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Recognition and Treatment of Anxiety Disorders In the Primary Care Setting

JOINT SPONSORSHIP STATEMENT

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ESTIMATED TIME TO COMPLETE THIS EDUCATIONAL ACTIVITY

This activity should take approximately 1 hour to complete.

STATEMENT OF NEED

Although most primary care physicians recognize broad-spectrum mood and anxiety disorders, many do not make a distinct diagnosis. Thus, educational issues for primary care audiences may include symptom recognition and the diagnosis of various anxiety disorders, as well as the differentiation and selection of anxiolytic agents. This activity addresses current concepts in the treatment of anxiety disorders.

TARGET AUDIENCE

This activity is intended for primary care physicians. There are no prerequisites.

LEARNING OBJECTIVES

At the conclusion of this activity participants should be able to:

1. Describe the pathophysiology of anxiety disorders and the characteristic symptoms of each of the major anxiety disorders.
2. Discuss the treatment goals of anxiety disorders as they relate to both nonpharmacologic and pharmacologic approaches.
3. Identify the major classes of anxiolytic agents, and discuss strategies for choosing the appropriate class and agent according to diagnosis.
4. Discuss the benefits and drawbacks associated with each anxiolytic class (including antidepressants) and treatment outcomes of monotherapy and combination therapy.

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COURSE DIRECTOR

Glenn J. Treisman, MD, PhD
Associate Professor of Psychiatry and Behavioral Sciences
Associate Professor of Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

FACULTY LIST AND QUALIFICATIONS

Larry Culpepper, MD, MPH
Professor and Chair
Department of Family Medicine
Boston University School of Medicine
Boston, Massachusetts

James W. Jefferson, MD
Distinguished Senior Scientist
Madison Institute of Medicine, Inc
Clinical Professor of Psychiatry
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

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OFF-LABEL PRODUCT DISCUSSION

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are not approved for the treatment of anxiety disorders. None of the benzodiazepines are approved for treating social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), or obsessive-compulsive disorder (OCD), and clonazepam is not approved for generalized anxiety disorder (GAD). Fluoxetine is not approved for GAD, SAD, or PTSD, sertraline is not approved for GAD, and escitalopram is not approved for panic disorder, SAD, PTSD, or OCD. Venlafaxine is not approved for PTSD or OCD. Buspirone is not approved for panic disorder, SAD, PTSD, or OCD.

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Anxiety disorders are a diverse set of syndromes characterized by different clinical features. Most begin in childhood, adolescence, or early adulthood and continue throughout adulthood. There are 11 anxiety disorders classified in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision (*DSM*-IV-TR).[1] The anxiety disorders that are observed most often in the primary care setting are social anxiety disorder (SAD)/social phobia, generalized anxiety disorder (GAD), and panic disorder.

Epidemiology and Economic Impact of Anxiety Disorders

According to the National Comorbidity Survey Replication, the lifetime prevalence of any anxiety disorder is approximately 28.8%.[2] Additional data from this survey, which estimated the 12-month prevalence, severity, and comorbidity of *DSM*-IV-TR disorders, showed that anxiety disorders are the most prevalent class of disorders (18.1%),

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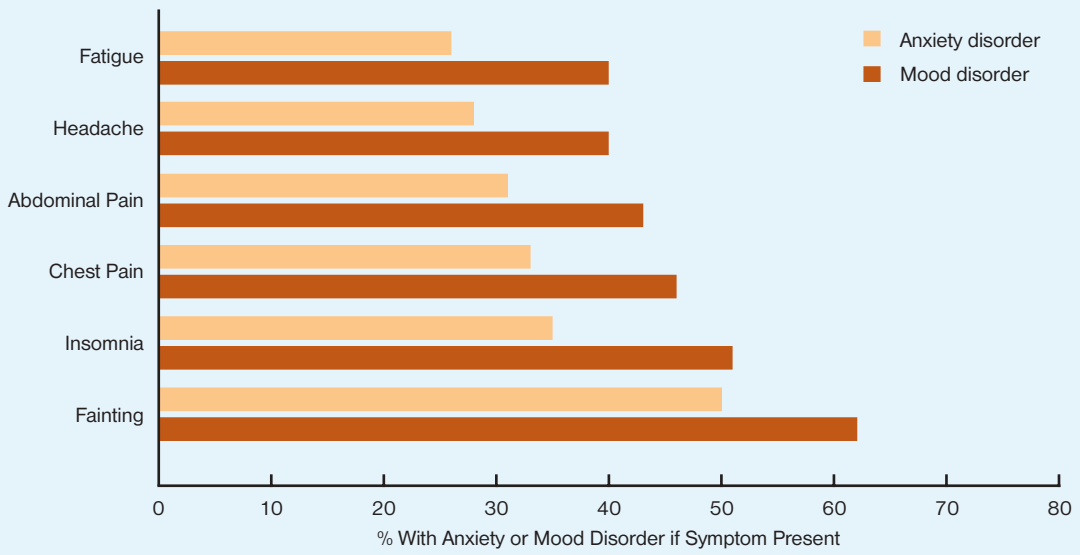

Figure 1. Relationship between common physical symptoms and psychiatric disorders in primary care patients.*

