Generalized Anxiety Disorder

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LEARNING OBJECTIVES

1. Distinguish between generalized anxiety disorder (GAD) and other psychiatric or medical disorders.
2. Using validated screening tools and procedures, develop a screening and diagnostic plan for the patient with possible GAD.
3. Develop a treatment and monitoring plan, including patient education on the goals, expected outcomes, and risks of treatment, for the patient with GAD.
4. Justify the use of second- and third-line agents in the treatment plan for a patient with GAD.
5. Design an appropriate treatment plan for GAD for patients requiring special considerations including children, the elderly, and patients who are pregnant.

ABBREVIATIONS IN THIS CHAPTER

CBT	Cognitive behavioral therapy
CSTC	Cortico-striato-thalamo-cortical circuitry
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder 7-Item Scale
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Table of other common abbreviations.

INTRODUCTION

Overview of Anxiety Disorders

Anxiety disorders are common among patients in primary care and share a common thread: focusing on future threats. Worry, avoidant behavior or behavioral adaptations, and autonomic and other somatic complaints are also common. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) lists separation anxiety, selective mutism, specific phobia, social anxiety disorder (also called social phobia), panic disorder, agoraphobia, generalized anxiety, substance abuse/medication-induced anxiety, and anxiety disorder caused by another medical condition in its chapter on anxiety disorders (APA 2013). Of note, in prior *DSM* editions, posttraumatic and obsessive-compulsive disorders were included in the chapter on anxiety disorders. The *DSM-5* reclassified these into separate chapters. Box 1-1 lists common disorders in primary care clinics and the characteristics that help differentiate them.

Anxiety disorders are problematic for both patients and providers. Although anxiety disorders are common, with a lifetime prevalence of up to 31%, they are often unrecognized and underdiagnosed (Katzman 2014). Patients may not disclose their symptoms, or they may focus on somatic complaints and not attribute them to anxiety. If the patient does not disclose any underlying anxiety, most clinicians initially focus on the physical problems and somatic complaints. The result is that less than one-third of patients receive therapy for the underlying anxiety disorder (Revicki 2012). Clinicians should be aware that these disorders are common and provide appropriate screening and diagnostic workups. This chapter focuses on generalized anxiety disorder (GAD).

Definitions and Diagnostic Criteria for GAD

The characteristics of GAD as described in the *DSM-5* are shown in Table 1-1. The issues assessed on two common screening instruments (i.e., the Generalized Anxiety Disorder 7-Item scale (GAD-7) and the Penn State Worry Questionnaire) are shown beside these criteria for reference. A score greater than 10 on the GAD-7 suggests a diagnosis of GAD. The score on the Penn State Worry Questionnaire designates an acuity level of worry as low (16–39), moderate (40–59), or high (60–80). These screening tools are readily available and easy to use in the ambulatory setting.

For the main features of GAD, see Table 1-1. Anxiety and worry occur as a normal part of life. What distinguishes pathologic anxiety from normal worry is the severity of anxiety, difficulty in controlling it, and significant social and functional impairment it causes. Anxiety and worry may focus on potential future events, but they are out of proportion to what might really happen. Of interest, although excessive worry is a central feature of GAD, it appears to be a psychological defense mechanism to allow some sense of control over what might happen if the feared event occurs (Behar 2009). Excessive worry can become a learned cycle of thinking that becomes a cognitive pattern, leading to impairment.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Clinical pharmacology of the antidepressants, anxiolytics, benzodiazepines, anticonvulsants, and second-generation antipsychotics discussed in this chapter
- Recognition of signs and symptoms of anxiety
- Basic patient educational points for the medications described in this chapter

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Institute for Health and Care Excellence (NICE). Clinical Guideline: Generalized Anxiety Disorder and Panic Disorder in Adults.
- Canadian Medical Association. Clinical Practice Guidelines for the Management of Anxiety, Posttraumatic Stress, and Obsessive-Compulsive Disorders.
- Harvard Medical School, Department of Psychiatry, South Shore Program. Psychopharmacology Algorithm Project.

Box 1-1. Characteristics of Selected Anxiety Disorders in the *DSM-5*

Generalized Anxiety Disorder

Psychological symptoms: Excessive anxiety, uncontrolled worry, feeling on edge, poor concentration, restlessness, irritability, impaired social or occupational functioning

Physical symptoms: Fatigue, muscle tension, difficulty sleeping

Panic Disorder

Recurrent panic attacks manifested by these symptoms:

Psychological: Fear of losing control or dying, fear of inability to escape from fearful situations

Physical symptoms: Chest pain or discomfort, dizziness, shortness of breath, tachycardia, tremor, nausea, palpitations, sweating

Agoraphobia

Agoraphobia may result from repeated panic attacks

Psychological symptoms: Fear, anxiety, and avoidance in two or more of the following situations: public transportation, open spaces, enclosed places, standing in line or being in a crowd, being away from home alone

Social Anxiety Disorder

Psychological symptoms: Fear of being embarrassed, humiliated, or evaluated by others; fear of situations such as speaking, eating, or interacting in a group of people or with authority figures; public speaking; talking with strangers

Physical symptoms: GI upset – diarrhea; sweating, flushing, tachycardia, tremor

Information from the *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).*

Somatic features of GAD are common, which can be why patients seek medical care. Complaints such as muscle aches and tension, headaches, backaches, GI issues, problems with sleep, and fatigue are common. Anxiety disorders are also associated with several medical illnesses such as thyroid disease and respiratory disease. This association leads to increased disability and decreased quality of life (Saren 2006). One study found that patients with anxiety disorders and depression had higher rates of somatic disease such as asthma, heart disease, back problems, ulcer, migraines, and eyesight problems (Niles 2015). In addition, a 1-SD increase in the severity of the anxiety and depressive symptoms was associated with a 15% increase in the number of medical conditions. To put this in perspective, 1 SD in BMI is associated with a 12% increase in medical conditions (Niles 2015). Thus, anxiety disorders are associated with physical health risks similar to being overweight. Therefore, patients with somatic complaints for which no organic causes can be identified should be assessed for an anxiety disorder.

Table 1-1. *DSM-5* Criteria for GAD and Screening Questions

Characteristics of GAD according to the *DSM-5*	Excessive worry and anxiety occur most of the time for at least 6 mo The worry is difficult to control The anxiety and worry are associated with at least three of the following core symptoms: • Feeling restless, keyed up, or on edge • Fatiguing easily • Difficulty concentrating or the mind going blank • Irritability • Increased muscle tension • Difficulty falling asleep, staying asleep, or restlessness The symptoms cause significant distress or impairment The problems are not attributable to a physical ailment The problems are not explained by other mental disorders
Factors screened for by the GAD-7	Feeling nervous, anxious, or on edge Not being able to stop or control worrying Worrying too much about different things Trouble relaxing Being so restless it is hard to sit still Becoming easily annoyed or irritated Feeling as if something awful might happen
Factors screened for by the Penn State Worry Questionnaire	If I do not have enough time to do everything, I do not worry about it My worries overwhelm me I do not tend to worry about things Many situations make me worry I know I should not worry about things, but I just cannot help it When I am under pressure, I worry a lot I am always worrying about something I find it easy to dismiss worrisome thoughts As soon as I finish one task, I start to worry about everything else I have to do I never worry about anything When there is nothing more I can do about a concern, I do not worry about it anymore I have been a worrier all my life I notice that I have been worrying about things Once I start worrying, I cannot stop I worry all the time

GAD = generalized anxiety disorder.

Information from the American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

IMPACT OF GAD

Functional Impact and Quality of Life

Comorbidity is common among anxiety disorders. A study of primary care patients assessed the impact of several anxiety disorders, with one of them being GAD. The study included 965 patients who completed the GAD-7 questionnaire. Generalized anxiety disorder was present in 7.6% of patients. Of importance, one-third of the patients with one anxiety disorder had at least one other; thus, comorbidity among patients is common. This finding underscores the need for careful and complete assessments of patients thought to have an anxiety disorder to ensure that all issues are identified (Spitzer 2006).

In the same study, 41% of the patients were not receiving treatment. Of those treated, 42% were receiving medications alone, 4% were receiving psychological therapy, and 13% were receiving both. These data show that anxiety disorders are often unrecognized and untreated. In addition, scores on the Medical Outcomes Study Short Form-20 functional status for patients with GAD showed significant impairment on all scales (mental health, social function, role function, general health, bodily pain, physical function). Clearly, anxiety

disorders like GAD significantly affect patient health and reduce quality of life.

Other studies have also documented the impact of GAD. A recent systematic review studied the effect of GAD on humanistic and economic outcomes among patients in the United States and Europe (Revicki 2012). A total of 144 papers met the study inclusion criteria of evaluating patients with GAD and reporting humanistic and economic outcomes. When health-related quality-of-life outcomes were evaluated, psychosocial functioning, role function, work productivity, and disability days were significantly impaired. These findings are similar to those of prior studies. One study found that all SF-36 (36-item short-form health survey) subscales were affected for patients with GAD compared with patients without GAD, indicating significant impairments (Wetherell 2013). Patients with GAD also report more occupational impairment and missed days of work; they tend to use more health care resources and are 1.6 times more likely to see a primary care provider more than four times per year. However, only 19.8% of these patients are receiving pharmacotherapy for the symptoms (Wittchen 2001). This again shows that GAD causes significant impairments but is often untreated.

