

PSYCHIATRY II



ANXIETY DISORDERS

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Learning Objectives

1. Design a treatment plan for the long-term management of panic disorder.
2. Distinguish the essential features of generalized anxiety disorder (GAD), panic attacks, and panic disorder.
3. Demonstrate the proper use and reasonable expectations for use of pharmacotherapeutic treatments for a patient with an anxiety disorder.
4. Evaluate the role of antidepressant drugs in managing GAD.
5. Construct a hierarchy of pharmacotherapeutic choices for the treatment of anxiety disorders based on existing literature.
6. Assess the therapeutic outcome of pharmacotherapy for anxiety disorders using clinical rating scales.
7. Design a plan for the initiation of pharmacotherapy for new-onset panic disorder.
8. Construct a patient education strategy to use when treating anxiety disorders.
9. Evaluate a patient-specific regimen for appropriateness of treatment for an anxiety disorder.
10. Devise a plan for discontinuation of pharmacotherapy in GAD.

Introduction

Recent population-based surveys estimate that 1 in every 4 Americans will experience and meet diagnostic criteria for an anxiety disorder in their lifetimes. Patients with untreated symptoms of anxiety report a poorer quality of life and have been shown to be high users of medical services. The total cost of anxiety disorders is about \$45 billion annually, 75% attributed to indirect costs of lost productivity and medical morbidity.

Recognition and treatment of symptoms by both clinicians and patients are essential for managing anxiety disorders effectively. Approaches that can bridge access to

care, improve physician and pharmacist recognition of these disorders, and educate patients and their social supports regarding illness and treatment should be of the utmost priority. Mental illnesses are described in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR), a vital tool for clinicians to learn and identify the essential features and core symptoms of each primary disorder. The descriptions in this chapter are based on the criteria in the most recent text revision of the DSM-IV-TR, which describes 12 types of anxiety disorders in adults. This chapter focuses on the identification and pharmacotherapeutic management of generalized anxiety disorder (GAD) and panic disorder.

Background of Generalized Anxiety Disorder and Panic Disorder

Pathophysiology

The physiologic processes that modulate feelings of fear and anxiety are not well understood. Research suggests that multiple cortical and subcortical brain structures of the limbic system, including the amygdala, hypothalamus, hippocampus, and brain stem, play roles in the processing and mediation of fear and anxiety. The amygdala is involved in fear conditioning and can be stimulated by the sensory thalamus (after sight or sound of a potential threat), the hippocampus (stored emotional thought or memory), or the prefrontal cortex. Projections from the amygdala integrate other brain structures in modulating fear and anxiety. Stimulation of the amygdala can lead to activation of the periaqueductal gray, hypothalamus, and locus coeruleus. Activation of the periaqueductal gray is responsible for the affective “defense” motor responses to fear, including freezing and fleeing. In the normal stress response, the release of cortisol shuts down the release of corticotrophin-releasing factor from the hypothalamus via a negative feedback loop, thus ending the stress response. However,

Abbreviations in This Chapter

5-HT	Serotonin
BZD	Benzodiazepine
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder
HAM-A	Hamilton Rating Scale for Anxiety
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
XR	Extended-release

this complex cascade of events is theorized to somehow be disrupted in persons with anxiety disorders and is not yet fully understood.

Abnormal function of several neurotransmitter systems has been implicated in the pathophysiology of anxiety disorders, namely norepinephrine, serotonin (5-HT), and gamma-aminobutyric acid (GABA). Both 5-HT and norepinephrine systems are regulated to some degree by GABA. Binding of GABA to the GABA_A receptor opens the chloride channel of the receptor, which permits an influx of chloride into the neuron; the result is decreased cell excitability. Pharmacologically, benzodiazepines (BZDs) modulate GABA neurotransmission by potentiating GABA's ability to increase conductance of chloride through this channel. One postulated theory is that anxiety is secondary to an endogenous BZD imbalance, either from a decrease in quantity of endogenous BZD substances, a decrease in sensitivity of receptors to the endogenous BZD substances, or an abnormality in the conformation of the receptors, limiting the binding of GABA or endogenous BZD to these receptor complexes.

Models of 5-HT dysregulation have also been postulated in anxiety disorders. Serotonergic neurons are a diverse group with projections throughout the cortex and limbic system. It has been suggested that anxiety manifests via various theorized mechanisms, including enhanced 5-HT release, supersensitivity of postsynaptic 5-HT receptors, abnormal uptake at the serotonin reuptake transporter, and dysregulation of presynaptic 5-HT uptake. Patients often report experiencing an initial activation, described as an increase in anxiety symptoms, within the first few weeks of treatment with antidepressant drugs. This biphasic course of response seen with serotonergic antidepressants in patients with anxiety disorders may be explained by the actions of 5-HT on multiple neuronal sites. The anxiolytic properties of serotonergic drugs may be the result of hippocampal neurogenesis, which has been shown in animal models after chronic stimulation of hippocampal 5-HT_{1A} receptors.

The noradrenergic system is also a likely contributor to the manifestation of anxiety symptoms, particularly autonomic symptoms, including tachycardia, diaphoresis,

tremor, hyperventilation, and mydriasis. The locus coeruleus serves as an alarm system in anxiety, activating norepinephrine release and, in turn, stimulating the sympathetic and parasympathetic nervous systems. Hypersensitivity of these autonomic pathways has been hypothesized as a possible neurochemical basis of GAD and panic disorder symptoms. Drug-induced models of agents that acutely increase norepinephrine activity corroborate the role of norepinephrine in subjective feelings of anxiety. Drugs that decrease noradrenergic activity have been shown to be effective, particularly in treating the physical symptoms of anxiety. However, the role of norepinephrine in the pathogenesis of anxiety remains to be clearly delineated.

Epidemiology

The lifetime prevalence of GAD, derived from population-based surveys, is about 5%. Current prevalence estimates show that GAD affects as many as 5 million Americans. The illness occurs in twice as many females as males (2:1).

Current estimates report that as many as 2.5 million people in the United States are afflicted with panic disorder. Lifetime prevalence of panic disorder reported from population-based samples nears 3.5%. The illness is more common in females than males (2.5:1) and the difference in prevalence by gender appears to increase with age.

Clinical Presentation and Patient Evaluation

Clinical Presentation

Generalized Anxiety Disorder

Clinical Characteristics and Diagnostic Criteria

Recognition of the features and symptoms of GAD is essential in making the clinical diagnosis. The length of time that the anxiety and excessive worry have been present should be considered. Symptoms must be present on most days for a period of at least 6 months to meet the criteria for GAD described by the DSM-IV-TR. Also essential is establishing that the patient feels a lack of control over the anxiety. Worry and anxiety may not always be consistently focused in one life area. Symptoms of anxiety are usually portrayed as disturbing and impeding. The clinician should display empathy and sensitivity to the impairment in social, occupational, or other functioning of these symptoms. Three or more subjective symptoms must be present to make a diagnosis of GAD, including restlessness, feeling easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep difficulties. The clinician should discern that the worry and other symptoms manifested are not related to another primary psychiatric diagnosis or medical problem, or the result of medication or substance use.

Course and Prognosis

Onset of symptoms in GAD typically occurs sometime within childhood, adolescence, or early adulthood. In patients with other co-occurring anxiety disorders, GAD may present later in adulthood. There is generally a

considerable delay between the time of initial symptomatology and diagnosis of GAD. Life stressors appear to play a sizeable role in the persistence of symptoms and course of illness. Persons affected by GAD generally experience symptoms of varying severity in a chronic, lifelong course.

Panic Disorder

Clinical Characteristics and Diagnostic Criteria

Panic disorder is a complex illness that is characterized by panic attacks. When presented with a clinical picture of panic attacks, however, panic attacks may occur in the context of most anxiety disorders. Therefore, panic attacks are not necessarily indicative or diagnostic of panic disorder. During a panic attack, at least four psychic and somatic symptoms will be present. Psychic symptoms may include depersonalization (a dreamlike state where the person feels separated from the world), fear of dying, derealization (an altered sense of reality), fear of losing control, or fear of going “crazy.” These feelings of psychological discomfort may be accompanied by somatic, or physical, symptoms, which may include sweating, trembling, or shaking; a feeling of choking; chest pain or discomfort; nausea or

abdominal distress; paresthesias; palpitations; accelerated heart rate; sensations of shortness of breath or smothering; feeling dizzy or unsteady; lightheadedness; chills; and hot flushes. During a panic attack, symptoms usually arise within minutes and persist for as long as 1 hour.

