoms of irritability more common in bipolar illness, as well as individual and family history of depression or bipolar disorder. Complete a family genogram to identify depression, bipolar illness, substance abuse, and bipolar behavior patterns that may help uncover a family history suggestive of bipolar illness.

The acronym ATM (Affect, Thinking, and Mood) can remind clinicians of features that differentiate the type of depression. Observe, then evaluate the patient’s affect and thinking for distortions, delusions, grandiosity, or unwarranted fears. Observe the mood for depression, hypomania, or a mixed state expressed during the visit.

Ask patients if they have experienced panic attacks. PD may occur with or without agoraphobia, or panic attacks may occur with other anxiety disorders. Symptoms may include fear, avoidance, or anxious anticipation.

Specific anxiety disorders with their diagnostic criteria are described in the DSM-IV-TR. Some of these disorders include social anxiety (SA), which may begin as shyness in childhood and may lead to other comorbidities such as substance abuse and depression. GAD may present in patients with worry and fearfulness or somatic symptoms (abdominal pains, urinary frequency, nausea, sweating, and palpitations). When assessed further, these patients are often worried, have difficulty sleeping, and feel on edge all the time. This disorder may have future sequelae such as depression, obsessive-compulsive disorder (OCD), and PD when left untreated.

Steiner suggested that a global internalizing disturbance, untreated over time, leads to more differentiation of disorders and ultimately to depression. The progression is birth ➞ simple phobia ➞ OCD ➞ major affective disorders. This model of illness progression further supports the need for accurate detection and early intervention.