Impact on Society and Health Care Economics

Generalized anxiety disorder is a significant health care economic burden. The Anxiety and Depression Association of America reports that anxiety disorders annually cost the U.S. health care system more than $42 billion, which is almost one-third of total health care expenditures (Facts and Statistics at www.ADAA.org). About half of these costs are the result of repeated use of health care resources. One review found that the annual median medical cost for patients with GAD was $2375 versus $1448 for those without GAD (Revicki 2012). Two contributors may be higher health care use and the impact of anxiety on morbidity from comorbid medical conditions.

PATHOPHYSIOLOGY AND ETIOLOGY OF GAD

Psychological Theories

Psychological theories form the basis of several therapeutic approaches. Common interventions including cognitive behavioral therapy (CBT), relaxation therapy, stimulus control, cognitive restructuring, and self-monitoring are based on these theories. Medications do not cure anxiety disorders. They suppress activity in the amygdala and other areas of the brain that underlie the disorder (Stahl 2013). If fear and anxiety are conditioned responses in GAD, medications will not alter this neuronal learning. Some form of psychological therapy, and probably in an ongoing manner, will be required to control the anxiety. Thus, the combination of these two modalities is commonly suggested. However, as discussed later in the text, data confirming the superiority of a combination approach over monotherapy are lacking.

Fear and anxiety share many features and can be difficult to differentiate. One helpful way to conceptualize them is to think of fear as a response to an immediate threat, whereas anxiety is usually an anticipatory response to perceived or real future events (APA 2013). Worry is the cognitive response to fear and anxiety. Worry involves negative mental images and emotions. Although some might think of worry as a cause of anxiety, worry appears to be an attempt at self-protection from the more catastrophic consequences of the feared object (Behar 2009). The individual may falsely view worry as an effective coping mechanism. Worry, however, becomes pathologic when it is excessive and is a core feature of GAD.

Acquiring fears is a normal part of development. Fears can develop in a classical conditioning paradigm. Aversive occurrences in life can be viewed as unconditioned stimuli. When paired with a neutral stimulus, these eventually become a conditioned stimulus that can elicit fear (CR). Under normal circumstances, this process is adaptive because it helps the patient avoid potentially harmful things. If other neutral stimuli become feared (conditioned stimulus and CR), the person's fears become more generalized. This paradigm involves circuits in the amygdala, hypothalamus, and prefrontal cortex. Investigators have suggested that patients with anxiety have exaggerated responses to danger cues and a reduced response to safety cues that would mitigate the fear response (Lissek 2005). Serotonin appears to be involved in modulating responsiveness to threatening cues. One study found that citalopram decreased amygdala responses to threat presentations, suggesting this as one way that selective serotonin reuptake inhibitors (SSRIs) affect anxiety (Harmer 2006). Because fear acquisition is a learning process, psychologic approaches such as CBT may also affect fear conditioning.

Neurobiological Theories

The amygdala is the area of the brain where fear conditioning is centered. Sensory input is received from areas of the brain such as the sensory thalamus, sensory cortex, and prefrontal cortex. Connections between the amygdala and areas of the prefrontal cortex regulate the experience of fear and the resulting psychological responses. Motor responses may be controlled by connections with the periaqueductal region of the brain. Together, these form the responses to fear. Again, when this system is not regulated appropriately, a clinical anxiety syndrome may result.

In a similar fashion, worry, a cognitive process, may be regulated by cortico-striato-thalamo-cortical circuitry (CSTC). These circuits involve neurotransmitters and receptors that may be targets for pharmacotherapy. Several neurotransmitter circuits in the amygdala and CSTC are involved in fear, anxiety, and worry (Stahl 2013; Stein 2009; Kim 2005). Y-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the brain. Circuits in both the amygdala and the CSTC involving GABA are thought to be

important in fear, anxiety, and worry. For anxiety, the $GABA_A$ receptor appears most relevant. This receptor complex involves five subunits and a central channel through which chloride ions enter into the cell when an agonist such as GABA binds to it. These subunits have been designated α, β, Y, and δ. Inflow of chloride reduces neuronal electrical activity and thus is inhibitory. Ligands such as benzodiazepines bind and act as allosteric modulators. The $GABA_A$ receptor subtypes where benzodiazepines appear to exert anxiolytic properties have two β subunits plus either Y_2 or Y_3 plus two from the α_1, α_2, or α_3 types. In the presence of GABA, benzodiazepines appear to further enhance inhibition and reduce anxiety and fear responses in the amygdala and worry in the CSTC.

Serotonin is an important neurotransmitter in both the amygdala and the prefrontal cortex. Neuronal projections involving serotonin from the dorsal raphe nucleus to the amygdala and frontal cortex are thought to be involved in anticipatory anxiety and avoidance, which is conditioned fear (Nutt 2001). Overactivity of the serotonin system may be involved in anxiety disorders (Connor 1998). Activation of presynaptic serotonin-1 receptors leads to an initial decrease in serotonin activity, followed by an increase. It is thought that the action of buspirone at these receptors explains its activity. The delayed action of buspirone may suggest that long-term neuronal adaptation is responsible for its therapeutic benefit, rather than the acute increase in serotonin function (Stahl 2013).

Serotonergic drugs are effective for depression, which has several symptoms that overlap with GAD. Patients with both depression and anxiety treated with SSRIs not only had improvements in depressive symptoms but also improvements in anxiety, which led to trials of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) for anxiety disorders, which are indeed effective for GAD. The initial increase in serotonin activity can cause anxiety symptoms, but with time, there is neuronal and receptor adaptation and more normal output from the amygdala and the CSTC (Stahl 2013). The exact mechanism for the initial increase in serotonin activity, which is unclear, may involve more than one neurotransmitter action. Stimulation of postsynaptic serotonin-2 receptors in the limbic system may also lead to avoidance and anxiety (Conner 1998). Blocking these receptors can be beneficial. Quetiapine, which may act as a serotonin-1 partial agonist and serotonin-2 antagonist, is beneficial for anxiety (Sheehan 2013).

Another important receptor type is the voltage-sensitive calcium channel (VSCC). This receptor is similar to the GABA receptor because it is made up of several subunits. These are found in both the amygdala and the prefrontal cortex. Overactivity of this receptor in the amygdala is thought to result in the fear/anxiety response and worry in the CSTC (Stahl 2013). The VSCC that includes the $\alpha_2\delta$ subunit appears to be the target for both pregabalin and gabapentin, both of which reduce anxiety.

CLINICAL PRESENTATION AND DIAGNOSIS OF GAD

Clinical Features

Any time a patient has symptoms of worry and anxiety, especially without a medical cause, an anxiety disorder should be considered. The first diagnostic step is to consider the possible differential diagnoses, including medical conditions. When appropriate, obtaining a CBC, comprehensive metabolic panel, thyroid function, and urinalysis is helpful. Any somatic complaints suggestive of cardiovascular problems should be assessed with an ECG or other tests, as indicated. See Box 1-1 for a comparison of how the different anxiety diagnoses appear. The symptoms presented should be compared with the central features of each disorder. When evaluating symptoms, it is important to recall that many patients have more than one anxiety disorder.

Diagnosis and Screening for GAD

The diagnosis of GAD is confirmed using the criteria outlined in the *DSM-5*. The key features are shown in Table 1-1. Obtaining a careful history of the patient's descriptions and course of symptoms should be the first step. For GAD, one of the simplest ways to understand whether anxiety is a problem is simply to ask the patient, "Do you worry excessively over minor matters?" (Stein 2015). The GAD-7 screening tool can be used in primary care settings. A score of 10 or greater suggests possible GAD, with 5 suggesting mild, 10 moderate, and 15 or above severe anxiety. A shorter version of the GAD-7 (GAD-2) using just the first two items also provides a very brief screening tool that can reduce the time required to diagnose GAD. Both the GAD-7 and the GAD-2 appear to have acceptable validity and reliability (Plummer 2016; Kroenke 2007). Scores on the GAD-7 may also correlate with the degree of disability (Ruiz 2011). The GAD-7, which also appears to be sensitive to change, can be used to monitor the effect of therapy over time (Baldwin 2016). Screening adults with dementia is a challenge. These instruments have not been well validated in this population. An alternative approach would be to use caregiver-assessed symptoms with the anxiety subscale of the Neuropsychiatric Inventory (Cummings 1994, Breitve 2016). It is important to keep in mind that screening tools do not confirm the diagnosis of GAD. That requires meeting the criteria outlined in DSM-5.

Other screening tools may also be helpful in primary care. The Penn State Worry Questionnaire has also been validated for its ability to distinguish GAD from other anxiety disorders (Fresco 2003; Meyer 1990). Factors screened for with this instrument are shown in Table 1-1. Finally, because anxiety commonly co-occurs with depression, the Patient Health Questionnaire-9 item instrument should be used if there is any suggestion of depression (Kroenke 2001). Comorbid depression can prolong the course and increase functional impairment of GAD.