To meet diagnostic criteria for panic disorder, recurrent panic attacks must be described by the patient. In the patient’s lifetime experience of having panic attacks, at least one attack had to have been followed by a period of 1 month of persistent fear about having additional attacks, worry about the repercussions of the attack or its end result, or a significant change in behavior related to the panic attacks. The clinician should rule out the direct effects of a substance or medical condition in causing the symptoms.

Course and Prognosis

Symptoms in panic disorder typically surface sometime between late adolescence and early to mid-adulthood for both men and women. Persons affected by panic disorder will likely experience symptoms of varying frequency in a chronic, lifelong course. Some persons experience continuous symptoms with panic disorder, whereas others incur a more waxing and waning symptomatology.

Table 1-1. Dosing and Available Strengths of Newer Antidepressant Drugs for the Treatment of Anxiety Disorders

Generic Name	Trade Name(s)	Recommended Initial Dose	Usual Dosing Range	Suggested Increments for Dose Titration	Recommended Dosing Schedule	Available Dosages and Forms	Generic
SSRIs							
Fluoxetine	Prozac	5 mg/day	10–40 mg/day	5 mg	Daily	10, 20, 40, mg capsule 10, 20 mg tablet	Y Y
Sertraline	Zoloft	25 mg/day	50–200 mg/day	25–50 mg	Daily	25, 50, 100 mg tablet ^a 20 mg/mL solution	Y Y
Paroxetine	Paxil	10 mg/day	20–60 mg/day	10 mg	Daily	10, 20 ^a , 30, 40 mg tablet 10 mg/mL oral suspension	Y N
	Paxil CR	12.5 mg/day	25–62.5 mg/day	2.5 mg	Daily	12.5, 25, 37.5 mg tablet	N
Citalopram	Celexa	10 mg/day	20–60 mg/day	10 mg	Daily	10, 20 ^a , 40 ^a mg tablet 2 mg/mL solution	Y Y
Escitalopram	Lexapro	5 mg/day	10–20 mg/day	5 mg	Daily	5, 10, 20 mg tablet ^a 5 mg/5 mL solution	N N
Fluvoxamine	Luvox	25 mg/day	100–300 mg/day	25 mg	Daily–twice daily (no single dose >100 mg)	25, 50 ^a , 100 ^a mg tablet	Y
SNRIs							
Venlafaxine	Effexor	37.5 mg/day	75–225 mg/day	37.5–75 mg	2–3 times/day	25, 37.5, 50, 75, 100 mg tablet	Y
	Effexor XR	75–225 mg/day	75 mg		Daily–twice daily	37.5, 75, 150 mg capsule	N

^aScored tablet.

CR = controlled release; N = no; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XR = extended release; Y = yes.

Patient Evaluation

Psychiatric Comorbidities

Both panic disorder and GAD have been shown to be significantly associated with other comorbid DSM-IV-TR disorders. Recent estimates have reported that 90% of patients with GAD have a comorbid psychiatric condition. In general, in the presence of current (illness within the last 12 months) psychopathology, the odds of having a comorbid disorder are higher than the odds associated with lifetime association of either panic disorder or GAD. In patients with GAD, dysthymia and bipolar I disorder are the mood disorders that have been shown in a recent epidemiological survey to have the strongest associations. Panic disorder is also frequently associated with lifetime bipolar I disorder. Those reporting a lifetime history of panic disorder have 6 times the odds of a lifetime mood disorder as those not reporting history of panic disorder. The odds of lifetime mood disorder in those with lifetime GAD is nearly twice this magnitude.

Comorbid anxiety disorders are also common. Panic disorder and GAD are more strongly related to each other than to the remaining anxiety disorders. Drug dependence is also strongly associated with lifetime panic disorder or GAD.

Medical Comorbidities

Studies have reported that patients with a lifetime history of an anxiety disorder report higher rates of illnesses, including cardiovascular disease, autoimmune disease, chronic pain and arthritis, infectious disease, diabetes, dyslipidemia, respiratory disease, irritable bowel syndrome, gastrointestinal illness, genitourinary disorders, and migraine headaches. Patients with anxiety disorders are also high users of medical services, which may lead to an increased detection of co-occurring medical illness.

Differential Diagnosis

Other medical disorders that may have similar symptoms to those of anxiety disorders should be ruled out. Metabolic conditions that may be confused with anxiety symptoms include hyperthyroidism, hyperparathyroidism, electrolyte disturbances, and vitamin B₁₂ deficiency. Other disease states such as dementia, Parkinson's disease, seizure disorder, and inadequate pain control can have symptoms that can be confused with symptoms of anxiety. Cardiac conditions should also be ruled out as the source of physical symptoms; these may include arrhythmias, congestive heart failure, and myocardial infarction. Symptoms of respiratory conditions, such as asthma and chronic obstructive pulmonary disease, as well as vestibular dysfunction can be mistaken for anxiety symptoms and should be ruled out in the differential diagnosis.

Illicit substance use can cause anxiety and related symptoms. Substances such as stimulants, cocaine, and marijuana, as well as withdrawal from central nervous system depressants, can induce anxiety-like states. Another possible source of anxiety symptoms is prescribed medication, including bronchodilators, corticosteroids, dopaminergic drugs, adrenergic drugs, nasal decongestants, and stimulant medications. Over-the-counter supplements

should also be considered as a possible source of anxiety symptoms. Excessive caffeine use and withdrawal from nicotine are known to induce and exacerbate anxiety.

Pharmacotherapy of Generalized Anxiety Disorder and Panic Disorder

Generalized Anxiety Disorder

Pharmacological Approaches

Numerous pharmacotherapeutic treatment choices have been shown to be efficacious in the treatment of GAD. Few head-to-head treatment studies have been performed that compare the efficacy of drugs in different therapeutic classes. As a consequence, there is limited guidance as to the preferred sequence of available treatments. Psychotherapeutic options including cognitive behavioral therapy have also been shown to improve patient outcomes, either alone or in combination with pharmacotherapy. The drugs available for the treatment of GAD, which have well-documented evidence of efficacy and effectiveness in clinical settings, include selective serotonin reuptake inhibitors (SSRIs), venlafaxine, tricyclic antidepressants (TCAs), BZDs, and buspirone.

Selective Serotonin Reuptake Inhibitors

A mainstay of treatment of GAD is SSRIs. The two SSRIs that carry Food and Drug Administration indications for the treatment of GAD are escitalopram and paroxetine. A main reason that SSRIs are considered first-line therapy is their favorable efficacy and tolerability profile. Response rates, as measured by clinical global improvement ratings, are near 70% with SSRIs. Discontinuation occurred in 5%–18% of patients in pivotal trials; common adverse events include nausea, somnolence or insomnia, and sexual dysfunction.

Of note, SSRIs are considerably safer in overdose than many other alternative treatments, particularly BZDs and TCAs. Dosing of SSRIs in GAD (see Table 1-1) is initiated at low doses and is slowly titrated to doses that would be considered moderate antidepressant drug doses. It is important to “start low and go slow,” as fast titration during initial SSRI therapy has been associated with an increase in stimulatory adverse events, such as anxiousness and jitteriness. Some clinicians prefer to initiate SSRIs and overlap with a 2–4-week course of BZD therapy to help alleviate some of the initial stimulatory effects and regulate sleep. Patients should be advised that immediate relief is not to be expected when initiating treatment with an SSRI. Noticeable improvement may be seen after 4 or more weeks of treatment; however, acute trials were 8–12 weeks in length, and this is the accepted adequate trial length for SSRIs in managing GAD. Failure due to lack of efficacy or tolerability with one SSRI can be followed with a trial of an alternate antidepressant drug, such as a different SSRI or venlafaxine. Various strategies may also be effective for

tolerability issues, such as decreasing the drug dose or augmenting with an additional drug. If breakthrough withdrawal symptoms are occurring, the importance of daily adherence to the treatment regimen should be emphasized to the patient.