***N=1,000 patients (except somatoform symptoms, where complete data were available for 933 patients).**

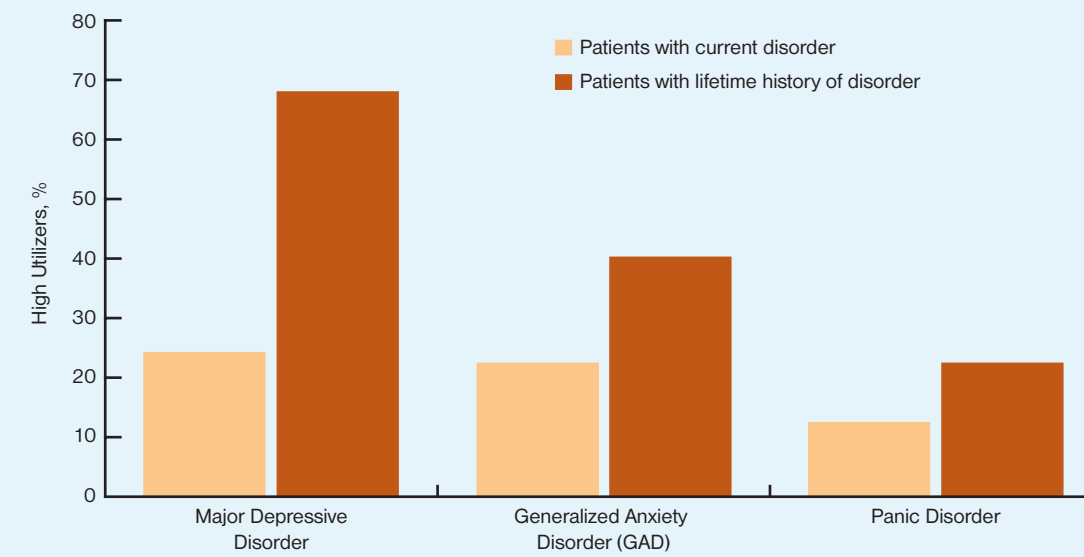

Figure 2. One-month and lifetime DSM-III-R diagnoses of distressed high utilizers.*

***N=119**

followed by mood disorders (9.5%), impulse control disorders (8.9%), and substance disorders (3.8%).[3] The prevalence of the anxiety disorders combined actually exceeds that of major depression.

Anxiety disorders typically start early in life; the median age at the onset of anxiety disorders is 11 years, much earlier than that at the onset of substance abuse (20 years) or mood disorders (30 years).[2] For example, SAD frequently presents in children as school phobias. There is a bimodal peak of age at onset of SAD that includes adolescence and early childhood.[4] Individuals in whom SAD develops during adulthood commonly experience significant anxiety during childhood and adolescence. Among individuals with SAD and a comorbid psychiatric disorder, SAD preceded the comorbid disorder in 77%.[4] Patients with SAD have a 4-fold increased risk for the development of major depressive disorder, obsessive-compulsive disorder, or panic disorder, up to a 3-fold increased risk for the development of posttraumatic stress disorder (PTSD), and at least a 2-fold increased risk for the development of alcohol and drug dependence.[5] The fact that SAD often precedes other anxiety disorders is not viewed as a risk factor but rather as a sign that the individual has the neurocircuitry that predisposes to additional anxiety disorders and major depression.

Anxiety disorders impose great psychological and financial burdens on individuals as well as on society. Because these disorders tend to be chronic, they require ongoing treatment, straining healthcare resources through psychiatric and nonpsychiatric care, emergency care visits, hospitalizations, and prescription drugs. In the United States, the total estimated cost for anxiety disorders comprises more than 30% of the total expenditures for mental illnesses.[6] In 1990, data from the National Comorbidity Study estimated the annual cost of anxiety disorders to be approximately $42.3 billion in the United States, or $1,542 per sufferer.[7] Work impairment is one of the adverse consequences of psychiatric disorders, and indirect workplace costs total $4.1 billion.[7,8] Work impairment is more strongly concentrated among the 3.7% of the workforce with comorbid psychiatric disorders than among the 14.5% with pure disorders or the 81.8% with no disorder.

Pathophysiology of Anxiety Disorders

Anxiety disorders appear to result from an interaction between biological factors and external situations, stress, or trauma to produce clinically significant symptoms. The pathophysiologic mechanisms underlying anxiety disorders are not definitive and are just now beginning to be understood. Evidence about the neuroanatomy of anxiety comes from animal experiments and human studies in which static and functional neuroimaging is used, and it appears that neural circuits, rather than distinct anatomic sites, underlie different types of anxiety.[9] The amygdala and the hippocampus work in synergy and play significant roles in the pathophysiology of anxiety disorders. The amygdala is believed to be a hub of communication between the parts of the brain that process incoming sensory signals and the parts that interpret these signals, alerting the rest of the brain that a threat is present and triggering a fear or anxiety response.[10] The hippocampus is the area of the brain that encodes threatening events into memories. In the anxiety disorders, the amygdala and the hippocampus operate at a level beyond what is adaptive for modern society. As a result of the output from these 2 areas of the brain, activation of corticotropin-releasing factor and cortisol occurs.

Most work in the neurochemistry of anxiety has centered on the serotoninergic and noradrenergic (norepinephrine) systems, the γ-aminobutyric acid (GABA)–benzodiazepine receptor complex, and a number of unrelated compounds that are known to provoke anxiety and/or panic on challenges.[9] The noradrenergic theory of anxiety contends that increased noradrenergic release leads to anxiety via excessive or dysfunctional arousal. Serotonin (5-HT) has been implicated in the neurochemistry of anxiety for many years, but interest in the role of the serotoninergic system in anxiety disorders has increased during the last decade. The relationship between anxiety and 5-HT is indeed complex; the classic theory that anxiety is secondary to excessive 5-HT activity is now being challenged by more sophisticated models that place emphasis on different serotoninergic neural circuitry and receptors mediating different aspects of anxiety.[9]

Presentations of Anxiety Disorders in Primary Care

The presentations of anxiety in primary care are more numerous and broader in spectrum than the presentations of depression, challenging the primary care physician (PCP) to find a diagnosis from a full spectrum of anxiety disorders.[11] Persons with anxiety disorders often experience physical symptoms and distress and thus present to their PCP with somatic complaints, which may temporarily distract the clinician from the underlying symptoms of anxiety. Three frequent modes of presentation of anxiety disorders in primary care are the following[11]:

- *Somatic*—This is the most common presentation and includes a variety of somatic complaints, such as pain syndromes, headaches, fatigue, irritability, sweating, sleep disturbance, and gastrointestinal symptoms.
- *Psychiatric*—In a less common presentation, patients consider their symptoms to be emotional in origin.