Another common instrument, the Hamilton Anxiety Rating Scale (HAM-A), administered through interview, is a 14-item scale that is often used in clinical trials and is considered the gold standard rating tool for anxiety. Unlike other scales, it is completed by the clinician, not the patient. The HAM-A is appropriate for both clinical and research settings. However, it is time-intensive and requires training to administer.

Risk Factors, Epidemiology, Course, and Prognosis

Several risk factors for GAD have been identified. Temperament factors including tendency toward negative affect, harm avoidance, and behavioral inhibition may increase risk (APA 2013). Female sex, low socioeconomic status, intolerance to uncertainty, and early childhood adversity have also been suggested as risks (Stein 2015). Heritability studies suggest a genetic component, but its contribution appears to be moderate (Stein 2015; APA 2013).

The 12-month prevalence of GAD in adults has been reported to be 2.9% (APA 2013). Data from the National Comorbidity Survey (NCS) suggest a lifetime prevalence of 5.1%, with 3.6% in men and 6.6% in women. The NCS also reported a 12-month prevalence of 3.1%, with 2.0% in men and 4.3% in women. One of the problems in comparing data on prevalence is that definitions of GAD have changed with successive editions of the *DSM*. However, the data are consistent with respect to prevalence. In primary care settings, 7%–8% of patients may have GAD (Stein 2015).

The onset of GAD differs from that of other anxiety disorders because the onset of GAD is usually later, with an average age at onset of 31 years (Weisberg 2009; Wittchen 2001). The diagnosis of GAD in children and adolescents is complicated, and prevalence rates are low in those younger than 25 years. The prevalence of GAD in adults older than 65 is about 4% (Weisberg 2009).

Generalized anxiety disorder is a relapsing disorder with anxiety that waxes and wanes. The Epidemiologic Catchment Area study, which was done quite some time ago using the *DSM-III* criteria, showed that GAD persisted for 5 years or more in 40% of patients (Regier 1990). Predictors of recurrences include low overall life satisfaction, poor spousal or family relationships, personality disorders, and low overall global assessment score (Yonkers 2000). Other poor prognostic factors include comorbidities (both psychological and medical), substance use disorders, and female sex (Yonkers 2000). These findings have implications for the types of treatment chosen. The etiology of GAD has a learned component. Medications may help control neural contributions to anxiety and worry, but they will not erase previously learned responses (Stahl 2013). This implies that other measures like psychologically based interventions are important for learning coping behaviors. In addition, these data suggest that ongoing treatment and adherence to therapeutic interventions are important for recovery.

TREATMENT OF GAD

Identifying Patients Who Need Specific Treatment for GAD

Patients with GAD have symptoms of anxiety ranging from mild to debilitating. Clinicians need to determine who needs treatment. This decision depends on many factors, including symptom intensity and duration, impact on the patient's ability to function in daily life, comorbid conditions such as depression, and medical conditions. Patients with mild anxiety and worry who do not meet the *DSM-5* criteria for GAD often benefit from supportive therapy and encouragement. For those who do meet the criteria, one of the specific interventions described is indicated. Severe symptoms (e.g., a GAD-7 score greater than 15 and causing significant functional impairment) may need more intense initial therapy.

The clinical must ensure that the patient's anxiety is not caused by medical conditions or medications. Box 1-2 lists some of the more common causes of anxiety that can mimic GAD (Melton 2014; House 2002). These should be corrected, if possible. Similarly, the patient's medication regimen should be assessed for its potential to cause anxiety symptoms and addressed, when possible.

Box 1-2. Medical Conditions and Medications That Can Cause Anxiety

Medical Conditions

- Pain (acute and chronic)
- Thyroid disorders
- Pulmonary conditions (hypoxia and hypocapnia with asthma or COPD)
- Diabetes and hypoglycemia
- Epilepsy
- Electrolyte abnormalities
- Neoplasms
- Anemia
- Substance abuse
- Pheochromocytoma
- Cardiovascular diseases
- Poor sleep habits
- Other mental illnesses

Medications

- Anticonvulsants (carbamazepine, ethosuximide)
- Inhaled β-agonists
- Estrogens
- Antibiotics (quinolones, isoniazid)
- Corticosteroids
- Sympathomimetics (e.g., pseudoephedrine, phenylephrine)
- Caffeine
- Nicotine
- Psychostimulants
- Thyroid hormones
- Drugs of abuse (stimulants, marijuana)
- Alternative medications (ginseng, ma huang, ephedra)
- Antihistamine (toxicity)
- Anticholinergics (toxicity)

COPD = chronic obstructive pulmonary disease.

Evidence-Based Treatment

Several evidence-based guidelines are available for GAD; Table 1-2 is based on four of these guidelines and two recent reviews. Of note, authors of the various guidelines have interpreted data from literature reports and have drawn conclusions on the basis of not only efficacy data, but also risks of adverse effects, reported tolerability, drug-drug and drug-disease interactions, and other issues. As a result, these guidelines may differ regarding when a certain drug or drug class might be used. Table 1-2 represents these references and suggests a sequence of steps for treating GAD with an attempt to find commonalities and give readers the spectrum of options at each step.

Step 1: Potential GAD

The clinician should use a patient-centered approach for GAD (NICE 2011). This means the patient is engaged, communicates well with the clinician, makes needs and preferences known, and shares decision-making responsibility. Successful treatment of GAD is a long-term process that often requires several trials of interventions. Treatment adherence is a key goal of therapy. Building a therapeutic alliance between clinician and patient should start with the first encounter.

Patient preferences play an important role in selecting psychological or medication management. Considerations include prior treatments and the patient's experience with them, concerns about adverse effects of medications, attitudes, expectations, patient misconceptions about treatment approaches, and logistical concerns such as where and how treatment will be provided. Treatment availability must also be considered. For psychotherapy, availability of and access to qualified therapists are important. For medications, cost and prescription coverage must be considered. Treating GAD is a long-term process, and it is important to have patient buy-in before selecting a modality.

It is also important to set up a supportive treatment environment. Assuring patients that there are effective treatments that can be tailored to their needs and preferences is important. In fact, providing education, support, and therapeutic monitoring can help with symptoms (Locke 2015). The goal of treatment is symptom resolution. However, complete remission may not always be possible, or it may require a treatment intensity that the patient is unwilling or unable to tolerate. If so, alternative goals must be set. Box 1-3 lists the goals of acute and maintenance therapy and some of the issues to consider.

Box 1-3. Treatment Goals and Considerations

Acute Treatment

Goals

- Reduce severity of symptoms
- Achieve remission
- Improve functional status
- Minimize adverse drug reactions

Considerations

- What is the history of this patient (e.g., chronicity, course and severity of prior episodes, precipitating factors)?
- Are there medical or other conditions that would affect treatment selection?
- Does the patient have a preference for psychological or pharmacotherapy?
- How severe are the symptoms on presentation?
- How functionally impaired is the patient?
- Are factors such as cost or availability of therapy important?

Maintenance Treatment

Goals

- Prevent relapses
- Improve quality of life
- Minimize adverse drug reactions

Considerations

- Are there comorbid conditions that may affect the course of GAD (e.g., depression or other psychiatric diagnoses)?
- Will the patient require combination therapy for long-term improvement?
- How well will the patient adhere to treatment recommendations?
- Avoid long-term benzodiazepine therapy, whenever possible

GAD = generalized anxiety disorder.

Step 2: GAD Has Been Confirmed

The goal of acute therapy for GAD is to reduce the symptoms of anxiety and worry so that the patient can return to normal functioning. The patient's severity, distress, and functional impairment should be considered, which can provide direction in choosing the approach to initial treatment. For instance, patients with severe distress and functional impairment may have more rapid relief of symptoms with pharmacotherapy than with psychotherapy. Many clinicians treat with a short course of a benzodiazepine if impairment is significant, to allow first-line therapy time to become effective. Benzodiazepines should be avoided in patients with a history of a substance use disorder. The overarching goal of initial treatment is to match the level of intervention to the symptoms and the time interval within which relief needs to occur.