Serotonin-Norepinephrine Reuptake Inhibitor

Venlafaxine, a 5-HT-norepinephrine reuptake inhibitor with efficacy in treating GAD, was approved by the Food and Drug Administration for this indication in 1999. Doses ranging from 37.5 mg/day to 225 mg/day in extended-release (XR) formulations have been studied in placebo-controlled trials. All doses greater than or equal to 75 mg/day showed superiority over placebo, with higher doses showing greater reductions in primary anxiety scale measurements. Norepinephrine reuptake is not believed to be significant until doses of 225 mg/day or greater of venlafaxine have been achieved. In the acute (8-week) treatment studies, nearly 30% of patients discontinued study treatment due to emergent adverse events, often in the first week of therapy. Nausea, insomnia or somnolence, dry mouth, and dizziness were the most commonly reported adverse events.

Two long-term studies (24 weeks) in GAD showed patients receiving venlafaxine XR 75 mg/day, 150 mg/day, or 225 mg/day significantly improved compared with placebo through 24 weeks of treatment. Adverse events were similar to those reported in acute treatment studies.

Studies have been conducted to compare treatment of GAD with venlafaxine to other antianxiety treatments. One earlier study randomized patients to venlafaxine XR (75 mg/day or 150 mg/day), buspirone 30 mg/day, or placebo for 8 weeks of treatment. By week 2, venlafaxine XR 75 mg showed statistical superiority over both placebo and buspirone in primary anxiety subscale measures. A second study compared 3 months of treatment with either venlafaxine XR (75–225 mg/day), fluoxetine (20–60 mg/day), or placebo in patients with comorbid major depressive disorder and GAD. Response, defined as a 50% or greater decrease in anxiety subscale scores, was greater in the venlafaxine-treated patients (59%) than in the placebo-treated patients (24%). Response with fluoxetine was 45%, which did not separate from placebo. In pairwise comparisons between venlafaxine XR and fluoxetine, the treatments were not significantly different when comparing rate of response.

Treatment with venlafaxine is generally initiated with the XR formulation for ease of once-daily dosing. An initial dose of 75 mg/day can be slowly titrated at a rate of 75 mg/week based on clinical response and tolerability. Doses greater than 225 mg/day have not been studied in patients without other comorbid psychiatric illnesses.

Tricyclic Antidepressants

Imipramine, a TCA, has positive randomized trials for its use in the treatment of GAD. A four-arm, parallel group trial compared imipramine (average dose = 143 mg/day), trazodone (average dose = 225 mg/day), and diazepam (average dose = 26 mg/day) to placebo. Marked-to-moderate improvement was reported by 73% of patients completing 8 weeks of treatment with imipramine, 69% of

patients taking trazodone, and 66% of patients taking diazepam. When compared with diazepam, anxiolytic efficacy (particularly psychic symptoms of anxiety) was markedly improved in weeks 3 through 8. A high rate of adverse events have been reported with imipramine treatment, particularly drowsiness, dizziness, dry mouth, and constipation. However, retention rates in treatment studies were similar in both the imipramine and placebo groups.

A second randomized trial of imipramine using active comparators paroxetine and chlordesmethyldiazepam, a BZD, found similar improvement (about 66%) among study completers in all three treatment groups. Similar to previously published findings, initial improvement in the first 2 weeks was notable with BZD treatment (primarily with somatic symptoms), but, by week 8, both paroxetine (dose = 20 mg/day) and imipramine (dose = 50–100 mg/day) showed significantly greater improvement in anxiety rating scale scores compared with BZD treatment.

Buspirone

Treatment with buspirone, an azapirone with agonistic activity at 5-HT_{1A}, is effective in managing symptoms of GAD. Numerous trials, some as short as 4 weeks, have shown buspirone to be superior to placebo in reducing anxiety symptoms as measured by change in clinician-rated anxiety scale scores. Onset of action for buspirone is delayed and similar to antidepressant treatment. Generally improvements are seen within 2–3 weeks, at doses ranging from 20mg/day to 60 mg/day given in divided doses. Response rates in short-term studies using buspirone are similar to response rates seen in treatment trials using antidepressants and other anxiolytics for GAD. However, in those patients with previous use of BZDs, buspirone appears to be less effective. Adverse events with buspirone can be problematic; those most commonly reported include gastrointestinal upset, headache, dizziness, and lightheadedness.

Benzodiazepines

The efficacy and tolerability of BZDs in the treatment of GAD have been well studied. Short-term, randomized, placebo-controlled studies have found BZDs to rapidly improve anxiety symptom severity. Response rates, as defined by marked or moderate improvement in clinical global ratings of 70%–80% have been reported in 3–4-week treatment trials. Continued use of BZDs, for periods up to 6 months, are also effective. Dosing of BZDs should start at low doses, with titration occurring at regular intervals as needed until an anxiolytic effect is achieved. Intermittent dosing is also an option with BZDs, whereas continuous use is necessary with antidepressants and buspirone. If BZDs are used, the goal should be to find and maintain the lowest effective dose to minimize the potential for adverse events. Some of the more commonly reported adverse events associated with BZD treatment include dizziness, drowsiness, and motor incoordination. Symptom improvement with BZD occurs rapidly, usually within a few days, and tolerance to problematic adverse events generally occurs within the first 2 weeks of treatment. Dependency and discontinuation reactions (withdrawal) can occur with

BZD treatment and limit the use of these medications on a long-term basis. Within the therapeutic class, there is no conclusive evidence from head-to-head comparison trials that would direct treatment choice to any specific drug. Table 1-2 includes BZDs whose efficacy is demonstrated by placebo-controlled, short-term studies in GAD.

Antiepileptic Drugs

Pregabalin is indicated for managing postherpetic neuralgia, neuropathic pain associated with diabetic peripheral neuropathy, and as adjunctive therapy in treating partial seizures in patients with epilepsy. There is interest in its potential use as an anti-anxiety drug. Pregabalin is a structural derivative of the neurotransmitter GABA and has been studied in four short-term efficacy trials. Most acute treatment trials with pregabalin have also included an active

Table 1-2. Dosing and Available Strengths of Older Antidepressant Drugs and Other Pharmacotherapies for the Treatment of Anxiety Disorders

Generic Name	Trade Name(s)	Recommended Initial Dose	Usual Dosing Range	Suggested increments for Dose Titration	Recommended Dosing Schedule	Available Dosages and Forms	Generic
Azapirones							
Buspirone	BuSpar	15 mg/day	15–60 mg/day	5 mg	2–3 times/day	5, 7.5, 10, 15, 30 mg tablet*	Y
TCAs							
Clomipramine	Anafranil	25 mg/day	75–250 mg/day	25 mg	Daily–twice daily	25, 50, 75 mg capsule	Y
Desipramine	Norpramin	25 mg/day	150–300 mg/day	25 mg	Daily	10, 25, 50, 75, 100, 150 mg tablet	Y
Imipramine	Tofranil	10–25 mg/day	150–300 mg/day	10–25 mg	Daily	10, 25, 50 mg tablet	Y
Nortriptyline	Pamelor	25 mg/day	75–150 mg/day	25 mg	Daily	10, 25, 50, 75 mg capsule 10 mg/5ml solution	Y Y
MAOIs							
Phenelzine	Nardil	15 mg/day	45–90 mg/day	15 mg	Daily–twice daily	15 mg tablet	N
Tranylcypromine	Parnate	10 mg/day	20–60 mg/day	10 mg	2–3 times/day	10 mg tablet	Y
Benzodiazepines							
Alprazolam	Xanax	0.5–1 mg/day	0.5–4 mg/day	0.25–0.5 mg	2–3 times/day	0.25, 0.5, 1, 2 mg tablet ^a	Y
	Xanax XR	0.5–1 mg/day	0.5–6 mg/day	0.5–1 mg	Daily	0.5, 1, 2, 3 mg tablet	N
Chlordiazepoxide	Librium	5–15 mg/day	15–100 mg/day	5–10 mg	3–4 times/day	5, 10, 25 mg capsule	Y
Clonazepam	Klonopin	0.5 mg/day	0.5–4 mg/day	0.25–0.5 mg	2–3 times/day	0.5, 1, 2 mg tablet ^a	Y
Diazepam	Valium	2 mg/day	2–10 mg/day	2 mg	2–3 times/day	2, 5, 10 mg tablet ^a	Y
Lorazepam	Ativan	1–2 mg/day	1–6 mg/day	1 mg	2–3 times/day	0.5, 1, 2 mg tablet ^a	Y
Oxazepam	Serax	20 mg/day	10–45 mg/day	10 mg	3–4 times/day	10, 15, 30 mg capsule	Y

^aScored tablet.