- *High utilizer*—A more subtle presentation, in which the patient visits the PCP frequently with a myriad of complaints, is characterized by a decreased ability to function in life and the need for the physician as support.

In an outpatient mental health survey encompassing 4 primary care clinics, 1,000 adult patients were assessed for psychiatric disorders, the presence or absence of 15 common physical symptoms, and functional status.[12] In addition to the fact that each of the 15 common symptoms was frequently somatoform (range, 16%-33%), the presence of any physical symptom increased the likelihood of a diagnosis of mood or anxiety disorder 2-fold to 3-fold, and somatoform symptoms (lacking an adequate physical explanation) had a particularly strong association with psychiatric disorders (Figure 1). The number of physical symptoms was found to be a powerful correlate of functional status.

Persons with anxiety disorders are high utilizers of healthcare services, including primary care. Among a sample of 767 high utilizers of healthcare who were screened with the Symptom Checklist-90-Revised (SCL-90-R), 51% were identified as distressed by an elevated score on the SCL anxiety, depression, or somatization scale, or by their PCP.[13] These distressed utilizers had made an average of 15 medical visits and 15 telephone calls to the clinic in the prior year and reported approximately 1 self-initiated request for a specialty referral in the past year. Although no comparisons were made with the general population, many patients with high healthcare utilization were currently experiencing or had a history of major depression, panic disorder, or GAD (Figure 2).

Comorbidity and Anxiety Disorders

Comorbidity is the rule rather than the exception in anxiety and depressive disorders. Anxiety disorders are often comorbid with other psychiatric disorders and with one another.[14] Moreover, anxiety disorders frequently coexist with chronic medical conditions such as cardiovascular disease and diabetes mellitus. The coexistence of anxiety disorders and major depressive disorders is associated with barriers to treatment, including treatment resistance, increased risk for suicide, greater chance for recurrence, greater utilization of medical resources, and worse psychiatric outcomes.

The long-term clinical course of anxiety disorders and the influence of comorbid psychiatric disorders on recovery from or recurrence of panic disorder, GAD, and social phobia have been examined in a prospective, naturalistic, longitudinal study conducted over 12 years.[15] Of 711 patients assessed at intake, 473 remained in the study at the 12-year follow-up. Patients were evaluated at 6-month intervals during the first 2 years, annually during years 3 to 6, and every 6 months during years 7 to 12. Patients were considered to have recovered from an anxiety disorder if they exhibited psychiatric status ratings of 2 or less on a rating scale of 1 to 6 (1, without any residual symptoms of disorder; 2, presence of symptoms of no more than mild degree) for 8 consecutive weeks. Twelve years after study entry, estimates showed that patients with panic disorder without agoraphobia were likely to have had a recovery at all time points (recovery probability, 0.82), whereas the recovery probabilities during 12 years of follow-up were much lower in patients with GAD, panic disorder with agoraphobia, or social phobia (0.58, 0.48, and 0.37, respectively; Figure 3). A higher probability of recovery from major depressive disorder than from any of the anxiety disorders was observed, with the exception of panic disorder without agoraphobia. In terms of comorbidity, investigators found that patients with comorbid major depressive disorder were half as likely to subsequently recover from GAD or panic disorder with agoraphobia ($P<0.01$) as patients without comorbid major depressive disorder.

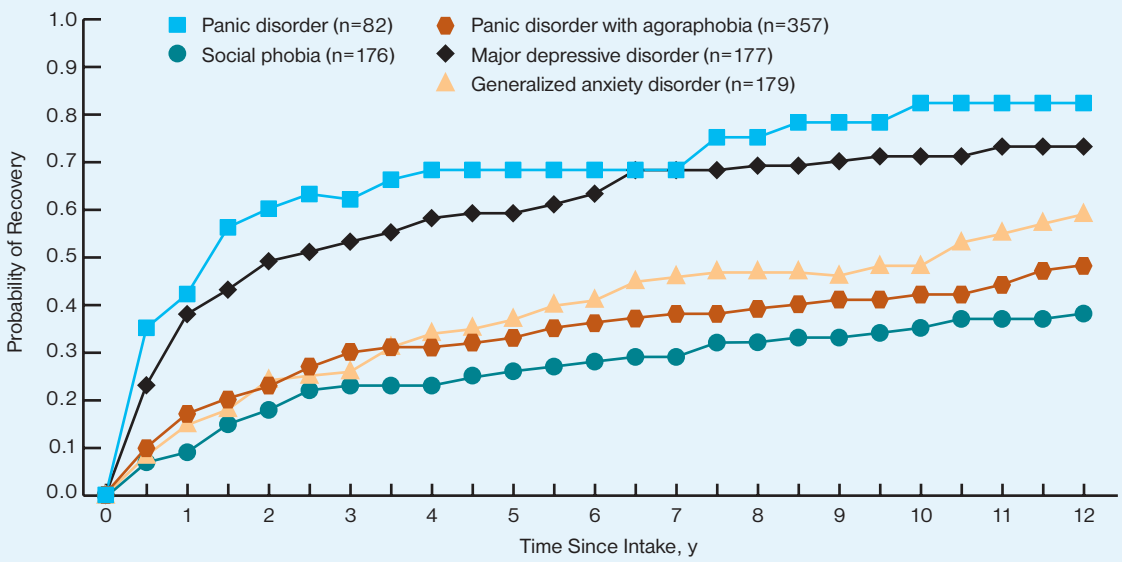

Figure 3. Twelve-year cumulative probability of recovery in patients with anxiety disorders and patients with comorbid major depressive disorder at presentation.