Patients with confirmed GAD should be educated about their disorder. The health care provider plays a central role in this, but the patient should also be connected with other sources of information and support. Patients can learn about GAD and treatment options at several online sites. These include the National Alliance on Mental Illness (NAMI; www.nami.org), the Anxiety and Depression Association of America (www.adaa.org), and the National Institute of Mental Health (www.nimn.nih.gov). These sites have reliable, up-to-date information on GAD. In addition, both NAMI and the Anxiety

Table 1-2. Treatment Approach to GAD

Stage	Considerations
Step 1: Potential GAD	• Obtain medical history and physical examination to identify any potential medical concerns or causes • Identify the anxiety/worry complaints • Screen for GAD • Assess for other mental illnesses (e.g., depression), substance abuse, sleep patterns, and insomnia • Apply the *DSM-5* criteria to confirm the diagnosis of GAD • These factors should be reconsidered at each treatment step when patient has an inadequate response
Step 2: GAD has been confirmed	• Determine the severity and level of functional impairment *(for severe symptoms that cause significant impairment, move to step 4 and begin psychotherapy or pharmacotherapy)* • Establish a therapeutic alliance, a supportive care environment, and a "patient-centered" approach • Establish agreed-on goals of therapy • Initiate patient education about evidence-based treatment options • Connect the patient with national educational sites such as National Alliance on Mental Illness, National Institute of Mental Health, Anxiety and Depression Association of America • Counsel on lifestyle changes • Educate family and elicit support • Provide self-help information about relaxation techniques • Initiate active monitoring and follow-up for lifestyle changes and symptoms
Step 3: Initiate self-directed approaches and support	Poor or partial response in step 2 • Begin low-intensity psychotherapeutic interventions such as online CBT, guided self-help, supportive groups • Consider mindfulness-based interventions • Monitor to determine whether symptoms continue
Step 4: Initiate psychotherapy or pharmacotherapy	Poor or partial response in step 3 • Discuss options of psychotherapy and pharmacotherapy with the patient, and make a shared decision • Initiate therapy with one modality and generally not a combination of CBT and medication • Psychotherapy: Provide or refer for clinician-delivered CBT or applied relaxation therapy • Pharmacotherapy: Initiate SSRI. May consider short-term benzodiazepine for severe symptoms or impairment if there is an urgent need to control symptoms and no history of substance abuse. Allow 4–6 wk after achieving therapeutic dose to assess response. Alternatives include an SNRI, buspirone, hydroxyzine, pregabalin, and bupropion • Monitor initially every 2 wk • Continue medication for at least 12 mo after response
Step 5: Modify psychotherapy or pharmacotherapy	Poor or partial response in step 4 • Assess for complications that may reduce response: review diagnosis, complete medication review including adherence, ongoing psychosocial stressors, relationship issues, work problems • If psychotherapy inadequate, consider increasing number of sessions or adding pharmacotherapy • If pharmacotherapy inadequate, consider the following: 1. Poor response: Change to another antidepressant (SSRI or SNRI) 2. Partial response: Can augment first antidepressant with buspirone, hydroxyzine, pregabalin, or short course of BZD; change to another antidepressant; or add CBT, depending on clinical and patient preference • Continue chosen option for at least 12 mo if the patient has a good response to the chosen option

Table 1-2. Treatment Approach to GAD (*continued*)

Stage	Considerations
Step 6: Modify psychotherapy or pharmacotherapy	Poor or partial response in step 5 • Consider specialist referral • Reassess diagnosis, psychiatric comorbidities, and other explanations for treatment failure • Add psychotherapy to pharmacotherapy, if not already done • Pharmacotherapeutic options 1. Poor response: Try an SNRI if not already used. Try alternative antidepressants (mirtazapine, bupropion, vortioxetine, imipramine). Try other agents such as buspirone, hydroxyzine, pregabalin, or BZD 2. Partial response: Try any of the augmenting agents listed earlier
Step 7: Modify pharmacotherapy	Poor or partial response in step 6 • Poor response: Change to another combination of antidepressant and augmenting agent not used earlier • Partial response: Try augmenting with another agent listed previously not already used or an SGA (quetiapine, risperidone) or valproate
Step 8: Continue to modify pharmacotherapy	Poor or partial response in step 7 • Reassess diagnosis, comorbidities, and adherence • Consider less-preferred medications with some data to support use 1. Aripiprazole 2. Ziprasidone 3. Olanzapine 4. Gabapentin

BZD = benzodiazepine; CBT = cognitive behavioral therapy; SGA = second-generation antipsychotic; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Information from: Abejuela H, Osser D. The psychopharmacology algorithm project at the Harvard South Shore Program: an algorithm for generalized anxiety disorder. Harv Rev Psychiatry 2016;24:243-56; Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults. In: UpToDate, Stein M, ed. Waltham, MA: UpToDate. Accessed August 18, 2016; Craske M, Bystritsky A. 2016b. Approach to treating generalized anxiety disorder in adults. In: UpToDate, Stein M, ed. Waltham, MA: UpToDate. Accessed August 18, 2016; Baldwin D, Anderson I, Nutt D, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014;28:403-39; Katzman M, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;14(suppl 1):S1-S83; and National Institute for Health and Care Excellence (NICE). Generalised Anxiety Disorder and Panic Disorder (With or Without Agoraphobia) in Adults: Management in Primary, Secondary and Community Care. NICE Clinical Guideline 113. 2011. Available at www.nice.org.uk/CG113.

and Depression Association of America can help patients find a local support group and therapists in their community. Family education is also an important component because family understanding and support is important.

Lifestyle changes are an important aspect of addressing anxiety and worry. Clinicians can direct patients to self-help programs that teach relaxation strategies and/or mindfulness-based meditation approaches that can help relieve anxiety (Marchand 2013; NICE 2011). Active clinician monitoring can lead to improvements because it gives patients a sense of support. Other lifestyle interventions include diet, exercise, and avoidance of caffeine or other nonprescription drugs that can cause anxiety. These low-level interventions are appropriate for all patients with GAD.

Step 3: Initiate Self-Directed Approaches and Support

Patients who do not respond adequately to step 3 interventions may benefit from more directed therapy. Guided self-help, recommended in the National Institute for Health and Care Excellence (2011) guidelines, was developed in the UK. Guided self-help is based on the principles of CBT and is usually given over only a few sessions, often by non-psychiatrist/psychologist practitioners. The National Health Service for the UK (NHS) has a well-developed system for this that is unmatched in the United States. Still, some mid-level counselors in the United States can provide counseling according to these principles and be of help. Another, similar option is online-delivered CBT. Initial results for this approach are

Patient Care Scenario

A 46-year-old woman is in the clinic for a follow-up for GAD. She received this diagnosis 12 weeks ago, at which time she was given sertraline 25 mg daily. Her baseline GAD-7 score was 13. She was educated about GAD, and an online CBT program was recommended. The dose was gradually titrated to her current dose of 150 mg/day, which she has continued for 8 weeks and tolerated well. Her GAD-7 score today in the clinic is 7, and she states that her level of anxiety is still interfering with her quality of life. She has difficulty going to sleep at night, but once asleep, she is able to maintain it. She has tried the online CBT program suggested, but she has had problems keeping up with it. Her other medical conditions include poorly controlled hypertension, migraine headaches, and a history of alcohol abuse (abstinent for 2 years). What changes should be made to her treatment plan?

ANSWER

This patient has had a partial response. Her GAD-7 score at the start of therapy was in the moderate range of severity. Her current score is in the low-moderate range, a 46% improvement. Her statement that her anxiety is still interfering with her life indicates that her therapy should be changed. Several options would be appropriate.

- **Even though she has improved somewhat, the medication could be changed. The first-line option is using another SSRI or initiating an SNRI. The patient has no factors that would make one SSRI preferred to another. The SNRIs duloxetine and venlafaxine would be options. Venlafaxine could be problematic because of the patient's poorly controlled hypertension. Duloxetine is an option, but if her alcohol abuse has caused any liver problems, this drug could be problematic. She could be initiated on buspirone. However, it would take time to become effective, and many clinicians would consider an SSRI before buspirone.**
- **Hydroxyzine at bedtime would also be an option. It is a sedating drug that has an anxiety-relieving effect.**
- **Benzodiazepines would be a risk because of her history of alcohol abuse. Most clinicians would avoid them for this patient. Although still associated with some risk of abuse, pregabalin could be considered.**
- **With her history of migraine headaches, either changing to or adding a tricyclic antidepressant (TCA) could be justified. Imipramine could improve her anxiety symptoms, and if she has migraines, it might reduce their frequency. However, imipramine is difficult for many patients to tolerate because of its adverse effects.**
- **Another option would be to institute CBT with a therapist rather than asking her to continue the online version. The combination of pharmacotherapy augmented by the CBT might be effective.**
- **It would be too early to consider second-generation antipsychotics (SGAs) or valproate until other drugs with more evidence for efficacy have been tried.**

Again, different clinicians might make different choices, but it seems likely that another SSRI, or possibly buspirone or hydroxyzine, could be added as augmenting agents. If sertraline is changed to another medication, it will have to be tapered before discontinuation.

promising enough that clinicians can recommend it at this level (Andrews 2010). Several programs can be found on an Internet search, and many are free to the patient. A good resource for this type of approach can be found at the NHS website, which has an approved computerized CBT program (www.nhs.uk/conditions/online-mental-health-services/pages/introduction.aspx).

Other approaches often used at this level are the mindfulness-based practices. Mindfulness is being focused on the here and now and the present state in a nonjudgmental way. It can be used with meditation, stress reduction, and CBT. Mindfulness is effective and can be recommended as an adjunctive intervention (Hoge 2013; Marchand 2013). Qualified therapists can provide training for the patient.

Step 4: Initiate Psychotherapy or Pharmacotherapy

At this point, the patient and clinician need to decide on psychological interventions or pharmacotherapy. Cognitive behavioral therapy and pharmacotherapy are similarly effective for GAD (Baldwin 2014; Katzman 2014; NICE 2011). Although several studies have looked at whether initiating therapy with a combination of psychotherapy and pharmacotherapy is a better approach than using just one modality, there is little evidence to support the combination initially (Crits-Christoph 2011; Foa 2002). None of the evidence-based guidelines referenced suggest using a combination approach to start.