MAOI = monoamine oxidase inhibitor; N = no; TCA = tricyclic antidepressant; XR = extended release; Y = yes.

comparator treatment arm, such as venlafaxine, lorazepam, or alprazolam. Pregabalin at doses of 200, 300, 400, 450, and 600 mg/day was shown, like all the active comparators, to be significantly superior to placebo in reducing symptoms from baseline to end of treatment. Adverse events commonly reported during the 4-week treatment studies included somnolence, dizziness, dry mouth, and weight gain. These adverse events were rated as mild to moderate severity. Similar tolerability has been reported with 2 times/day and 3 times/day dosing of pregabalin.

Despite the apparent efficacy of pregabalin in treating GAD, use of this drug should be limited because it does not have a Food and Drug Administration-labeled indication for use in GAD. Evidence is inconclusive as to whether pregabalin is as effective as other available pharmacotherapeutic options.

Tiagabine is another antiepileptic treatment that has been evaluated for use in patients with GAD. Like pregabalin, its use in treating anxious symptoms centers on a novel mechanistic action. Tiagabine is a selective GABA reuptake inhibitor via the GABA transporter 1. One open-label and one randomized, controlled trial with tiagabine have shown short-term efficacy in treating core anxiety symptoms of GAD. One caveat regarding the use of tiagabine is that it does not have an approved label indication by the Food and Drug Administration for treating anxiety disorders. Studies have shown an increased risk of new-onset seizures and status epilepticus with tiagabine use when taken for off-label indications. The use of this drug should be limited until further information is available regarding safety and efficacy.

Miscellaneous Drugs

The efficacy of mirtazapine in the treatment of GAD has been examined. One open-label study included 44 outpatients with GAD who were treated with fixed-dose mirtazapine (30 mg/day) for 12 weeks. Nearly 80% of subjects were classified as responders at the end of the treatment period. Adverse events were not uncommon and included weight gain, sedation, dry mouth, and constipation. Adverse events accounted for 2 of 5 dropouts in the treatment group. No randomized, placebo-controlled studies of mirtazapine have been reported.

One small, open-label, fixed-dose study in subjects with DSM-IV-classified GAD has reported efficacy of riluzole, a presynaptic glutamate release inhibitor. In this study, riluzole was titrated to a dose of 100 mg/day. Two-thirds of the patients had positive improvement after 8 weeks of treatment; sleep disturbance, nausea, somnolence, dry mouth, and transient increases in hepatic aminotransferases were the most common adverse events reported.

Atypical antipsychotic drugs have also been increasingly studied in anxiety disorders, mostly as augmenting strategies for both patients with and without the presence of co-occurring mood disorders. Aripiprazole, risperidone, olanzapine, and ziprasidone have all been studied in the treatment of GAD. Daily doses used have been low to moderate (aripiprazole 15–30 mg; risperidone 0.5–1.5 mg; olanzapine 5–20 mg; ziprasidone 20–80 mg). Symptomatic improvement has been noted in some subjects; however, it

is important to keep in mind that most studies entered patients who were considered treatment-refractory.

Panic Disorder

Pharmacological Approaches

Medical management centers on the use of antidepressant drugs. Key advancements have been made in the use of different classes of antidepressants in treating panic disorder. As with the treatment of GAD, psychotherapeutic options have been shown to improve patient outcomes, either alone or in combination with pharmacotherapy. The drugs with well-documented evidence of efficacy and clinical effectiveness for the treatment of panic disorder include SSRIs, venlafaxine, TCAs, BZDs, and monoamine oxidase inhibitors.

Selective Serotonin Reuptake Inhibitors

Similar to the treatment of GAD, SSRIs are considered first-line treatment options in panic disorder. Fluoxetine, sertraline, and paroxetine have labeled indications from the Food and Drug Administration for the treatment of panic disorder. All the SSRIs have shown to be effective in the treatment of panic disorder. A meta-analysis of 12 randomized, placebo-controlled trials using SSRIs found a modest effect size (0.55) for acute treatment of panic disorder with SSRIs compared with placebo. The effectiveness was not found to be different from that reported with imipramine (0.48). The SSRI treatment trials included in the meta-analysis had smaller sample sizes compared with studies using imipramine. This is an important consideration, as differences in sample size could slightly inflate the effect sizes found for SSRIs. This meta-analysis did not find any evidence of favorable tolerability of SSRIs over imipramine.

However, a second, more recent, meta-analysis also contrasted the efficacy of SSRIs and TCAs in treating panic disorder. It included pooled data from both randomized and non-randomized treatment trials and found that both classes of antidepressants were efficacious in the treatment of panic, agoraphobia, and anxiety related to panic disorder. Effect sizes reported for those constructs were 1.26, 1.10, and 1.55 for TCAs, respectively, and 1.46, 1.15, and 1.27 for SSRIs, respectively, with no significant differences. Tolerability in this meta-analysis favored treatment with SSRIs. Dropout rates were significantly lower in subjects treated with SSRIs (18%) versus TCAs (31%) in this second meta-analysis.

Treatment response rates reported in large clinical trials of SSRIs in panic disorder range between 50% and 80%, with remission rates from 42% to 70%. The SSRIs are well tolerated, and treatment discontinuation due to adverse events in acute panic disorder studies with SSRIs is about 10%. Slow titration is required, and time to response with SSRIs in panic disorder is similar to the initial treatment of GAD. Common adverse events of antidepressant drugs as well as management strategies are listed in Table 1-3.

Venlafaxine

In late 2005, the Food and Drug Administration approved labeling for venlafaxine in treating panic disorder. Dosing for the XR formulation should start at 75 mg/day and may be increased to 225 mg/day. Efficacy was

Table 1-3. Common Adverse Effects and Management Strategies for Selective Serotonin Reuptake Inhibitors and Venlafaxine

Adverse Effects	Management Strategies	Adverse Effects	Management Strategies
Gastrointestinal upset	Start low and titrate slowly Take with food Reduce dose Switch to evening dosing Alternative agent	Headache	Wait for possible tolerance Treat with adjunctive pain reliever Alternative agent if headaches persist
Insomnia	Reduce dose Morning dosing Promote good sleep hygiene Adjunctive medication for sleep	Sexual dysfunction	Reduce dose Wait for possible tolerance Switch to another medication Add adjunctive medication: • Bupropion • Cyproheptadine • Sildenafil, vardenafil or tadalafil
Somnolence	Reduce dose Evening dosing Promote good sleep hygiene Avoid concurrent sedating medication Wait for possible tolerance	Weight changes	Generally see an initial decrease Sometime increases in long-term use Encourage: • Diet • Exercise Healthy coping skills
Discontinuation syndrome	Consider 4–8-week taper of drug by reducing dose in weekly increments If discontinuation symptoms occur: Lengthen intervals of dose reduction Decrease increments of dose reduction	Initial increase in anxiety	Reduce initial dose Titrate slowly Wait for tolerance in first 2 weeks Combine with 2–4 weeks of concomitant benzodiazepine treatment

established versus placebo in acute treatment studies using 75 mg/day, 150 mg/day, and 225 mg/day. Another more recent study incorporated flexible dosing of venlafaxine XR (75–225 mg/day) for 10 weeks and reported a lower mean number of panic attacks and higher response and remission rates compared with placebo.