Clinical Symptoms and Diagnostic Features Of Anxiety Disorders Seen in Primary Care

The PCP plays a significant role in the initial screening and diagnosis of anxiety disorders. Some of the challenges to the detection of anxiety disorders by PCPs include the *DSM*-IV terminology, patient resistance to diagnostic test procedures, translating the symptoms into a diagnosis, and eliminating organic possibilities. For a patient with symptoms of anxiety to be given a proper diagnosis, the *DSM*-IV-TR criteria must be met. The diagnosis is often complicated by the simultaneous presence of another psychiatric disorder, such as depression or substance abuse. Because several anxiety disorders have overlapping signs and symptoms, it is important for clinicians to use several lines of questioning to determine the primary diagnosis. Obtaining a good medical and psychiatric history is fundamental to the diagnosis of an anxiety disorder. Medical disorders that may be contributing to the distress must be ruled out, in addition to substance abuse or dependence.

Social Anxiety Disorder

SAD, also referred to as *social phobia*, is the anxiety disorder that presents most often in the primary care setting. SAD is characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur. Common associated features of SAD include hypersensitivity to criticism, negative evaluation or rejection, difficulty being assertive, and low self-esteem or feelings of inferiority. Associated features may include poor social skills (eg, poor eye contact) and observable signs of anxiety (eg, cold clammy hands, tremors, shaky voice). A diagnosis of SAD is appropriate only if an individual's normal routines, occupational functioning, or social activities or relationships are significantly impaired as a result of such fears (Table 1).[1]

Table 1. Diagnostic Criteria for Social Anxiety Disorder[1]

- Patient experiences extreme anxiety in social or performance situations
- Individual recognizes that the fear is excessive or unreasonable
- The feared social or performance situations are avoided or else are endured with intense anxiety or distress
- Individual finds that normal routines, occupational functioning, or social activities or relationships are significantly impaired as a result of his/her fears

Table 2. Diagnostic Criteria for Generalized Anxiety Disorder[1]

- Anxiety and worry are out of proportion to likelihood of feared event
- Patient finds anxiety difficult to control
- Symptoms occur more days than not for at least 6 months
- Adults experience 3, or children experience 1, of the following:
  - restless, keyed up, or feeling on edge
  - easily fatigued
  - difficulty concentrating
  - irritable
  - muscle tension
  - sleep disturbance

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Generalized Anxiety Disorder

GAD is characterized by chronic, excessive, uncontrollable worry and anxiety about everyday issues (eg, health, money, family, work) that are not provoked by any specific event. Although persons with GAD generally realize that their anxiety is more intense than the situation warrants, they find it difficult to control their worry and concerns. Constant worry affects daily functioning and frequently manifests as physical complaints. Persons with GAD are unable to relax, startle easily, have difficulty concentrating, and often have trouble falling asleep or staying asleep. GAD does not characteristically result in avoidance of certain situations, and the individual is usually able to function in social settings or on the job if the impairment is mild. However, persons with severe GAD may have difficulty carrying out the simplest daily activities. Individuals with GAD generally present to their PCPs when the anxiety peaks and they can no longer cope. As many as 83% of patients present initially to their PCP with general, vague, or nonspecific somatic complaints, such as pain syndromes, symptoms of autonomic arousal (chest pain, palpitations, hyperventilation), headache, fatigue, insomnia, and gastrointestinal symptoms.[16] The diagnostic criteria for GAD are shown in Table 2.[1]

Table 3. Diagnostic Criteria for Panic Disorder[1]

- Recurrent unexpected panic attacks
- At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
  - persistent concern about having additional attacks
  - worry about the implications of the attack or its consequences
  - a significant change in behavior related to the attacks.
- The panic attacks are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hyperthyroidism)

Table 4. Drugs With FDA-Approved Indications for Anxiety Disorder

	Panic	GAD	SAD	PTSD	OCD
Benzodiazepines					
Alprazolam	•	•			
Alprazolam ODT	•	•			
Alprazolam XR	•				
Clonazepam	•				
Clonazepam ODT	•				
Tricyclic antidepressant					
Clomipramine					•
SSRIs					
Escitalopram		•			
Fluoxetine	•				•
Paroxetine	•	•	•	•	•
Paroxetine CR	•		•		
Sertraline	•		•	•	•
SNRI					
Venlafaxine XR	•	•	•		
Other					
Buspirone		•			

CR, controlled release; **GAD**, generalized anxiety disorder; **OCD,** obsessive compulsive disorder; **ODT,** orally disintegrating tablet; **PTSD,** posttraumatic stress disorder; **SAD,** social anxiety disorder; **SNRI,** serotonin norepinephrine reuptake inhibitor; **SSRI,** selective serotonin reuptake inhibitor; **XR,** extended release

Panic Disorder

Recurrent, unexpected panic attacks—and discrete periods of intense fear or discomfort in the absence of real danger—are the essential features of panic disorder.[1] A panic attack has a rapid onset and generally lasts 10 to 15 minutes, and it may produce a sense of unreality, a fear of impending doom, or a fear of losing control. Physical symptoms such as a pounding heart, sweatiness, weakness, faintness, and dizziness often accompany a panic attack. By itself, a panic attack is not considered a mental disorder and does not necessarily constitute panic disorder. Panic disorder is differentiated from single panic attacks by the anticipatory anxiety that one will have future panic attacks and the restriction of function that results from that concern. The diagnostic criteria for panic disorder are shown in Table 3.[1]

Anxiety Secondary to Organic Causes

Anxiety secondary to an organic cause should be considered in patients in whom symptoms begin after age 35 and in whom the following are lacking: a personal or family history of anxiety disorder; a childhood history of anxiety, phobia, or separation anxiety; a significant life event that would precipitate an anxiety disorder; avoidance behavior. An organic cause should also be considered in patients who fail to respond to psychiatric treatment.[17] Frequently, individuals with an organic cause of anxiety deny a history of or a tendency to have feelings of anxiety or an anxiety disorder. In such cases, the PCP should look beyond a psychiatric diagnosis to rule out other possible origins of the anxiety, such as hyperthyroidism, undiagnosed cancer, a cardiac event, or any number of other medical conditions.