Patient perceptions about the two approaches to treatment are important and can inform choices. One study looked at how patients perceived either psychotherapy (CBT) or pharmacotherapy. Patients felt that both modalities were effective and acceptable. However, they felt that CBT was more acceptable than pharmacotherapy and more likely to be effective in the long run. They were more likely to choose CBT than medication, even though many had current or recent medication use. However, patients who were using medications had a more favorable view of them than those who were not. The authors speculate that concerns about adverse drug effects are lessened by experience with them (Deacon 2005). Thus, many factors can influence the type of therapy a patient prefers.

Psychological Therapy

Several psychotherapeutic approaches have been used for GAD, including CBT, psychodynamic psychotherapy, and

applied relaxation. Of these, CBT has the most evidence-based support and is the most common modality used today (Hoyer 2009). Cognitive behavioral therapy is based on social and cognitive psychology. It emphasizes the role of thoughts on the patient's mood and actions. A structured approach, CBT focuses on problems and the thought process that affects them, identifies distorted thoughts and maladaptive behaviors, and then develops ways to change them, including problem solving and homework. A more thorough discussion is available on the National Association of Cognitive-Behavioral Therapists website.

Cognitive behavioral therapy requires fewer sessions than other traditional forms of psychotherapy. High-intensity CBT recommended at this treatment level should be provided by a trained clinician such as a mid-level licensed therapist or a psychologist. Availability of therapists in the community and coverage of services for patients with and without insurance must be addressed. In some instances, especially for patients in rural areas, these barriers can limit psychotherapy as a treatment option. Local mental health facilities can serve as referral resources.

Pharmacotherapy

For the steps for pharmacotherapy, see Table 1-2; the medications used are listed in Table 1-3. Serotonergic antidepressants (SSRIs and SNRIs) and buspirone can be considered as first-line options. Although there are few head-to-head comparisons of SSRIs and SNRIs, most data derived from meta-analyses suggest that their efficacy is about equivalent (Bystritsky 2016; Craske 2016b; Baldwin 2011b). For SSRIs and SNRIs, about 60%–75% of patients will respond compared with the 40%–60% response rate for placebo. Choice of medication is not as much influenced by differences in effectiveness as by other considerations like the patient's previous experiences, the agent's potential adverse effects, the patient's other comorbidities, and drug-drug or drug-disease interactions. Cost can also be a factor. Buspirone is also effective for GAD, but its onset of action is delayed for up to 4 weeks. Buspirone may not be as robust for anxiety, and antidepressants are often preferred (Bystritsky 2016). Buspirone is usually used when the patient has a history of substance abuse because it lacks abuse potential. Buspirone may also be used as an adjunctive medication when the patient has had a partial response to an antidepressant. It is not effective for depression if that is one of the patient's comorbidities.

Antidepressants take on average 4 weeks to become effective. The dose can be titrated every 2 weeks until a therapeutic dose is achieved or until the highest dose the patient can tolerate is achieved. This dose should be continued for another 4–6 weeks to assess its effect. Data suggest that a partial response at 2 weeks predicts the drug's future efficacy (Baldwin 2011a).

For the most commonly used SSRIs and SNRIs, see Table 1-3. Although some are FDA approved for GAD, clinicians often use others that are not, and there appears to be a therapeutic class effect. Some medications such as the TCAs were FDA approved for "anxiety" before the GAD diagnosis was developed in the *DSM*, so the term *generalized anxiety disorder* may not appear in the labeling. Maintenance doses used for GAD are the same as for depression. The dose can be reassessed and adjusted every 1–2 weeks until a therapeutic dose is achieved. An important consideration when using these medications is that patients often have activating adverse effects like agitation, restlessness, and insomnia. These generally become less problematic as treatment continues. The risk can be reduced using initial doses lower than those used for depression. Patients should be educated about the possibility that their anxiety becomes worse during initial therapy. A short-term, small dose of benzodiazepine (if the patient has no history of substance abuse) or hydroxyzine can help patients through this period (Craske 2016b) if their symptoms are severe enough to warrant it. If a benzodiazepine is added, it is usually prescribed for 2–4 weeks and then discontinued. Treatment for this period does not require tapering when discontinuing the drug.

The SSRIs are generally well tolerated. The most common adverse effects include GI complaints (nausea, cramping, diarrhea), insomnia, restlessness, headache, and sexual dysfunction. All the SSRIs can be associated with a discontinuation syndrome if abruptly discontinued; however, fluoxetine has a long half-life and is less likely to cause this problem. Symptoms of discontinuation syndrome include dizziness, anxiety, irritability, paresthesia, nausea, and vomiting. More serious adverse effects include hyponatremia, bleeding (especially in older adults or those taking NSAIDs, antiplatelets, or anticoagulants), serotonin syndrome, and possible decreased bone mineralization with long-term treatment. The SNRIs cause adverse effects similar to SSRIs. Venlafaxine can cause increased blood pressure, especially at the higher end of the dose range, where noradrenergic actions are more prominent. Patients taking 150 mg/day or more should consider monitoring their blood pressure, and this medication should be avoided in patients with uncontrolled hypertension. Finally, all antidepressants carry a boxed warning for increased risk of suicidal thoughts and behaviors, particularly early in therapy or when the dose is changed in children, adolescents, and young adults up to age 24. The FDA has mandated that all patients receiving these medications receive medication guides when the prescription is dispensed.

Benzodiazepines are not considered first-line agents for GAD because of concerns for adverse effects, dependence, tolerance, and abuse potential. Patients should be made aware of these concerns associated with long-term treatment. However, they do play a role in initial therapy if the symptoms are severe or the patient is significantly impaired, provided the patient has no history of substance abuse. These drugs will relieve anxiety within minutes to hours. This effect may lead some patients to prefer them to the antidepressants; however, they are not appropriate for long-term therapy in most instances. The lowest effective dose should

Table 1-3. Medications for GAD

Agent	Dosing[a]	FDA Approval Status[b]
SSRIs		
Citalopram	Start 10 mg PO once daily in the morning. Max 40 mg/day Elderly: Max 20 mg/day	Off-label use
Escitalopram	Start 10 mg PO once daily. Max 20 mg/day Elderly: Consider starting 5 mg/day. Max 10 mg/day	GAD
Fluoxetine	Start 10–20 mg PO once daily. Max 60 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	Off-label use
Paroxetine	Start 20 mg PO once daily. Max 60 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	GAD
Sertraline	Start 25–50 mg PO once daily. Max 200 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	Off-label use
SNRIs		
Duloxetine	Start 30–60 mg PO daily. Max 120 mg/day Elderly: Start 30 mg/day. Max 120 mg/day	GAD
Venlafaxine XR	Start 37.5–75 mg PO daily. Max 225 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	GAD
TCAs		
Imipramine	Start 50–75 mg PO per day in divided doses or one daily dose at bedtime. Max 200 mg/day Elderly: Start 30 mg to 40 mg/day. Max 100 mg/day	Off-label use
Azapirone		
Buspirone	Start 7.5 mg PO twice daily. Max 60 mg/day Elderly: Same	Anxiety Disorders
BZDs		
Alprazolam	Start 0.25–0.5 mg PO three times daily. Max 4 mg/day Elderly: Start 0.25 mg 2-3 times per day.	Anxiety Disorders
Chlordiazepoxide	Start 5–25 mg PO three or four times daily Elderly: Start 5 mg 2-4 times per day.	Anxiety Disorders
Clonazepam	Start 0.25 mg PO twice daily. Max 4 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	Off-label use
Clorazepate	Start 7.5–15 mg PO divided or once daily at bedtime. Max 60 mg/day Elderly: Start 7.5-15 mg/day and titrate as tolerated	Anxiety Disorders
Diazepam	Start 2–10 mg PO two to four times daily. Max 40 mg/day Elderly: Start 1-2 mg once or twice daily and titrate as tolerated	Anxiety Disorders
Lorazepam	Start 0.5–1 mg PO two or three times daily. Max dose 10 mg/day Elderly: Start 1-2 mg/day in divided doses and titrate as tolerated	Anxiety Disorders
Oxazepam	Start 10 mg PO three or four times daily. Max 120 mg/day Elderly: Start 10 mg three times daily and titrate as tolerated to 15 mg 3-4 times daily.	Anxiety Disorders

Table 1-3. Medications for GAD (*continued*)

Agent	Dosing[a]	FDA Approval Status[b]
Misc Agents		
Hydroxyzine	50 – 100 mg four times daily Elderly: Consider 50% reduction in dose and titrate carefully	Anxiety Disorders
Quetiapine XR	Start 50 mg PO at bedtime. Max 300 mg/day Elderly: Start 50 mg/day and titrate by increments of 50 mg/day as tolerated	Off-label use
Pregabalin	Start 25–50 mg PO two or three times daily. Max 300 mg/day Elderly: adjust dose based on renal function. Refer to package label.	Off-label use
Mirtazapine	Start 15 mg PO once daily. Max 60 mg/day Elderly: Consider 50% reduction in dose and titrate carefully	Off-label use

[a]Dosing for FDA-approved drugs is based on the package label. Dosing for off-label use is based on Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults. In: UpToDate, Stein M, ed. Waltham, MA: UpToDate, accessed August 18, 2016, and Melton S, Kirkwood C. Anxiety disorders: generalized anxiety, panic, and social anxiety disorders. In: DiPiro J, Talbert R, Yee G, et al., eds. Pharmacotherapy: a Pathophysiologic Approach, 10th ed. New York: McGraw Hill, 2017:1079-98. Dosing for elderly: if guidelines appear in the package label they are used. If not, a 50% reduction in the usual dose is suggested.