A comparison study of venlafaxine XR to paroxetine in treating panic disorder has reported no significant difference in treatment effects between the two drugs. Panic-free days were reported by 54%, 61%, and 60% of subjects taking venlafaxine XR 75 mg/day, venlafaxine 150 mg/day, and paroxetine 40 mg/day, respectively. All treatment groups showed significant improvement compared with placebo, but no significant differences were noted between any of the active treatment arms. Remission was achieved by nearly 45% of subjects receiving the active treatments; tolerability of both venlafaxine doses and paroxetine was similar.

The adverse events reported with venlafaxine from the acute Phase III panic disorder treatment studies, with incidence greater than 5% and at twice the incidence of patients treated with placebo, include anorexia (8%), constipation (9%), dry mouth (12%), somnolence (12%), tremor (5%), abnormal ejaculation (8%), and sweating (10%).

Treatment initiation and dose titration recommendations with venlafaxine are the same in panic disorder as in GAD. Doses greater than 225 mg/day have not been studied in patients without other comorbid psychiatric illness.

Tricyclic Antidepressants

Panic disorder is well studied, and initial pharmacotherapeutic treatment modalities included the TCAs. Nearly two dozen treatment studies have assessed the efficacy of TCAs in treating panic disorder. Most trials of TCAs have reported response rates between 50% and 80% in the acute treatment of panic disorder. At least 10 positive randomized trials have studied the use of imipramine in the treatment of panic disorder. Controlled trials also support the use of clomipramine, nortriptyline, and desipramine in treating panic disorder.

Of all the TCAs, clomipramine is known to have the greatest activity on the 5-HT system. In early trials, the number of full panic attacks and the total number of anxiety attacks were significantly fewer in the clomipramine-treated patients than in those treated with imipramine. Clomipramine efficacy has been compared with desipramine in the short-term treatment of panic disorder. In a double-blind, crossover study, clomipramine was superior to desipramine, with fewer panic attacks and lower overall anxiety scores reported after 6 weeks of treatment. Seventy-eight percent of patients had their weekly frequency of attacks reduced to one or fewer during clomipramine treatment, whereas only 54% of patients achieved this milestone during desipramine treatment. The average doses of clomipramine and desipramine during treatment were 140 mg/day and 190 mg/day, respectively.

Few studies have attempted to delineate relationships between serum TCA concentrations and the level of

improvement of panic symptoms. Initial and target doses for TCAs are included in Table 1-2.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors have antipanic effects and may be useful alternatives in treatment-resistant patients. Reservation about the use of monoamine oxidase inhibitors centers on the dietary restrictions and potential for severe drug interactions. Response rates are similar to those reported with SSRIs and other antidepressant drugs. Adverse events may also limit therapeutic benefit. Orthostasis, insomnia, dizziness, and edema are commonly experienced in patients taking monoamine oxidase inhibitors. Dosing and titration recommendations for monoamine oxidase inhibitors in treating panic disorder are included in Table 1-2.

Benzodiazepines

As with the treatment of GAD, BZDs are effective in managing panic disorder. Their use should be reserved for short-term alleviation of panic attacks and initial activation while the patient becomes stable on treatments that will be used for long-term management of symptoms. Clonazepam is a long-acting BZD, whereas alprazolam and lorazepam have shorter half-lives and need to be dosed more frequently. Clonazepam may be the preferred drug in patients who experience interdose anxiety or panic attacks due to its longer duration of action. Response rates in treatment studies are reported to be as high as 70%–80% of patients over the course of 8 weeks. Symptomatic improvement is generally noticed within the first week with BZDs, so patients with severe symptomatology may benefit from an initial short-term course due to the rapid onset of effect. Patients who fail to respond adequately to or who cannot tolerate antidepressants may manage symptoms of panic disorder with combination or monotherapy treatment with BZDs.

Dosing should be initiated in the low end of the dosing range, then increased slowly until clinical improvement is noted. Most patients who are managed with long-term BZD therapy will require scheduled dosing, as these patients are often treatment-refractory and have a more severe course of illness. Studies have reported that patients taking scheduled dosing of BZDs for extended time periods rarely experience tolerance to the antianxiety and anti-panic effects, but appear to better tolerate sedation and psychomotor changes as time on therapy extends. BZDs should be used cautiously in patients with previous history of alcohol or substance abuse. Dosing recommendations for the use of BZDs in managing anxiety disorders are listed in Table 1-2.

Miscellaneous Drugs

Nefazodone and mirtazapine have open-label data supporting their efficacy in panic disorder. Use of these drugs may be reserved for patients who are treatment-resistant or for those who are sensitive to adverse events with first-line therapies. Reports of adverse hepatic events, including jaundice, hepatitis and hepatocellular necrosis, resulted in the manufacturer discontinuing sales of the branded nefazodone. Augmentation of treatment-refractory patients with panic disorder in a recent open-label study has

shown therapeutic benefits for atypical antipsychotic drugs, including risperidone, quetiapine, aripiprazole, and olanzapine. Bupropion has equivocal efficacy, based on one small open-label and one small randomized, controlled trial, in panic disorder.

Role of the Pharmacotherapist

Goals of Therapy

Improvement of overall functioning and quality of life through the reduction of symptom frequency and intensity should be primary treatment goals. Symptoms of anxiety, including physical symptoms, should begin to improve with treatment. Relapse and recurrence of anxiety symptoms frequently occurs, but complete remission of illness should always be a long-term treatment goal.

Treatment Selection

Selection of treatments to manage anxiety disorders should come from what has been shown to be safe and effective treatments, both in clinical study and clinical practice. Consensus- or evidence-based treatment algorithms for GAD and panic disorder have not been published recently. A therapeutic algorithm summarizing current literature is illustrated in Figure 1-1 and can be used in guiding the management of GAD and panic disorder. Venlafaxine and SSRIs have been well-studied and should be considered first-line choices in managing both GAD and panic disorder. The number of trials that should be attempted with well-evidenced first-line therapies has not been well defined by clinical consensus. The TCAs have shown similar efficacy to SSRIs and venlafaxine; however, whether the tolerability of TCAs is similar to that of first-line therapies is debated.

Consideration of patient-specific factors should also play into treatment selection. Depression, a common co-occurring illness with all anxiety disorders, can be managed with SSRIs, venlafaxine, and the other antidepressant drugs. The broad effectiveness of antidepressant drugs in both mood and anxiety disorders contributes to their favorable status in treatment choice. Suicidality should also be addressed when initiating antidepressant drug therapies. Children and adolescents treated with antidepressant drugs for any indication should be closely observed for clinical worsening, unusual changes in behavior, and suicidality. Appropriate monitoring parameters involving the patient, social supports, and care provider should be outlined in managing severe symptomatology and suicidal ideation. Use of serotonergic antidepressant drugs has several advantages, including documented long-term safety, efficacy in prevention of relapse, and no abuse potential.

One disadvantage of using antidepressant drugs for anxiety and panic is the delayed onset of action of days or weeks. In addition, they often initially activate and transiently worsen anxiety, which may be upsetting to the patient. Sexual dysfunction also is common. Patients often experience discontinuation symptoms when they stop antidepressant drug therapy. Weight gain is commonly seen