Treatment Strategies

Pharmacotherapy with or without cognitive behavioral therapy (CBT) is first-line treatment and may be prescribed concurrently or serially with therapy. The treatment goal is complete remission of the anxiety and depressive symptoms and a return to preillness functioning, which requires time, persistence, and patience to change the patient’s established response patterns. Incomplete remission with only partial symptom control increases the risk of relapse, further impairment, and more complex medication treatments. Choice of treatment may initially be directed to the patient’s most bothersome symptoms that interfere with function-
## Medications for Anxiety With or Without Depression\(^{30,39}\)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Advantages</th>
<th>Use</th>
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</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td>First-line medication therapy for depression and anxiety disorders; minimal cardiovascular risk; antidepressant and anxiolytic effects</td>
<td>PD, GAD, social phobia, OCD, posttraumatic stress disorder (PTSD), mixed anxiety, and depression</td>
</tr>
<tr>
<td>• Fluoxetine</td>
<td>Broad spectrum</td>
<td>FDA approval for depression, PD, OCD</td>
</tr>
<tr>
<td>• Fluvoxamine</td>
<td>Broad spectrum; few cytochrome P-450 interactions</td>
<td>Depression and all anxiety disorders</td>
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<tr>
<td>• Sertraline</td>
<td>Used with elderly</td>
<td>Depression but may be used in anxiety</td>
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<tr>
<td>• Citalopram (Celexa)</td>
<td></td>
<td>Depression and being reviewed for social anxiety disorder (SAD)</td>
</tr>
<tr>
<td>• Escitalopram (Lexapro)</td>
<td></td>
<td>Depression, PD, OCD</td>
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<tr>
<td>• Paroxetine</td>
<td></td>
<td></td>
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<tr>
<td><strong>SSNRIs</strong></td>
<td>Well tolerated; few drug-to-drug interactions; may be effective in relieving somatic symptoms, especially pain with depression and/or anxiety disorders</td>
<td>Depression, PTSD, GAD, SAD</td>
</tr>
<tr>
<td>• Venlafaxine ER</td>
<td>Effective antidepressant and anxiolytic</td>
<td>Depression; added in combination to SSRI or SSNRI to reverse GI side effects. Useful in PD, GAD, and other anxiety disorders. Used in cancer and HIV patients to assist sleep, relieve depression, and increase appetite</td>
</tr>
<tr>
<td><strong>Dual Action Serotonin and Norepinephrine Antidepressant (alpha-2 antagonist, NaSSA)</strong></td>
<td>Effective; lower cost</td>
<td>OCD, PD</td>
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<tr>
<td>• Mirtazapine</td>
<td></td>
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<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td>Manages anxiety symptoms for immediate symptom control; distressing symptoms during antidepressant initiation “lag effect”; residual anxiety not controlled by antidepressant treatment. Low cost; high patient acceptance; Alprazolam XR allows once- or twice-a-day dosing</td>
<td>Acute anxiety, PD, GAD</td>
</tr>
<tr>
<td>• Clomipramine (Anafranil)</td>
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<tr>
<td>• Imipramine</td>
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<tr>
<td><strong>MAOI</strong></td>
<td>New patch; does not require dietary restrictions</td>
<td>May be third line after switching to another medication in the same class or a different class and augmenting has been tried</td>
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<tr>
<td>• Selegiline</td>
<td></td>
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<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Reduces anxiety; may be used with patients who are abusing alcohol; no withdrawal effect; more effective in alleviating psychic versus somatic symptoms</td>
<td>GAD</td>
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<tr>
<td>• Diazepam</td>
<td></td>
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<tr>
<td>• Alprazolam XR</td>
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<tr>
<td>• Clonazepam</td>
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<tr>
<td><strong>Beta-adrenergic blocking agents</strong></td>
<td>Reduces somatic symptoms and tremors in performance anxiety</td>
<td>Used in stage fright, public speaking, and test anxiety</td>
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<tr>
<td>• Propranolol</td>
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<tr>
<td><strong>Partial agonist 5-HT1A</strong></td>
<td>Symptom and functional improvement; anxiolytic effects and effectiveness shown in preliminary studies in PTSD, PD, and GAD</td>
<td>Anxious depression</td>
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<tr>
<td>• Buspirone</td>
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<tr>
<td><strong>Selective GABA reuptake inhibitor</strong></td>
<td>Possible use as augmentation for anxiety disorders with effectiveness in decreasing anxiety symptoms</td>
<td>Augmentation therapy for treatment resistant or refractory mood and anxiety disorders; augmentation with risperidone, quetiapine, or olanzapine in OCD showed effectiveness in reducing symptoms; risperidone effective as adjunct in managing PTSD and comorbid depression.</td>
</tr>
<tr>
<td>• Tiagabine (Gabitril)</td>
<td>Divalproex sodium—long acting form is better tolerated. Evidence of usefulness as mood stabilizer to prevent cycling. Lamotrigine—bipolar depression (in clinical studies, off-label) Lithium—gold standard for mood stabilizers; has antidepressant effect</td>
<td>Divalproex sodium—trial decreased depression in panic disorder and social phobia. Carbamazepine—potentially beneficial treatment of PTSD but not for PD. Gabapentin—decrease anxiety. Lithium—augment refractory depression</td>
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<tr>
<td><strong>Atypical antipsychotics</strong></td>
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<tr>
<td>• Olanzapine (Zyprexa)</td>
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<td>• Risperidone (Risperdal)</td>
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<td>• Quetiapine (Seroquel)</td>
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<tr>
<td><strong>Antiepileptics/mood stabilizers</strong></td>
<td></td>
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<tr>
<td>• Divalproex sodium</td>
<td></td>
<td></td>
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<tr>
<td>• Lamotrigine (Lamictal)</td>
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<tr>
<td>• Carbamazepine</td>
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<tr>
<td>• Gabapentin</td>
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<tr>
<td>• Lithium</td>
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</tbody>
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\(^{30,39}\) Anxiety and Depression
ing. Establishing a therapeutic relationship with the patient is essential for the long-term goal of remission.

Integrating patients’ support systems (family, church, friends, employer) is important in the treatment process. Treatment occurs in a cultural context and must be individualized to the patient’s values and beliefs to increase adherence.

Referral/Consultation of Complex Cases
Anxiety, with or without depression, can be managed in primary care; however, complex cases with other comorbid psychiatric conditions should be referred. Consider referral for patients with anxiety who have comorbid alcohol abuse with depression. The International Consensus Group on Depression and Anxiety recommends immediate referral for those with high suicide risk, severe depression, melancholia, bipolar disorder, or marked OCD. Consultation or referral to a psychiatric specialist is recommended for patients whose primary care-initiated treatments are associated with poor response to therapy, failed remission, or deterioration in general well-being. 17, 28