[b]FDA-approved indication. Note that some drugs were approved for "anxiety disorders" before the term *GAD* had appeared in the *DSM*. Drugs not FDA-approved for anxiety disorders are listed as "off-label use."

BZD = benzodiazepine; PO = oral(ly); SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

be used for 2–4 weeks until the antidepressant becomes effective; the benzodiazepine should then be discontinued. Recommendations vary for how to taper benzodiazepines that have been prescribed chronically; however, a 25% reduction in the daily dose every 2 weeks until the lowest dose is reached followed by discontinuation is reasonable (Melton 2016). If the patient has had prior problems with discontinuation, the rate can be slowed and tapered over 6 months.

Monitoring

Patients should be seen every 1–2 weeks when treatment is started or if treatment is changed. The medication dose can be adjusted as needed and tolerated until the therapeutic range is reached. The patient should then be reassessed in 4–6 weeks for response. The term *response* usually means that symptoms have been reduced by some amount, typically 50%, whereas *remission* means that symptoms have resolved or the patient's current score on a rating scale would not be in the diagnostic range (Katzman 2014). Interventions for partial response are described in the text that follows. Patients should also be assessed for treatment adherence and potential adverse effects of therapy. Once anxiety symptoms are stable, the monitoring frequency can be reduced.

Step 5: Modify Psychotherapy or Pharmacotherapy

Therapy should be modified for patients with poor or partial responses to therapy or for those who did not tolerate the initial approach. Those with a poor response to CBT should be reevaluated for adherence to and active engagement with therapy. The number of sessions or therapeutic options can be changed. Combining a medication with CBT may also be considered at this time. Clinician and patient preferences will drive this decision.

Patients should be assessed for treatment adherence. If patients are not taking the medication, the reasons for this should be explored and the barriers addressed. If they are taking the medication, and it has been given in a therapeutic dose for an adequate time, a change in therapy should be made. The type of change will depend on the level of response. For no or poor response, an alternative SSRI or SNRI can be tried. A TCA may also be considered at this point; however, drugs like imipramine are poorly tolerated because of their sedative and anticholinergic adverse effects. Except for fluoxetine, the first antidepressant should be tapered to avoid discontinuation syndrome. The first antidepressant can be tapered before initiating the new one. Some clinicians will use a cross-taper in which the dose of the first agent is reduced while an initial dose of the second drug is added. The cross-taper can generally be accomplished over 2–4 weeks. Another alternative is to discontinue the original drug if the new agent is initiated at an equivalent dose. The possibility of serotonin syndrome should be considered whenever a combination of serotonergic drugs is used. Symptoms of serotonin syndrome include tachycardia, sweating, muscle twitching or rigidity, agitation, restlessness, diarrhea, headache, and dilated pupils. Patients

should be evaluated immediately if these signs and symptoms appear.

The approaches to partial responses vary among clinicians. It is reasonable to consider changing the medication. This strategy has advantages with respect to adherence and cost and avoids polypharmacy. An augmentation strategy could also be considered. Augmenting agents at this stage include buspirone, hydroxyzine, and pregabalin. Hydroxyzine is a sedating antihistamine with serotonin-2 antagonist properties with reasonably good data supporting its use in GAD (Abejuela 2016). Pregabalin has efficacy for GAD both as monotherapy and as adjunctive to antidepressants (Baldwin 2013). Pregabalin is a controlled substance in the United States, and although its dependence and abuse liability appear to be low, these risks should be considered before prescribing. The response to the combination should be reevaluated once the augmenting agent has been taken for 4–6 weeks. Finally, it is appropriate to consider adding psychotherapy to the medication regimen.

If the patient has a good response with CBT, the patient may simply complete a predetermined series of sessions (e.g., up to 12–20 weeks) and then be followed for relapse. Some clinicians will suggest monthly booster sessions to maintain the response, although this has not been well studied (Craske 2016a). For patients achieving remission with medications, the dose should generally be continued at the same dose as required for effect. Treatment should be continued for at least 12 months after treatment response. For patients with a significant history of relapses, long-term therapy may be necessary.

Step 6: Modify Psychotherapy or Pharmacotherapy

By this point, most patients should be treated with a combination of psychotherapy and pharmacotherapy. The number of CBT sessions and the methods used can be modified as needed. Pharmacotherapy should also be altered, and the change again will depend on the level of response. If the patient has had no or a poor response, another SSRI or SNRI not already used should be tried. Other antidepressants that have some empiric support could also be options. These include mirtazapine, bupropion, vortioxetine, and imipramine (Abejuela 2016; Craske 2016b; Bidsan 2012; Rothschild 2012; Huh 2011; Bystritsky 2008a). Pregabalin could also be considered as monotherapy. For a partial response, the augmenting agents listed in previous steps can be tried (i.e., buspirone, hydroxyzine, pregabalin, benzodiazepines). Treatment should continue for at least 12 months after response.

Step 7: Modify Pharmacotherapy

There is less evidence here to guide changes in medications. Medications can be changed to ones that have not been tried, or additional augmenting strategies can be used. The SGAs, particularly quetiapine, can be used, according to clinical trial data (Abejuela 2016; Sheehan 2013). Risperidone and aripiprazole have also been used with some success (Abejuela 2016; Huh 2011). These are generally used as augmenting agents, but quetiapine monotherapy has been used. Second-generation antipsychotics must be used with caution because of their metabolic effects (e.g., weight gain, hyperglycemia, diabetes, lipid abnormalities), sedation, cardiovascular effects (i.e., QTc prolongation, orthostatic hypotension) and extrapyramidal adverse effects. Patients receiving these drugs should have weight, comprehensive metabolic panel, and lipid panel routinely monitored. Valproate is another option (Abejuela 2016), though it is less well studied and has some significant adverse effects such as weight gain, hepatic dysfunction, and thrombocytopenia. Among these options, quetiapine has become one of the more popular.

Step 8: Continue to Modify Pharmacotherapy

Data to drive decisions are sparse at this point. Other SGAs like aripiprazole, ziprasidone, and olanzapine have limited data to suggest their use as adjunctive agents (Lorenz 2010). Gabapentin has also been suggested as an option, though it has little empiric evidence for efficacy (Abejuela 2016). Clinicians may have to use combinations of agents that have not already been tried.

SPECIAL POPULATIONS

Treating GAD During Pregnancy

The prevalence of GAD during any phase of pregnancy is 9.5% (Buist 2011). Treatment during this period presents challenges because of the lack of data from clinical trials. Several reviews have provided recommendations (Stewart 2016a; Stewart 2016b; Tran 2015; Ornoy 2014; Cohen 2010; Yonkers 2009). Benzodiazepines are category D drugs during pregnancy and should be avoided. They have been associated with cleft palate and lip. When used in the third trimester up to delivery, they can oversedate the neonate and cause "floppy baby syndrome," which includes low muscle tone, hypothermia, and low Apgar scores. The neonate may also have withdrawal. The SSRIs do not appear to be major teratogens. However, paroxetine has been associated with cardiovascular malformations, and although a causal relationship has not been established, it is a category D drug, whereas all the others are category C. Use of SSRIs during pregnancy has been associated with premature birth, low birth weight, tachypnea, hypoglycemia, temperature instability, irritability, seizures, and persistent pulmonary hypertension. Fluoxetine or citalopram might be preferred when treating depression, which may also apply to GAD (Cohen 2010). The SNRIs do not appear to be major teratogens. However, both duloxetine and venlafaxine are associated with an increased risk of postpartum hemorrhage. Venlafaxine may be associated with a higher risk of eclampsia because it can increase blood pressure. Bupropion poses little risk of major malformations. It

may increase the risk of spontaneous abortions. Buspirone is category B drug and appears to pose little risk. If there are concerns about medication use, psychotherapy may be suggested as first-line treatment.

Antipsychotics, particularly the SGAs, are commonly used off-label for anxiety disorders. A recent review of the Medicaid Analytic Extract database of exposures of SGAs during pregnancy concluded that these drugs do not "meaningfully" increase the risk of major malformations (Huybrechts 2016). The relative risk of individual agents such as aripiprazole, olanzapine, quetiapine, and ziprasidone was not significantly increased. However, the relative risk of risperidone was 1.26 (95% CI, 1.02–1.28). The authors concluded that the risk associated with the SGAs reviewed is low and that further assessment of risperidone is warranted.