Treatment of Anxiety Disorders

In general, 2 types of therapy—*pharmacotherapy* and *psychotherapy*—are used, either alone or in combination, for the treatment of anxiety disorders. Pharmacologic agents allow patients with anxiety disorders to bring their symptoms under control, whereas some forms of psychotherapy help patients to explore the beliefs or behaviors that maintain their anxiety disorder.

Several factors increase the effectiveness of treatment, including:

- patient compliance
- absence of comorbid conditions
- continuation of treatment to prevent relapse
- ease of use
- patient education.

When the clinician chooses an appropriate treatment for anxiety, the patient must first be evaluated for the presence of a comorbid condition. The appropriateness of the treatment for the individual patient should be considered. For example, some patients with severe anxiety may require the rapid relief afforded by benzodiazepines, whereas patients with a substance abuse problem may require a selective serotonin reuptake inhibitor (SSRI). Some clinicians will escalate the dose when a response is not achieved. The duration of treatment should be extended beyond the point of symptom relief to prevent relapse. The International Consensus Group on Depression and Anxiety recommends an 8-week initial treatment phase to establish efficacy and response, followed by a continuation phase of 1 year or more to achieve remission.[18]

Cognitive Behavioral Therapy

Of the various forms of psychotherapy, cognitive behavioral therapy (CBT) is perhaps the one for which the most evidence is available to support its effectiveness for anxiety disorders. The cognitive component of CBT helps to control unrealistic or negative patterns of thinking that contribute to anxiety and prevent the patient from overcoming his or her fears. In the behavioral component of CBT, the event or fear is recalled or experienced in a safe, controlled situation to help defuse the anxiety it provokes. CBT is useful alone and can be a valid first-line treatment for anxiety disorders, or it may be used in combination with medication for refractory symptoms; persistent cognitive factors, behavioral patterns, and anxiety sensitivity; and comorbid conditions. CBT may facilitate the discontinuation of anxiolytic medication.

Pharmacotherapy

The drug classes that have been found to be effective for the treatment of anxiety disorders include the benzodiazepines, buspirone, serotonin norepinephrine reuptake inhibitors (SNRIs), and SSRIs. Drugs with an FDA-approved indication for the treatment of anxiety are shown in Table 4.

Benzodiazepines

Benzodiazepines have been used extensively for the treatment of anxiety disorders since the 1960s; newer benzodiazepine formulations, such as extended-release tablets and orally disintegrating tablets, offer alternative dosing and delivery options. As anxiolytics, benzodiazepines potentiate the inhibitor effects of GABA through their action on the GABA-A receptor.[19] Benzodiazepines are generally considered effective and have other advantages, although this class also has a number of drawbacks that need to be considered (Table 5).[20]

The long-term use of benzodiazepines has raised concerns about the development of therapeutic tolerance, although results of follow-up studies do not suggest a significant loss of therapeutic anxiolytic effect over time or provide evidence for escalation of dose.[21,22] A study of 2,440 New Jersey Medicaid patients examined the long-term use of benzodiazepines with a focus on dose escalation (an increase to >40 mg of diazepam per day or its equivalent or to 20 mg of diazepam per day in the elderly over a 2-year period).[21] Investigators observed that the dose was increased above the prespecified level of concern in 1.6% of patients. For the majority of patients, the doses tended to remain stable over time, with the exception of those treated concomitantly with antidepressants and those filling duplicate prescriptions for benzodiazepines at different pharmacies. Nagy and colleagues[22] studied 60 patients with panic attacks or panic disorder who completed a 4-month combined program of alprazolam and behavior therapy and were interviewed 1.7 to 4 years after discharge. At follow-up, 60% of patients were taking alprazolam at a lower dose, 30% had discontinued alprazolam therapy altogether, and 5% had increased their dose.

The abuse of benzodiazepines can be divided into 2 patterns: *intentional abuse* by persons who use drugs for their euphoriant effects, and *unintentional abuse* by patients who begin using benzodiazepines to treat an anxiety disorder and then use them inappropriately.[23] Intentional abusers generally take high doses of benzodiazepines and engage in the abuse of multiple drugs and alcohol. Most unintentional abusers are unaware of their benzodiazepine dependence until they try to abruptly discontinue the drugs.

To help patients avoid withdrawal symptoms when it is time to discontinue a benzodiazepine, the drug must be tapered very gradually. When withdrawing patients from a benzodiazepine, clinicians must observe carefully for the following: (1) recurrence of the anxiety symptoms being treated, (2) a temporary rebound in the number of anxiety attacks (eg, panic), (3) withdrawal symptoms associated with abrupt discontinuation, and (4) pseudowithdrawal due to a psychological dependence on the medication. It is important to keep in mind that if the taper involves a fixed-dose decrease, the percentage of the drug dose being removed increases as lower doses are reached. Therefore, as lower doses are approached, a smaller amount should be removed with each step of the taper. During the process of benzodiazepine discontinuation, CBT can be valuable in helping patients transition off the medication.

Buspirone

After the benzodiazepines, buspirone, classified as an azapirone, was the first agent to gain FDA approval for the treatment of GAD. Buspirone is classified as a 5-HT_{1A} agonist; although its mechanism of action is rather complex and not completely understood, its main effects are mediated by the serotonin-1A (5-HT_{1A}) receptors. Buspirone is an agonist primarily at presynaptic 5-HT_{1A} receptors and is a partial agonist at postsynaptic 5-HT_{1A} receptors in several brain regions involved in stress, fear, and anxiety.[24] Additionally, buspirone acts as a dopamine agonist, possessing a weak affinity for both dopamine D_2- and D_3-receptor subtypes.