Education and Lifestyle Changes
Patients and their families need education about lifestyle changes. Commitments are needed over time to eliminate caffeine, avoid self-medication with alcohol or drugs, establish healthy sleep patterns, decrease stress, and keep a regular schedule including exercise. Education about triggers of anxiety, treatment options, benefits, risks, and side effects of medication is essential. Providing the rationale as to why a particular medication is chosen and why maintenance medications are needed is important to increase the therapeutic alliance and patient cooperativeness. Education should include the natural history of the disorder, what the patient should expect during treatment, how to monitor symptoms and side effects, follow-up information including how often visits are to be made, how and when telephone contacts will be made, early warning signs and symptoms of relapse, and the length of treatment. 29

Psychotherapy Techniques
Evidence supports the effectiveness for CBT and interpersonal therapy for depression, and CBT and exposure therapy for anxiety disorders. Combination with medications has been found more effective than either therapy or medications used alone. 27 In addition, using rational emotive psychotherapy 30 can introduce patients to cognitive distortions and irrational beliefs that affect their feelings, anxiety, and mood. For example, patients may use terms such as “always,” “never,” “must,” and “should” in their conversations with the provider. Ask the patient what evidence there is to support the belief. What are the worst and best things that could happen if the belief were true and actually occurred? Help the patient realize that holding on to the belief will increase distress; changing the belief to be more realistic will decrease distress. Likewise, distortions in thinking such as exaggerating, overgeneralizing, polarized thinking, and others increase negative feelings.

Pharmacologic Interventions
The antidepressants SSRIs and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and mirtazapine (Remeron) are the most often used first-line monotherapy pharmacotherapy due to a broad spectrum of efficacy and better tolerability than older tricyclic (TCAs) antidepressants 31, 32 (see Table: “Medica-
tions for Anxiety With or Without Depression”). Little evidence supports that SSNRIs are more efficacious than SSRIs in treating comorbid anxiety and depression; more head-to-head studies are needed. Use of algorithms with sequential steps and a collaborative care approach produces better outcomes in treating comorbid anxiety and depression than treatment as usual.  

After a trial with an adequate dose and duration of a first-line medication choice, the recommendation is to augment if there is a nonresponse or partial response. If there continues to be only a partial or a nonresponse after augmentation, switch to a different medication class (monotherapy with SSRI, venlafaxine XR, mirtazapine, TCA) of medication other than the one used initially; continue therapy if there is a response and augment if there is partial response or nonresponse. With augmentation, continue the therapy if the patient responds; go to combination therapy (TCA+SSRI, bupropion SR+SSRI, SSRI + trazadone) if partial or nonresponse occurs. If there are still subsyndromal symptoms or residual symptoms, seek psychiatric expert consultation. The last step is to follow any of the algorithms for treatment that have not been tried.

Augmentation

Augmentation is a treatment step in current treatment algorithms for residual symptoms, comorbid disorders, or an underlying bipolar disorder. Augmentation medication strategies include the use of thyroid hormone, specifically synthetic T₃ (liothyronine sodium), lithium, antiepileptics, bupropion, and atypical antipsychotics. 

In addition to medication augmentation, psychotherapy is important when partial response or nonresponse to medication therapy occurs. The presence of residual or subsyndromal symptoms of anxiety or depression results in higher relapse rates, impaired functioning, and increased use of healthcare resources. Although no single alternative first- or second-line treatment exists to treat all the anxiety disorders with depression, comorbid depression will worsen the clinical outcomes of anxiety disorders such as PD, social phobia, and GAD.

Gorman cites the International Consensus Group on Anxiety and Depression’s recommendation for the use of an SSRI or SSNRI for GAD or patients with long-term conditions. For example, long-term use of antidepressants such as paroxetine (Paxil) or venlafaxine (Effexor) are reasonable approaches to managing patients with GAD.

SSRIs, SSNRIs, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and mirtazapine have a Food and Drug Administration (FDA) black box warning for the possible increased risk of suicidal thoughts and actions for children and adolescents. Clinicians should be sure that patients and their families know of the risk and behaviors that might indicate the patient is suicidal or the depression is worsening and protective action is needed. The FDA also issued a Public Health Advisory in June 2005 regarding the increased risk of suicidal thinking and behavior in adults taking antidepressants. Frequent monitoring for change in symptoms early in treatment is extremely important to detect increased risk.