Treating GAD in Children and Adolescents

The prevalence of GAD is difficult to reliably determine in children and adolescents. In early editions of the *DSM*, children with anxiety were most often given a diagnosis of overanxious disorder. Beginning with the *DSM-IV*, young people could be given a diagnosis of GAD. It is difficult to compare estimates based on older studies with newer ones. The prevalence of anxiety disorders among children and adolescents is 9%–32% (Creswell 2014).

Both CBT and medication management have evidence to support their efficacy (Creswell 2014). Online CBT-type programs are available and may appeal to this group. Patients and their family members should be given self-help information and education.

The SSRIs are generally considered the agents of choice (Creswell 2014). Benzodiazepines have not been adequately studied, and their adverse effect profiles and dependence and abuse liability suggest that they should not be used. Few data support other medications in this group. Those not responding to first-line approaches should be referred to a child and adolescent psychiatrist.

The American Academy of Child and Adolescent Psychiatry published a set of guidelines for anxiety disorders, and although they are now dated, they contain helpful recommendations (Connolly 2007). These guidelines suggest a multimodal approach that includes the child and parents and collaboration with school personnel, the primary care physician, and therapists who can deliver the appropriate psychotherapeutic approach. In addition, pharmacotherapy is recommended, when appropriate. The SSRIs are recommended as first-line agents. None of the SSRIs is approved for GAD in children or adolescents, so dosing guidelines are not readily available. If used, initial doses should be low and titrated slowly. In addition, because these drugs are known to increase suicidal thinking and behavior in this age group, patients and parents should be counseled to monitor for this. Fluoxetine, sertraline, and paroxetine have data supporting their efficacy for broad types of anxiety in this group (McVoy 2009). Because paroxetine was the first SSRI found to increase suicidality, many clinicians avoid it in this patient group. Sertraline may be a reasonable first-line agent (Creswell 2014).

Treatment of GAD in Older Adults

Generalized anxiety disorder is common among older adults. In one study, the lifetime prevalence in people 65 and older was 11%, with 24.6% having the first episode after age 50 (Zhang 2015). Approaches to treatment in this group are the same as in younger adults. Psychotherapy – primarily CBT – is effective (Goncalves 2012). Pharmacotherapy with psychotropics in older adults poses significant risks. In general, doses in this age group should be half of usual. SSRIs are considered first-line agents, particularly sertraline and escitalopram (Abejuela 2016). However, there are risks that need to be considered. Older adults may be at increased risk of bleeding (particularly if also taking an NSAID), hyponatremia, and decreased bone mass. The SNRIs may also be effective, but the increase in blood pressure with venlafaxine could be problematic. Benzodiazepines increase the risk of falls, are sedating, and can cause memory impairment. They should generally be avoided in older adults, if possible. When one is required, lorazepam or oxazepam may be preferred because of a lower reliance on hepatic metabolism. Buspirone may be effective and is generally well tolerated in older adults. It may be a reasonable alternative if the SSRIs are not effective or are not tolerated. Second-generation antipsychotics like quetiapine should be used carefully, if at all, because of the metabolic adverse effects, prolongation of the QTc, α-adrenergic blocking that increases the risk of falls, and increased mortality if used in patients with dementia.

Treatment of GAD in Those with a History of Substance Abuse

Substance abuse complicates the treatment of GAD. Substance abuse disorders are common comorbidities, with up to 15% of patients with GAD also having these disorders (Abejuela 2016). People may self-medicate for anxiety with alcohol and other drugs. Doing this increases the risk of developing a substance use disorder (Robinson 2011). Therefore, when assessing patients with symptoms of anxiety, other substances should also be explored. Any substance use disorder identified should be addressed in therapy.

The SSRIs are first-line agents for GAD and those with a history of substance abuse. The SNRIs could be used, but duloxetine should be avoided if the patient has liver disease caused by alcohol. Buspirone is a good alternative to antidepressants in this group. Benzodiazepines pose a risk of abuse and dependence and should be avoided. Similarly, pregabalin has some risk of abuse and dependence, but the risk may be lower than for benzodiazepines. Overall, the SSRIs are the best options in this setting.

MONITORING AND EDUCATION

Frequency and Effectiveness

Patients should be seen every 2–4 weeks during the initial stages of treatment and later, every 3 months (NICE 2011). Therapy effectiveness can be assessed by patient self-report or a scale such as the GAD-7. It may take weeks for GAD to improve. Patients should be encouraged to continue with treatment, despite slow progress. In this respect, treatment adherence should be discussed and monitored.

Patient Education

Patient education is central to an effective treatment plan. Clinicians should reinforce self-directed approaches such as education from reliable sources, relaxation techniques, stress reduction, and exercise as ways to reduce tension and stress. Rapport and good communication should also be developed and continued to develop a therapeutic alliance. Effective strategies for GAD rely on patient engagement with whatever therapeutic modality is used. However, no medication magic bullet will heal GAD. Patients must be actively engaged with the process.

CONCLUSION

Generalized anxiety disorder is common, causing significant morbidity and complicating the treatment of other medical and psychiatric conditions. In addition, GAD causes personal, social, and functional impairments that reduce quality of life. It is a chronic, relapsing-remitting disorder; thus, patients and providers must be committed to effectively managing it.

Treatment of GAD is not as simple as taking a medication because the underlying etiology is complex and involves both neurophysiologic abnormalities and learned responses. Pharmacists play an important role in helping these patients. Medication regimens and OTC products and other substances can contribute to anxiety, and adherence to treatment can be a challenge, but it is essential. Many patients will also need to have several medication trials to find the optimal regimen. Pharmacists are uniquely positioned to help in all of these areas.

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Self-Assessment Questions

Questions 1–8 pertain to the following case.

K.K. is a 48-year-old man who returns to the clinic with complaints of back pain, muscle tightness, and occasional intestinal cramping. The symptoms first developed 6 months ago. K.K. began to have problems at work because of poor job performance caused by a constant struggle to perform up to expectations. A series of examinations and laboratory tests have failed to show physical causes for his complaints. Today, K.K. states that he feels tense and irritable most of the time. These symptoms are life-long but have worsened over the past year, and he's tense all the time now. He has problems getting to sleep, which he attributes to rethinking and going over and over work situations. He denies feeling depressed. K.K.'s medical history includes hypertension treated with hydrochlorothiazide 12.5 mg daily and lisinopril 10 mg daily. His chronic allergic rhinitis is treated with pseudoephedrine 240 mg and loratadine 10 mg daily. He has been given a diagnosis of hyperthyroidism in the past but currently takes no medications. Carisoprodol 350 mg three times daily was prescribed 6 months ago for his back pain. K.K.'s social history includes no nicotine use, but he smokes marijuana occasionally to "de-stress." He drinks 1 or 2 cups of coffee each day. He reports drinking 2 glasses of wine each evening. A review of systems shows worsening allergies and recent use of pseudoephedrine and intranasal fluticasone. No other complaints are noted. K.K.'s vital signs include blood pressure 156/101 mm Hg, temperature 98.6°F (37°C), and respiratory rate 28 breaths/minute. His last comprehensive metabolic panel showed Na 140 mEq/L, K 3.8 mEq/L, Cl 100 mEq/L, glucose 100 mg/dL, BUN 18 mg/dL, and SCr 1.0 mg/dL; liver function tests and CBC are normal. K.K.'s GAD-7 score is 16.

1. Which one of the following tests would best rule out medical causes of K.K.'s anxiety symptoms?

   A. Serum ferritin
   B. Thyroid-stimulating hormone
   C. A1C
   D. Sleep study

2. Which one of the following symptoms is K.K. most likely to have because of his generalized anxiety disorder (GAD)?

   A. Fear of social situations and embarrassment
   B. Discrete periods of intense anxiety and fear
   C. Complaints of muscle tension or back pain
   D. Unwillingness to leave the safety of home

3. Which one of the following drugs is most likely contributing to K.K.'s symptoms of anxiety?

   A. Carisoprodol
   B. Hydrochlorothiazide
   C. Pseudoephedrine
   D. Loratadine

4. Which one of the following is the best interpretation of K.K.'s GAD-7 score?

   A. Confirmation of GAD
   B. Indication of severe anxiety symptoms
   C. Indication for receiving a benzodiazepine
   D. Indication of unlikely response to cognitive behavioral therapy (CBT)

5. Which one of the following would be the most appropriate nonpharmacologic intervention for K.K. today?

   A. Guided self-help online programs
   B. CBT
   C. Self-help relaxation training
   D. Biofeedback

6. If K.K. prefers pharmacotherapy, which one of the following regimens is best to recommend?

   A. Lorazepam
   B. Sertraline
   C. Lorazepam plus sertraline
   D. Sertraline plus buspirone

7. K.K. is initiated on an antidepressant. Which one of the following educational points is best to provide to K.K.?

   A. Failure to see a 5-point reduction in the GAD-7 score at 2 weeks indicates he is unlikely to respond to the medication.
   B. It will take about 4–6 weeks to see the full impact of the current dose on anxiety symptoms.
   C. His level of symptoms will require a medication starting dose higher than normally recommended.
   D. Once this medication is started, he will not need to participate in CBT.