Buspirone has been demonstrated to have efficacy in the treatment of GAD, but not in other anxiety disorders or depression. Buspirone has a benign side-effect profile, does not potentiate alcohol or have any potential for abuse, and is relatively safe in overdose (Table 5).[25] Buspirone does not induce sedation, psychomotor or cognitive impairment, or physical dependence or tolerance, and it does not interact with alcohol. The 3- to 4-week lag before the onset of anxiolytic activity limits the utility of buspirone in patients requiring intervention for acute anxiety.

SSRIs and SNRIs

Before the discovery and approval of the SSRIs, 2 other classes of antidepressants, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs), were sometimes prescribed for the treatment of anxiety disorders. However, certain side effects associated with TCAs (eg, drowsiness, dry mouth, weight gain) and MAOIs (eg, potentially severe interactions with certain medications and foods), in addition to their potential lethality in overdose, have made the SSRIs more desirable when antidepressants are indicated for the treatment of anxiety disorders. The efficacy of the SSRIs in the treatment of depression has been well established in numerous controlled clinical trials and through clinical experience. The SSRIs and SNRIs have well-documented efficacy in the treatment of depression, and are effective in alleviating symptoms of anxiety. Their drawbacks include delayed onset of benefit, side effects such as sexual dysfunction, and lack of utility as agents that can be used on an as-needed basis (Table 5).[25] Some SSRIs and SNRIs have a high potential for drug-drug interactions, and cost may also be a concern. Although the advantages of SSRIs in treating anxiety disorders are not as well documented as their clinical utility in treating depression,[24] most agents in this class now have FDA approval for several anxiety disorders (Table 4). Bupropion, while effective for depression, is not efficacious as monotherapy for anxiety disorders, and it may even exacerbate agitation.

Table 5. Benefits and Drawbacks of Anxiolytic Agents[20, 25]

Benefits	Drawbacks
Benzodiazepines	
Effective Short response latency Well tolerated; high level of patient acceptance Rapid dose adjustment feasible Can be used PRN Reduce antidepressant-induced activation	Sedation, decreased reaction time, cognitive impairment Discontinuation difficulties Potential for abuse in predisposed individuals Interaction with alcohol Not effective for comorbid depression
Buspirone	
Efficacy in GAD Benign side-effect profile No alcohol potentiation No abuse potential Relatively safe in overdose	Delayed onset of benefit Dosing 2 or 3 times daily Limited spectrum of effect Drug interactions (CYP3A4 substrate)
SSRIs/SNRIs	
Well-documented efficacy in major depression Effective in alleviating anxiety symptoms Some have multiple indications for anxiety disorders	Delayed onset of benefit Cost Side effects (eg, sexual dysfunction) Potential for drug–drug interactions (eg, CYP450) Not useful as PRN treatment

CYP, cytochrome P-450 enzyme; **GAD,** generalized anxiety disorder; **PRN,** as needed; **SNRI,** serotonin–norepinephrine reuptake inhibitor; **SSRI,** selective serotonin reuptake inhibitor

The SSRIs have a common mechanism of action, although they differ considerably in chemical structure, metabolism, and pharmacokinetics. Perhaps the most important way in which the drugs in this class differ is in their potential to cause drug-drug interactions through the inhibition of cytochrome P-450 isoenzymes (ie, CYP1A2, CYP2C9, CYP2D6, CYP3A4), which are responsible for the oxidation and metabolism of numerous substrates and drugs.[26] Because of the chronic nature of anxiety disorders and depression, most patients require long-term treatment, which increases the likelihood that SSRIs will be prescribed together with other medications. Thus, the potential for clinically significant drug-drug interactions, which may be pharmacokinetic or pharmacodynamic, is considerable.

An understanding of the cytochrome P-450 isoenzymes involved in the metabolism of the SSRIs and coadministered drugs can help the PCP anticipate and avoid potentially dangerous drug-drug interactions. As shown in Table 6, citalopram is associated with minimal or no inhibition of CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and only mild inhibition of CYP1A2; escitalopram has little or no effect on any of the enzymes, so that its potential to cause drug-drug interactions is limited.[27,28] Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 and a mild inhibitor of CYP2C9, CYP2D6, CYP3A4. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, whereas sertraline is a mild inhibitor of CYP2D6. Because of the long half-life of fluoxetine and its metabolite norfluoxetine, its inhibitory effects on cytochrome P-450 activity can persist for several weeks after discontinuation.

Table 6. In Vitro Inhibition of Cytochrome P-450 Enzymes by SSRIs

	1A2	2C9	2C19	2D6	3A4
Citalopram	+	0	0	0	0
Escitalopram	0	0	0	0	0
Fluoxetine	+	++	+ to ++	+++	+
Fluvoxamine	+++	++	+++	+	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

0, minimal or no inhibition; **+**, mild inhibition; **++**, moderate inhibition; **+++**, strong inhibition

Treatment of Social Anxiety Disorder

As noted in Table 4, 2 SSRIs (paroxetine and sertraline) and the SNRI venlafaxine are approved for the treatment of SAD. Double-blind, randomized, placebo-controlled studies have demonstrated the efficacy of these compounds for the treatment of SAD.[29-34] Patients treated with paroxetine, sertraline, or venlafaxine over 12-week study periods report significant decreases in SAD symptoms as assessed with the Clinical Global Impression Improvement (CGI-I) Scale and/or the Liebowitz Social Anxiety Scale (LSAS) in comparisons with patients given placebo.