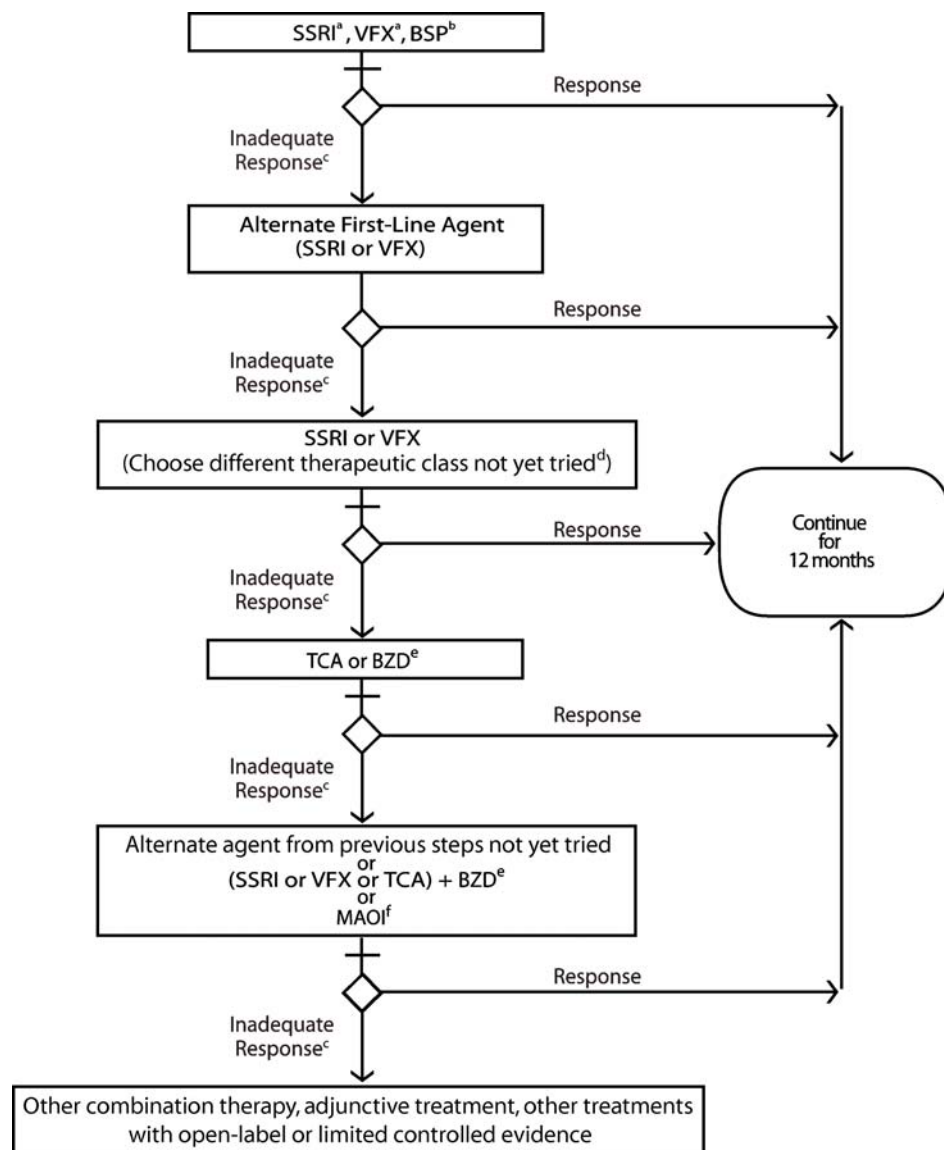


Figure 1-1. Algorithm for use in guiding the treatment of generalized anxiety disorder and panic disorder.

^aIf acute relief needed, or increase in anxiousness or insomnia upon initiation, may overlap with short term (2–4 weeks) of BZD.

^bOnly for initial, nonrefractory treatment of GAD.

^cAfter trial of 8–12 weeks at adequate dose. After 8–12 weeks, may try increasing dose if good tolerability.

^dTry VFX if not yet tried, or try and alternate SSRI therapy if patient has failed an adequate trial of both an SSRI and VFX.

^eBZD not recommended in patients with past or current comorbid substance abuse or dependence.

^fOnly for treatment of PD.

BSP = buspirone; BZD = benzodiazepine; GAD = generalized anxiety disorder; MAOI = monoamine oxidase inhibitor; PD = panic disorder; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VFX = venlafaxine.

with the long-term use of many antidepressant drugs, which may have implications for common medical comorbidities.

The BZDs have a role in short-term management of anxiety and jitteriness that occurs with the initiation of antidepressant drug therapy. They also can be used on an as-needed basis for breakthrough symptoms. Unlike serotonergic drugs, they are rarely associated with sexual dysfunction, which may be seen as a benefit in those who experience sexual dysfunction with antidepressant drug therapies.

A thorough psychiatric history should be obtained, including previous history of substance abuse or

dependence, before initiating treatment with BZDs. Long-term management of GAD and panic disorder should include effective antidepressant therapies whenever possible. Management of these disorders with long-term BZDs use should be limited to treatment-refractory patients who have failed multiple attempts of first-line therapies.

Previous adherence, previous response, and patient preference, including financial considerations, should also be discussed when selecting treatment. Many first-line SSRIs are available as generic products, making this treatment option more affordable. Third-party payer formularies may limit patient and practitioner access to

certain therapeutic modalities. The pharmacotherapist's goal, whenever possible, is optimization of treatment with an effective and tolerable monotherapy. Social support, including the patient's spouse, family, and friends, should be identified. Both supports and patients should be educated about the course of illness, target symptoms, self-management, psychotherapeutic and pharmacological treatment options, and realistic therapeutic goals with treatment.

Treatment Initiation and Adequate Trial Length

It is important to consider both dose and duration of use of the drug before determining treatment response. Low doses should be initiated in managing GAD and panic disorder and should be slowly titrated to at least the low end of the dosing range. Once an adequate dose is reached, this dose should be continued for a minimum of 8 weeks before determining whether a response has occurred. If a partial response has occurred, then treatment could continue for another 2–4 weeks to monitor for response or the dose could be increased. The dose should be maintained in the recommended dosing range with continued monitoring for response. If benefit is not seen after a dose has been maximized and the appropriate time has elapsed during which improvement should be seen, alternate drugs can be initiated.

Monitoring of Therapeutic Outcomes

Adequate response to a drug trial is defined in a variety of ways, including change in rating scale scores, reduction in number and frequency of attacks experienced, and functional impairment. Target symptoms of the disorder should be identified, monitored, and clearly documented at all follow-up visits to ensure symptom improvement and adequate response to treatment. Functional outcomes, including work productivity, family dynamics, and social interaction, should be assessed routinely at patient visits. Patients with panic disorder may be instructed to keep a panic diary to help self-monitor frequency, severity, and impairment resulting from unexpected or circumstantial panic attacks. Empathy and sensitivity directed at the patient by the clinician can help build and strengthen the patient-clinician relationship, as well as facilitate communication regarding clinical improvement and tolerability of treatment.

Clinical rating scales are one method by which clinicians can systematically monitor therapeutic outcomes. Measurement-based care has also been shown to improve cost outcomes in treating psychiatric disorders, and routine monitoring can help detect early relapse of illness. The Hamilton Rating Scale for Anxiety (HAM-A) is used for rating general symptoms of anxiety. The HAM-A is widely used in treatment studies of GAD. It contains 14 items that are rated on a scale of 0–4, relies on subjective patient report of symptoms, and is heavily weighted for somatic complaints. It evaluates changes in symptoms over time and, therefore, can be useful to measure treatment progress. Response is reflected by a change from baseline in HAM-A total score of greater than or equal to 50%. Clinical remission is demonstrated by a score less than or equal to 7.

The Panic Disorder Severity Scale is a rating scale instrument frequently used in treatment trials and can also be used in clinical settings in managing panic disorder. The Panic Disorder Severity Scale is a 7-item instrument, also rated on a scale of 0–4 and measures frequency of panic attacks, distress during panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, interoceptive fear and avoidance, impairment of work functioning, and impairment of social functioning. A 40% decrease from baseline in symptom score on the Panic Disorder Severity Scale is usually indicative of response to treatment. Achieving a score of 3 or less on the Panic Disorder Severity Scale is considered treatment remission.

Continuation and Maintenance of Pharmacotherapy

After an adequate clinical response has been achieved, pharmacological treatment for both GAD and panic disorder should be continued for 12 months to minimize risk of relapse. After 12 months of continued treatment, the patient and clinician should decide if and when to initiate appropriate tapering of medication. For the subset of patients who experience frequent relapse, lifelong maintenance treatment should be considered. Clinical judgment must be used to determine the appropriateness of long-term maintenance treatment.