Follow-up requires close monitoring and is important to assess medication response and ensure adherence to therapy. Initially, patients should be followed weekly to assess their response to medication and the side effects. Response to initial medication treatment for depression is usually seen in 3 to 4 weeks but may be 6 weeks or longer. Response for treatment of anxiety may take longer and require higher doses than with depression alone and can take up to 12 weeks in OCD. Medication treatment should be continued for a minimum of 9 to 12 months once remission has been achieved to decrease the risk of relapse. Maintenance therapy is recommended for those who have their first depressive episode at 50 years of age or older, have one recurrence at 40 years of age, and patients who have had more than three episodes.

Bupropion SR

Bupropion SR is a dopamine and norepinephrine reuptake inhibitor and recommended by the Texas Implementation of Medication Algorithms as a first-line pharmacotherapy for depression. It is effective in treating social anxiety disorder but has mixed results for combination with SSRIs for treatment-resistant depression.

Mirtazapine

Mirtazapine is also recommended as a first-line medication treatment and is an alpha-2 antagonist, noradrenaline, and specific serotonergic agent; therefore, it is a dual serotonin and norepinephrine antidepressant. Mirtazapine is much more sedating at lower doses than higher doses. Adding mirtazapine to an SSRI or SSNRI may reverse the gastrointestinal side effects that contribute to treatment nonadherence. The action and side effect profile make it an ideal medication to use for patients with oncology and immunosuppressant comorbidities due to sedation and stimulating appetite. Mirtazapine is contraindicated within 14 days of MAOI therapy.

Benzodiazepines

Benzodiazepines (BZDs) are effective for their anxiolytic effect and are useful during the initiation of antidepressant treatment for anxiety management during the “lag” period of antidepressant effect. Studies indicate that combined phar-
macrotherapy using an antidepressant plus a BZD has a faster onset of action than an antidepressant alone.32, 43 The SSRI may prevent the BZD’s depressant effect and combination therapy may decrease discontinuation of treatment.32 Using high potency BZDs (aloprazolam XR or clonazepam) as “rescue drugs” for a short time to manage anxiety until the antidepressants take effect is recommended,21, 32, 43 and continues to be a mainstay of long-term therapy for anxiety disorders.44 High potency BZDs are preferred due to their association with less rebound anxiety, peak effects such as sedation and euphoria and abuse potential, and discontinuation effects as compared to short-acting BZDs.45 Providers prescribing BZDs need to be aware of and monitor the short-term cognitive effects including sedation, psychomotor slowing, antegrade amnesia, and difficulty learning new material.46 The psychomotor slowing makes them inappropriate for use with elderly patients due to increased risk of falls and they are no longer covered as a medication by the new Medicare Prescription Drug Act. O’Brien recommends that BZDs be used with caution in persons with current/past substance abuse.47

MAOIs

The transdermal patch, selegiline (Emsam), is an MAOI approved for treatment of depression without any recommendation to restrict aged cheeses and other tyramine-enriched foods. If considering using other MAOIs for patients who have not responded to treatment, refer them to psychiatry for treatment due to the close follow-up required and danger of hypertensive crisis.48

Other Medications

Buspirone (Buspar), a non-sedating nonbenzodiazepine anxiolytic with effects on serotonin and dopamine receptors, may be used as an adjunct when the patient has a history of alcohol or drug abuse. Effectiveness has been shown in treating GAD symptoms of worry, tension, irritability, and apprehension but not as effective in addressing somatic symptoms. It takes a minimum of 2 to 3 weeks for the onset of action and as much as 6 weeks for beneficial effects to be seen. Divided doses are required.49

Beta-adrenergic blockers also are used to decrease the autonomic nervous system arousal response to stress and may be used to reduce performance anxiety,50 such as use of low-dose propanolol (Inderal) for students with test anxiety. A “rehearsal” dose prior to use for the actual performance is necessary to evaluate effectiveness and adverse effects.50

Remedies for Nonadherence Due to Side Effects

Many patients do not adhere to prescribed medication therapy due to side effects. Strategies such as reducing the dose or switching to another medication may increase adherence. When side effects are the primary reason for nonadherence, pharmacologic remedies to reduce side effects are often used.

The most important treatment strategies are collaborating with the patient in setting goals and establishing a relationship that allows open communication. Monitoring patient progress and the reduction of symptoms cannot be overemphasized to identify efficacy problems early in treatment.

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AUTHOR DISCLOSURE
The authors have disclosed that they have no significant relationship or financial interest in any commercial companies that pertain to this educational activity.

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