Treatment of Generalized Anxiety Disorder

Benzodiazepine Versus TCA Versus SSRI

Using *DSM*-IV-TR criteria for GAD, Rocca and colleagues compared the efficacy of diazepam (a benzodiazepine), imipramine (a TCA), and paroxetine (an SSRI) in an 8-week study of 81 patients.[35] During the first 2 weeks, diazepam showed greater efficacy in reducing symptoms of GAD than the other 2 treatments, but by week 4, patients treated with either imipramine or paroxetine showed significantly more improvement than those treated with diazepam. Diazepam predominantly affected somatic symptoms, whereas imipramine and paroxetine affected psychic symptoms.

Benzodiazepine Versus Buspirone

In a 6-week double-blind, placebo-controlled study that compared the benzodiazepine alprazolam (n=32) with buspirone (n=31) for GAD, the 2 drugs were similar in efficacy and more effective than placebo (n=31) for treating symptoms of anxiety and depression.[36] Alprazolam produced

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rapid and sustained improvement, whereas buspirone produced a more gradual effect. Significantly more buspirone-treated patients than alprazolam-treated patients failed to complete the study (11 vs 4 patients), primarily because of side effects or inefficacy. There were no significant differences noted between the vital signs, laboratory test results, and side effects of the patients treated with these 2 drugs; alprazolam caused more central nervous system side effects (eg, drowsiness, sedation), and buspirone produced more gastrointestinal side effects (appetite disturbances and abdominal complaints).

SNRI Versus Buspirone

Davidson and colleagues[37] compared the efficacy and safety of the SNRI venlafaxine XR at a dosage of 75 or 150 mg per day with buspirone in outpatients with GAD without concomitant major depressive disorder (efficacy analysis, n=365; safety analysis, n=405). Changes from baseline in Hamilton Anxiety Scale (HAM-A) total scores in all treatment groups were greater than those in the placebo group at all times; however, these differences failed to reach statistical significance. The difference between the proportions of responders in the treatment groups (defined by a decrease of at least 50% from baseline in HAM-A total scores) was not statistically significant at any time. For response based on CGI-I scores of 1 (very much improved) or 2 (much improved), venlafaxine XR at a dosage of 75 mg per day was better than placebo at all times after week 2 (P<0.03), and buspirone was better than placebo at weeks 6 and 8 (P<0.04). Venlafaxine XR and buspirone were both well tolerated.

SSRI Versus Placebo

More recently, the newer SSRI escitalopram was evaluated for the treatment of GAD in 315 outpatients who were randomized in double-blind fashion to treatment with escitalopram at a dosage of 10 mg per day or placebo.[38] Patients treated with escitalopram showed a statistically significant improvement on all efficacy parameters compared with patients given placebo. Response rates at week 8 were 68% for escitalopram and 41% for placebo (P<0.01).

Treatment of Panic Disorder

The pharmacologic treatment of panic disorder generally relies on antidepressants (with or without benzodiazepine therapy), and SSRIs are typically the first choice rather than other antidepressant classes. Recent clinical trials of patients with panic disorder have compared individual SSRIs. Adult outpatients with panic disorder with or without agoraphobia were randomized to 12 weeks of treatment with flexible dosages of sertraline (titrated up to 50-150 mg/d; n=112) or paroxetine (titrated up to 40-60 mg/d; n=113); the medication was then tapered over 3 weeks.[39] The 2 drugs were associated with equivalent levels of improvement on the Panic and Agoraphobia Scale total score, the primary efficacy measure. During the taper period, the proportion of panic-free patients increased by 4% with sertraline, but decreased by 11% with paroxetine (P<0.05).

Benzodiazepines, which have a rapid onset of effect, may help reduce panic attacks in the first weeks of antidepressant therapy. An early study by Tesar et al,[40] which compared the efficacy of alprazolam, clonazepam, and placebo in 72 patients with panic disorder, demonstrated that significantly more patients treated with either alprazolam or clonazepam were panic-free at end point, compared with patients given placebo. There were no significant differences between the active treatment groups.

Although there is debate about combining a benzodiazepine with an SSRI for the treatment of acute panic disorder, Goddard et al[41] found that patients who received both clonazepam and sertraline showed an earlier response to treatment. During the 12-week treatment period, patients received open-label sertraline at a dosage of 100 mg per day; in addition, patients were randomized to receive clonazepam 0.5 mg 3 times daily or placebo for 4 weeks, followed by a 3-week taper. The combination of clonazepam plus sertraline was significantly more effective at reducing panic symptoms than was sertraline alone during weeks 1 and 3 of the study; however, the dropout rates in the 2 groups were similar. These findings demonstrate that the addition of a benzodiazepine to an SSRI is well tolerated and can reduce the time to stabilization of panic symptoms.

Principles of Prescribing Antidepressants For Anxiety Disorders and Combining With Benzodiazepines

When antidepressants are prescribed, time and an adequate dose are required for a maximal response to be achieved. When treatment with an antidepressant is initiated, it is important to start with a low dose and titrate slowly to diminish the side effects that may limit patient acceptance. Although the jitteriness frequently experienced during initial SSRI therapy usually goes away and is modified by the use of a lower dose, patients should be educated about this side effect to avoid the abrupt discontinuation of medication. This side effect can also be modified by short-term concomitant therapy with a benzodiazepine. Combining benzodiazepines with antidepressants provides rapid anxiolysis during the antidepressant lag, decreases early antidepressant-associated anxiety, and helps to alleviate the residual anxiety associated with antidepressant therapy.[42]

Conclusion

Anxiety disorders typically begin early in life, tend to be chronic and unremitting, and are often comorbid with depression and substance abuse. Persons with anxiety disorders are high utilizers of health services in the primary care segment and frequently present to their PCP with myriad somatic complaints. The main goal of treatment is to achieve remission. The 2 forms of therapy used for the treatment of anxiety disorders are pharmacotherapy, which treats the symptoms of anxiety, and CBT, a form of psychotherapy that helps patients explore and control behaviors that sustain the disorder. Drug classes that have been found to be effective for the treatment of anxiety disorders are the benzodiazepines, the azapirone buspirone, and the SSRIs and SNRIs. Benzodiazepines are effective for GAD and panic disorder and are often used concomitantly with an antidepressant. Buspirone is effective for GAD. SSRIs and SNRIs are effective for various anxiety disorders and are of particular benefit in patients with comorbid depression.