Medication Discontinuation

Several pharmacotherapeutic treatments used in managing GAD and panic disorder require tapering of the dose or extension of daily schedules on treatment discontinuation. Physical symptoms may present on abrupt discontinuation of many antidepressant drugs, which is often referred to as the antidepressant discontinuation syndrome. Onset of symptoms of the syndrome occur within 1–3 days of discontinuation and may include flu-like symptoms, malaise, headache, dizziness, gastrointestinal upset, transient changes in mood, appetite disturbance, sleep changes, shock-like sensation in the extremities, vivid dreams, nightmares, and complaints of poor concentration. Drugs with shorter half-lives have been reported to have higher rates of occurrence of the syndrome upon treatment discontinuation. If left untreated, the discontinuation syndrome generally lasts for 1–4 weeks. Management strategies include slow tapering of the antidepressant drug at a rate of 10%–25% per week over 4–8 weeks. If intolerable symptoms occur following a decrease in the dose or on discontinuing treatment, the clinician can consider resuming the previously prescribed dose; then lengthening intervals of dose reduction to every other week or decreasing the percentage of dose reduction at each interval.

Abrupt discontinuation of BZDs can elicit several adverse outcomes, including physical withdrawal, relapse of illness, or rebound symptoms. Relapse is described as the gradual return of the original symptoms, whereas rebound is the experiencing of original symptoms at a level more severe than baseline. Physical withdrawal symptoms may also occur with discontinuation of BZDs and include nausea, vomiting, restlessness, insomnia, tremor, incoordination, sweating, and blurred vision. Withdrawal may occur in patients who take prescribed doses of BZDs

for 4 months or more. Switching to an equivalent dose of a long-acting BZD, if patients are not already taking a long-acting drug, and tapering the dose in an extended fashion over 3–4 months can help prevent and minimize symptoms of physical withdrawal and adverse outcomes. Tapering can be accomplished by decreasing the dose by 10%–25% every 7–14 days until half of the original dose is reached. At that point, the remaining dose can be decreased every 4–6 days over the course of 4–8 weeks, as tolerated by the patient.

Annotated Bibliography

1. Stahl SM, Gergel I, Li D. Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003;64:1322–7.

This randomized, double-blind, placebo-controlled, flexible-dose trial, which was funded by Forest Laboratories, compared the efficacy and safety of escitalopram and citalopram in 366 outpatients with panic disorder with or without agoraphobia over 10 weeks. A single-blind, 2-week placebo lead-in period preceded the double-blind treatment phase. Doses up to 20 mg of escitalopram and 40 mg of citalopram were used in the study, which could be decreased for intolerable adverse events. Patients with bipolar disorder, schizophrenia, obsessive-compulsive disorder, substance abuse, or psychotic disorders were excluded. The only psychotropic drug allowed was zolpidem, as needed for sleep. The primary outcome measure was panic attack frequency at week 10. Secondary assessments included the Panic and Agoraphobia Scale, Clinical Global Impressions-Severity Scale, Clinical Global Impressions-Improvement Scale, HAM-A, as well as global and quality of life assessments. A total of 250 patients completed the study, with most discontinuing due to adverse events. The mean daily dose was 10.8 mg of escitalopram and 21.3 mg of citalopram. There was a statistically significant decrease in panic attack frequency for the escitalopram group versus the placebo group. The proportion of patients with 0 panic attacks at study end point was greater for the escitalopram group versus placebo, but the difference was not statistically significant ($p=0.051$). The citalopram group was not statistically different from the placebo group on either measure. Other efficacy measures were statistically significantly improved at end point for the escitalopram group relative to placebo. The citalopram group experienced improvement similar to the escitalopram group on all measures other than panic attack frequency. Adverse events were similar for escitalopram-treated and citalopram-treated groups. One criticism of the study is that patients had a low mean baseline HAM-A score (16) compared with similar studies, which may have contributed to the high placebo response rate in this study. The high placebo response rate could have contributed to the differences noted in panic attack frequency between the escitalopram and citalopram groups.

2. Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. *J Psychopharmacol* 2003;17:276–82.

The use of combined SSRIs with short-term BZDs is one treatment strategy to help increase initial treatment compliance and to alleviate symptoms of panic disorder while antidepressant therapy has a chance to work. This

randomized, placebo-controlled, double-blind study investigated the use of paroxetine with and without clonazepam for treating panic disorder over the course of 12 weeks to discern whether there was any treatment benefit to continued use of BZDs combined with paroxetine. This study included 60 patients, and the treatment period was 12 weeks. Paroxetine was titrated to 40 mg/day by week 4 in all three treatment arms. In one of the arms, clonazepam was titrated to 2 mg/day in the same timeframe and the dose maintained for 12 weeks. In a second arm, paroxetine 40 mg was combined with clonazepam, titrated to 2 mg/day by week 4, and then tapered off over the following 3 weeks. The third treatment arm was given paroxetine 40 mg/day and placebo. There was a significant improvement in the combined paroxetine/clonazepam groups compared with paroxetine monotherapy beginning at week 1 and continuing through week 5. However, after week 5, there were no significant differences in efficacy between the three treatment groups, suggesting no additional benefit beyond 4 weeks of combining BZDs with antidepressants in treating panic disorder.

3. Pollack MH, Roy-Byrne PP, Van Ameringen M, Snyder H, Brown C, Ondrasik J, et al. The selective GABA reuptake inhibitor tiagabine for the treatment of generalized anxiety disorder: results of a placebo-controlled study. *J Clin Psychiatry* 2005;66:1401–8.

This study, funded by Cephalon Pharmaceuticals, evaluated the efficacy and safety of tiagabine in an 8-week study in adults with GAD. Two hundred sixty-six patients were randomized to a flexible dose of tiagabine or matching placebo. Tiagabine was initiated at 4 mg to a maximum dose of 16 mg/day until week 6. After week 6, the doses were fixed until week 8. Dose reductions were permitted for intolerable adverse events. Patients with bipolar disorder, obsessive compulsive disorder, psychotic disorder, mental retardation, or antisocial personality disorder were excluded from the study. Concomitant psychotropic medications were not allowed. Efficacy and global status were assessed using the change from baseline in HAM-A, Hospital Anxiety and Depression Scale, Clinical Global Impressions-Severity Scale, and Clinical Global Impressions-Improvement Scale at weeks 1, 4, 6, and 8. Safety and tolerability assessments, including the Montgomery Asberg Depression Rating Scale, were also performed at weeks 1, 4, 6, and 8. At study end point, the reduction from baseline in HAM-A score was not statistically significantly different between groups (last observation carried forward); however, the reduction in total HAM-A score from baseline for study completers at week 8 was statistically significant. Tiagabine had a statistically significant reduction in HAM-A scores from baseline to week 1 compared with placebo. Tiagabine was well tolerated and did not appear to adversely affect sexual functioning or mood. Dizziness (34%), headache (30%), and nausea (22%) were the adverse effects most commonly associated with tiagabine treatment. The authors speculated that the discrepancy in results between the analysis of completers and intent-to-treat analysis was due to a greater number of early discontinuations in the tiagabine group compared with the placebo group. Rapid escalation of dosing in the tiagabine group may have further contributed to adverse effects, including dizziness and fatigue, which then lead to the early study discontinuation. Seizure incidence was not reported from either the treatment period or the treatment discontinuation period. Further studies are under way to

assess the clinical efficacy and tolerability of tiagabine for treating GAD.

- Mitte K, Noack P, Steil R, Hautzinger M. A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol* 2005;25:141–50.

Previous meta-analysis including a small number of trials reported the superiority of antidepressant drugs compared with placebo in treating GAD, with similar tolerability between classes of antidepressant drugs. This meta-analysis, however, included results from 48 studies using primarily non-antidepressant anxiolytic therapies, including BZDs and azapirones. Methodological characteristics, including sample size and use of placebo run-in were considered in the computations. Efforts were made to control for the inflation of effect size found in smaller, positive studies. No differences in short-term efficacy between the two drug classes were found in this analysis, but differences in compliance were noted. Mean dropout rate was used as a proxy for compliance in this analysis. A mean dropout rate of 20.5% was associated with BZDs and patients given azapirones had a mean dropout rate of 30.7%. Inclusion of a placebo run-in period did not appear to increase the difference in efficacy between active drug treatment and placebo. Azapirones and BZDs appear to have similar efficacy, but BZDs may have a slight advantage in tolerability.

- Ball SG, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: a double-blind, prospective comparison between paroxetine and sertraline. *J Clin Psychiatry* 2005;66:94–9.