8. K.K. would like to know why an antidepressant would be beneficial in the absence of depression. Which one of the following is the best explanation to provide K.K.?

   A. His anxiety is the result of subclinical depression, and the antidepressant medication will improve it and then the anxiety.
   B. Anxiety and depressive disorders appear to involve alterations in neural systems in which serotonin is involved, and the antidepressant will act there to improve his anxiety.
   C. One of the adverse effects of the antidepressant is sedation, which will help calm his anxiety.
   D. The antidepressant acts at receptors for GABA, producing a calming effect.

Questions 9 and 10 pertain to the following case.

F.H. is a 72-year-old woman who was recently admitted to a long-term care facility (LTCF) after the death of her spouse, her primary caregiver. F.H. was given a diagnosis of Alzheimer disease 1 year ago and was prescribed donepezil 10 mg daily. On entering the LTCF, she was irritable, restless, and nervous. Family members also say she appears more nervous than in the past. When questioned, F.H. expressed significant worry and fear about the future without her husband to take care of her. She has difficulty initiating and maintaining sleep and appears restless and tense during the day because she is so worried. Family members state that her symptoms have been present for most of the past year. Her other medical history includes hypertension that is poorly controlled on hydrochlorothiazide, chronic obstructive pulmonary disease treated with a fluticasone/salmeterol inhaler, gastroesophageal reflux disease treated with omeprazole, and tension-type headaches treated with acetaminophen. All of F.H.'s laboratory test results are normal on admission. Her blood pressure today is 161/98 mm Hg. Staff members at the LTCF have tried redirection and counseling for F.H.'s symptoms, but these strategies have been ineffective. She refuses to attend any group activities and is disruptive if she is near the other patients.

9. Which one of the following is the best assessment of F.H.'s psychiatric symptoms?

   A. She must complete the GAD-7 before a diagnosis of GAD can be made.
   B. Diagnosis of GAD cannot be made because she has Alzheimer disease.
   C. She does not meet the time criteria for a diagnosis of GAD.
   D. She appears to meet the *DSM-5* criteria for a diagnosis of GAD.

10. Which one of the following is best to recommend for F.H.'s anxiety?

    A. Escitalopram 5 mg orally each morning
    B. Quetiapine XR 50 mg orally each morning
    C. Venlafaxine XR 37.5 mg orally each morning
    D. Lorazepam 0.5 mg orally four times daily

Questions 11 and 12 pertain to the following case.

W.T. is a 36-year-old man who was given a diagnosis of GAD 6 months ago and initiated on sertraline 25 mg daily. The dose was gradually increased to 150 mg/day. His initial GAD-7 score was 12; now, it is 9. W.T. is tolerating sertraline well. His medical history includes migraine headaches, for which he is prescribed sumatriptan 100 mg at the onset of migraine and long-acting propranolol 80 mg daily for prevention. At today's visit, W.T. and the prescriber have decided to change sertraline to duloxetine.

11. Which one of the following is most appropriate for transitioning W.T. to duloxetine?

    A. Stop sertraline today and initiate duloxetine in 3 days.
    B. Reduce sertraline to 100 mg daily today while initiating duloxetine 30 mg daily.
    C. Continue sertraline at 150 mg daily and initiate duloxetine 90 mg daily.
    D. Discontinue sertraline today, initiate duloxetine 60 mg daily, and add lorazepam 0.5 mg three times daily for the next 2 weeks.

12. Which one of the following sets of adverse effects caused by a drug interaction is most important to monitor for in W.T. because of the use of duloxetine?

    A. Severe sedation, dry mouth, constipation
    B. Agitation, muscle rigidity, diaphoresis
    C. Orthostatic hypotension, QTc prolongation, bradycardia
    D. Constipation, small bowel obstruction, urinary retention

Questions 13–18 pertain to the following case.

P.N., an 82-year-old woman, has been treated for coexisting GAD and depression for 2 years. These disorders have worsened over the past year since her spouse died. P.N. has had medication trials with paroxetine and citalopram with poor responses. Her major complaints are constant worry about being alone and vulnerable, taking care of finances, and being anxious about the ability to drive independently around town, which results in her staying home most of the time. Before his death, her husband did all the driving. Now, P.N. hardly goes out at all. When she does go out, her interactions with old friends are positive. Her mood is depressed with ruminations about the death of her spouse but negative for suicidal thoughts or behaviors. P.N.'s current drugs include sertraline 150 mg daily and bupropion extended release 150 mg daily. She takes alprazolam 0.5 mg, prescribed as needed at bedtime, two or three times per week. P.N. has been educated about the disorders and provided with counseling support, which she does not believe is effective. The prescriber is now considering adding a second-generation antipsychotic (SGA) and CBT. P.N.'s other medical conditions include osteoporosis, rheumatoid arthritis, and hypertension, for which she takes ibuprofen 600 mg three times daily, calcium carbonate 500 mg twice daily, hydrochlorothiazide 25 mg daily, and amlodipine 10 mg daily. Her vital signs today include blood pressure 130/88 mm Hg and heart rate 70 beats/minute, and the rest of her physical examination and laboratory test results are within normal limits. Her GAD-7 score today is 15. Refill records show adherence to medications.

13. Which one of the following best describes the risks that sertraline poses to P.N.?

    A. More difficulty controlling hypertension
    B. Increased risk of seizures
    C. GI bleeding
    D. Increased risk of hypokalemia

14. Which one of the following best describes the addition of CBT to P.N.'s treatment regimen?

    A. It is unlikely be beneficial at this time.
    B. An online, self-directed version is best to offer.
    C. It should include weekly sessions with a trained therapist.
    D. Relaxation therapy is preferable to CBT.

15. P.N.'s prescriber decides to initiate aripiprazole and instructs her to taper sertraline. Which one of the following variables is most important to monitor for P.N. because of adding aripiprazole?

    A. Blood pressure
    B. Fasting glucose
    C. Serum potassium
    D. Serum prolactin

16. Which one of the following risks is most important to counsel P.N. about regarding alprazolam?

    A. Falls
    B. Abuse
    C. Dependence
    D. Tolerance

17. If P.N.'s new regimen is effective, which one of the following best describes how long the medications should be continued?

    A. Until the CBT sessions are completed.
    B. For 6 weeks after her last CBT session.
    C. Until 12 weeks after her last CBT session.
    D. For at least 12 months regardless of CBT sessions.

18. Which one of the following best justifies GAD as a better description of P.N.'s complaints than social anxiety disorder?

    A. She has physical complaints in addition to emotional complaints.
    B. Her anxiety over getting out of the house is most consistent with GAD.
    C. Her worries focus on living without her husband to care for her.
    D. Her score on the GAD-7 confirms she has GAD, not social anxiety disorder.

Questions 19–22 pertain to the following case.

J.F. is a 28-year-old woman in her second month of pregnancy. She began to have anxiety at age 24 years but never pursued treatment. J.F. comes to clinic today with complaints of excessive worry most days that is difficult to control. Her worries and anxiety sometimes involve fear about her impending parenthood; at other times, she is just anxious and does not know why. J.F. says that she is really irritable and feels nervous all of the time. She notes that sometimes during the day she feels jittery, sweaty, and lightheaded. She also has trouble initiating sleep, which has often caused her to feel tired. The symptoms are so severe that she asks for help in treating them. Her medical history includes asthma treated with albuterol and fluticasone/salmeterol inhalers, gestational diabetes treated with insulin lispro and insulin glargine, and gastroesophageal reflux disease treated with ranitidine. J.F. notes that in the past month, her asthma has been more difficult to control. She also developed a UTI 1 week ago, for which she has 4 more days of nitrofurantoin. J.F.'s prenatal check today is normal. Her most recent laboratory test results include a fasting blood glucose of 70 mg/dL. She has been given the GAD-7 to complete.

19. Which one of the following possible treatments for J.F. has adverse effects most likely to mimic anxiety?

    A. Albuterol
    B. Fluticasone
    C. Nitrofurantoin
    D. Ranitidine

20. J.F. is concerned about using drugs during her pregnancy. She asks about psychological therapy. Which one of the following is the best educational point to provide J.F. about using CBT for anxiety?

    A. It is effective as pharmacotherapy for initial therapy in most patients
    B. It is not studied in pregnant patients, so efficacy compared with pharmacotherapy is unknown
    C. It is most effective for the patient if used together with a medication
    D. It is more effective than medications for her type of anxiety

21. J.F. wants to know what CBT involves when it is used to treat GAD. Which one of the following is the best explanation to give J.F.?

    A. The aim of CBT is to help patients identify and correct maladaptive thought processes.
    B. CBT is a type of relaxation therapy aimed at reducing the response to stressors.
    C. CBT is a form of mindfulness meditation that aims to help patients be in the here and now.
    D. CBT is a form of psychodynamic therapy that identifies unconscious memories of past experiences that influence present behaviors.

22. Which one of the following drugs is most likely to be teratogenic if added to the treatment plan for J.F.'s GAD?

    A. Fluoxetine
    B. Buspirone
    C. Alprazolam
    D. Venlafaxine