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CME Post-test

1. **The area of the brain that encodes threatening events into memories is the _____.**
   - A. cerebellum
   - B. hippocampus
   - C. hypothalamus
   - D. amygdala

2. **All of the following are features of an anxiety disorder secondary to an organic cause except:**
   - A. absence of significant life events generating anxiety symptoms
   - B. poor response to psychiatric treatment
   - C. personal or family history of an anxiety disorder
   - D. onset of anxiety symptoms after age 35 years

3. **Each of the following is considered a potential drawback associated with the SSRIs except:**
   - A. increased potential for nephrotoxicity
   - B. potential for drug–drug interactions (eg, cytochrome P-450 metabolism)
   - C. delayed onset of action
   - D. side effects (eg, sexual dysfunction)

4. **The rationale for adding a benzodiazepine to an SSRI for the treatment of panic disorder is based on which of the following:**
   - A. Antidepressants are associated with a lag time of several weeks before they achieve therapeutic effect.
   - B. Benzodiazepines have a rapid onset of action and may reduce panic attacks during initiation of an antidepressant.
   - C. B only
   - D. A and B

5. **The SSRIs that strongly inhibit the CYP2D6 enzyme are _____.**
   - A. sertraline and fluvoxamine
   - B. escitalopram and citalopram
   - C. paroxetine and fluoxetine
   - D. none of the above

6. **Which of the following statements describe(s) the treatment of anxiety disorders most accurately?**
   - A. Benzodiazepines must be tapered very gradually upon discontinuation to avoid withdrawal symptoms.
   - B. Antidepressants should be initiated at a low dose and titrated slowly.
   - C. Using a benzodiazepine to augment antidepressant therapy slows the treatment response and may enhance activating symptoms of SSRIs
   - D. A and B
   - E. A and C

7. **Which of the following anxiety disorders presents most frequently in the primary care setting?**
   - A. Social anxiety disorder
   - B. Posttraumatic stress disorder
   - C. Generalized anxiety disorder
   - D. Obsessive-compulsive disorder

8. **Each of the following characterizes patients with GAD except:**
   - A. They present to the primary care physician when anxiety peaks and they can no longer cope.
   - B. Constant worry affects daily functioning and frequently manifests as physical complaints.
   - C. Anxiety and worry are associated with the presence of at least 6 physical symptoms for 3 months or longer.
   - D. Despite the realization that their anxiety is more intense than the situation warrants, they find it difficult to control worry and concerns.

9. **In a study that examined the association of long-term benzodiazepine use and dose escalation, what percentage of patients increased their dose over a 2-year period?**
   - A. 10%
   - B. 5%
   - C. 2%
   - D. 25%

10. **Each of the following statements is true regarding the diagnosis of anxiety disorders *except*:**
    - A. The symptoms of the various anxiety disorders are discrete and easily recognized.
    - B. The diagnosis is often complicated by comorbidity such as depression and/or substance abuse.
    - C. The DSM-IV-TR criteria must be met for a patient to be given a proper diagnosis.
    - D. Obtaining a good medical and psychiatric history is fundamental to the diagnosis of an anxiety disorder.

Self-Report Credit Form

Recognition and Treatment of Anxiety Disorders In the Primary Care Setting

Date of Release: November 2006 Date of Expiration: November 30, 2007

In order to receive credit, participants must complete the self-report credit form, post-test answer section, and activity evaluation either online or by fax. Fax your submission to The Johns Hopkins University School of Medicine at (410) 614-7315. Your certificate will be mailed to you in approximately 6-8 weeks. For online submissions at CMEZone.com (availability may be delayed from original print date), enter the project number "IP06020" in the keyword field to directly access this activity. Upon passing the activity, a certificate will be displayed on-screen that participants can print and keep for their records. One re-take is allowed.

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Post-Test Answer Section

1.	**a**	**b**	**c**	**d**	
2.	**a**	**b**	**c**	**d**	
3.	**a**	**b**	**c**	**d**	
4.	**a**	**b**	**c**	**d**	
5.	**a**	**b**	**c**	**d**	
6.	**a**	**b**	**c**	**d**	**e**
7.	**a**	**b**	**c**	**d**	
8.	**a**	**b**	**c**	**d**	
9.	**a**	**b**	**c**	**d**	
10.	**a**	**b**	**c**	**d**	

Activity Evaluation Form

1. How did you hear about this course?
O Brochure O Colleague O Internet O Other (please specify) _____

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
2. This course met the objectives of:					
1. Describe the pathophysiology of anxiety disorders and the characteristic symptoms of each of the major anxiety disorders.	O	O	O	O	O
2. Discuss the treatment goals of anxiety disorders as they relate to both nonpharmacologic and pharmacologic approaches.	O	O	O	O	O
3. Identify the major classes of anxiolytic agents, and discuss strategies for choosing the appropriate class and agent according to diagnosis	O	O	O	O	O
4. Discuss the benefits and drawbacks associated with each anxiolytic class (including antidepressants) and treatment outcomes of monotherapy and combination therapy.	O	O	O	O	O

3. Will you change your practice in any way as a result of participating in this program? O Yes O No

If yes, please specify: _____

4. Do you feel the activity was objective, balanced, and free of commercial bias? O Yes O No

If no, please specify: _____

5. If presented, were discussions of off-label uses of drugs and/or devices properly disclosed? O Yes O No

If no, please specify: _____

	Poor	Fair	Good	Very Good	Excellent
6. Overall evaluation	O	O	O	O	O
7. Course content	O	O	O	O	O
8. Usefulness	O	O	O	O	O

Additional Comments

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