This randomized, double-blind, parallel-group, flexible-dose study, which was supported by an educational grant from Pfizer, compared the efficacy and safety of paroxetine and sertraline in 55 patients with GAD. Patients were assigned to treatment with sertraline 25 mg, titrated to a maximum of 100 mg/day, or paroxetine 10 mg titrated to a maximum of 40 mg/day over the first 4 weeks. Subjects were required to receive at least 50 mg of sertraline or 20 mg of paroxetine to remain in the study. After week 4, the dosages were fixed until week 8. Concomitant depressive disorder and anxiety disorder were allowed as long as GAD was determined to be the primary Axis I diagnosis by the screener and principal investigator. Concomitant psychotropic medications were not allowed. Primary outcome measures were response (50% decrease in HAM-A score from baseline to end point) or remission (Clinical Global Impressions-Severity Scale score of 1 or “normal” at end point or a HAM-A score less than 7). The Indiana University Generalized Anxiety Measurement Scale, Beck Anxiety Inventory, and Quality of Life and Satisfaction Questionnaire were secondary outcome measures. Of 55 patients, 78% completed the trial, with most discontinuing the trial because of adverse events. Both treatment groups experienced significant reductions in HAM-A scores from baseline to end point. There were no significant differences between groups with regard to treatment response or remission rates, even when analyses were performed only for those who finished the 8-week trial. There were no differences between the groups for secondary outcome measures. Critiques of the study included a small sample size, no placebo control group, and no placebo washout period. Overall, paroxetine and sertraline appear to have similar efficacy for managing GAD.

- Simon NM, Hoge EA, Fischmann D, Worthington JJ, Christian KM, Kinrys G, et al. An open-label trial of

risperidone augmentation for refractory anxiety disorders. *J Clin Psychiatry* 2006;67:381–5.

An increasing number of research studies in recent years have focused on treatment-refractory panic disorder. Attempts to find pharmacological drugs that may be useful in augmenting adequate and maximized initial treatments have included use of various classes of agents, including atypical antipsychotic drugs. Most information currently available involves open-label or small randomized, controlled studies with the atypical antipsychotic drugs ziprasidone, olanzapine, aripiprazole, quetiapine, and risperidone. This open-label trial included 30 patients with a primary diagnosis of panic disorder, GAD, or social anxiety disorder. Enrolled subjects had to fail at least one trial with an adequate (as defined in the protocol) or maximally tolerated anxiolytic. Nearly 60% of the study population was maintained on an antidepressant drug and 10% on a BZD. Risperidone at an average dose of 1.12 mg/day for 8 weeks was associated with an average decrease of 6.8 points on the HAM-A in patients with GAD (average score at baseline was 25.1 points) and an average decrease of 5.0 points on the Panic Disorder Severity Scale in patients with panic disorder (average baseline score of 16.4 points). Clinical improvement with low-dose atypical antipsychotic drug augmentation may result from mechanistic effects on 5-HT_{1A} or 5HT₂ receptors; however, clear conclusions cannot be drawn from results of small open-label trials.

- Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord* 2005;88:27–45.

This meta-analysis was performed to determine the efficacy of pharmacological and psychotherapeutic treatments for panic disorder. This was a third meta-analysis that reported comparisons of pharmacological treatments in panic disorder, but specifically compared the efficacy of the SSRIs, TCAs, and BZDs. No differences in efficacy were found between the three treatment classes (effect sizes for SSRIs = 0.41, TCAs = 0.41, BZDs = 0.40). Study dropout, which was used as a proxy for treatment tolerability, was not different among the drug classes (SSRIs = 23.1%, TCAs = 23.5%, BZDs = 17%). These findings were similar to previous meta-analytic studies of these pharmacotherapies in treating panic disorder. This meta-analysis also reported analyses to compare different psychotherapeutic modalities to each other, psychotherapeutic modalities to pharmacotherapy, and the psychotherapeutic modalities to the combination of pharmacotherapy and psychotherapy. Psychotherapy was at least as effective as pharmacological treatment and more effective than placebo.

- Pollack MH, Lepola U, Koponen H, Simon NM, Worthington JJ, Emilien G, et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. *Depress Anxiety* 2007;24:1–14.

Current literature is lacking studies comparing different classes of antidepressant drugs in the treatment of panic disorder. This study enrolled 664 adults with DSM-IV-diagnosed panic disorder and randomly assigned subjects to daily venlafaxine XR 75 mg, venlafaxine XR 150 mg, paroxetine 40 mg, or placebo for 12 weeks. Primary assessment included the Panic and Anticipatory Anxiety Scale, used to determine the percentage of patients free from panic attacks at study end point. Eligible patients were treated in outpatient settings and did not have a comorbid major depressive disorder. Severity of illness at baseline for the

study population was on average rated moderately ill using the Clinical Global Impressions-Severity Scale. No significant baseline differences were reported between the four treatment arms. All three active treatment groups were statistically improved on the primary outcome measure as compared to placebo at the end of the 12-week treatment period. These differences were statistically significant, despite a high placebo response. A 2-week, placebo run-in phase had been instituted before the beginning of the active treatment period in an effort to control for placebo response. No significant differences were found in primary treatment outcome between the venlafaxine XR 75 mg, venlafaxine XR 150 mg, and paroxetine 40 mg treatment arms, and the percentage of subjects free from full-symptom panic attacks at study end point ranged from 54.4% to 60.9%. Adverse event profiles were mild and similar for all the treatment groups. The study results imply similar efficacy and tolerability of venlafaxine XR and paroxetine in treating panic disorder.

statistically more efficacious than placebo at week 4 on all primary and secondary outcome measures. Sertraline treatment was also associated with a significantly higher response rate (defined as Clinical Global Impressions-Improvement Scale score of 2 or less) than placebo from week 4 to study end point. A higher percentage of patients in the sertraline group achieved remission (HAM-A score of 7 or less) than placebo at week 12. Improvement with sertraline was also associated with an increase in quality of life and functional outcomes when compared with placebo. The mean dose of sertraline was 95.1 mg/day at study end point.

9. Gambi F, De Berardis D, Campanella D, Carano A, Sepede G, Salini G, et al. Mirtazapine treatment of generalized anxiety disorder: a fixed dose, open label study. *J Psychopharmacol* 2005;19:483–7.

This study was designed to evaluate the use of mirtazapine in the treatment of GAD. Mirtazapine offers a unique mechanism of action, different from traditional, approved treatment options for GAD. It acts as an inhibitor of noradrenergic α_2 -autoreceptors and α_2 -heteroreceptors, thereby leading to enhanced noradrenergic and serotonergic transmission. This study was internally funded by study investigators. Patients in this study (n=44) were treated in an open-label fashion with fixed-dose mirtazapine (30 mg/day) for 12 weeks. Efficacy was measured using changes in score on the HAM-A. Response was defined as a reduction of 50% or more on the HAM-A, and remission was a score of 7 or less on the scale at end point. The mean HAM-A at baseline was 26.4. Using an intent-to-treat analysis, the authors reported that nearly 80% of study participants met criteria for response at the end of the treatment period, and nearly 33% achieved remission. Mirtazapine was reported as well-tolerated, with weight gain (25%) and drowsiness (20%) being the most commonly reported adverse events. The study results suggest the efficacy of mirtazapine in treating GAD and support further investigation using controlled design to corroborate these findings.

10. Allgulander C, Dahl AA, Austin C, Morris PL, Sogaard JA, Fayyad R, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 2004;161:1642–9.

This is a randomized, double-blind, placebo-controlled, 12-week trial of sertraline in 387 patients with GAD. Patients completed a 1-week placebo lead-in period before randomization to either sertraline or placebo. Sertraline was flexibly dosed throughout the 12-week study, which was funded by Pfizer, Inc. Psychotropic drugs other than zolpidem, zopiclone, or chloral hydrate were not permitted. The primary efficacy measure was the change in the HAM-A at weeks 1, 2, 4, 6, 8, and 12. Secondary outcomes included score changes in the Montgomery-Åsberg Depression Rating Scale, Clinical Global Impressions-Severity Scale, Clinical Global Impressions-Improvement Scale, Hospital Anxiety and Depression Scale, as well as global and quality of life assessments. A total of 286 patients completed the study; 14% reported a previous diagnosis of depression. Sertraline was