Chapter 13
Psychopharmacology of Anxiety Disorders

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Introduction

Anxiety disorders are frequent conditions associated with significant distress and dysfunction. In this chapter, we will start by briefly reviewing how we currently understand the neurobiological underpinnings of anxiety disorders. We will then go on to discuss some general principles which are useful for treating anxiety disorders with psychotropic medications. Finally, the remainder of this chapter will review the classes of medications and specific agents indicated for panic disorder (PD), generalized anxiety disorder (GAD), and social anxiety disorder (SAD).

Neurobiology of Anxiety Disorders

The neurocircuitry of anxiety disorders is described in detail in Chap. 2. While our understanding of the underlying neuroanatomy and brain circuitry involved in various anxiety disorders has expanded over the years, much remains to be elucidated. Much of this understanding has been gained through behavioral models in animals and functional neuroimaging studies that correlate the metabolic activity of areas of the brain to the activation of specific emotional and cognitive pathways. One of the main hypotheses to explain the disrupted brain activity in anxiety disorders (espe-

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cially PD and SAD, but also GAD) suggests dysregulation in the "fear circuit," where there is an imbalance of signaling between an overactive limbic system and underactive frontal cortical areas [47].

Dysfunction or dysregulation of certain central neurotransmitter systems including serotonin, norepinephrine, and gamma aminobutyric acid (GABA) has been suggested to underlie the pathophysiology of anxiety disorders [12, 19, 34, 41, 59] and may thus explain how different pharmacologic agents are efficacious in reducing anxiety symptom severity. A number of studies suggest that dysfunction of the serotoninergic system may be associated with anxiety disorders [22, 43]. For example, one study discovered a relative decrease in density of paroxetine binding sites on platelets (a proxy for density of serotonin transporters and thus serotonergic transmission) in patients with anxiety disorders relative to normal controls. Similarly, research suggests a potential role of norepinephrine in anxiety disorders. An early study reported that the stimulation of the locus coeruleus, a small region dense in norepinephrinergic neurons, may increase anxiety [42]. Further, other research reported abnormalities in central pre- and postsynaptic alpha-2 adrenergic receptors in individuals with anxiety disorders [1]. Finally, dysfunction in the inhibitory GABA system might also be implicated in the pathophysiology of anxiety disorders. A high density of GABA receptors in brain regions relevant for fear and anxiety such as the amygdala and hippocampus have thus been reported [10]. Selective serotonin reuptake inhibitor antidepressants (SSRIs) are believed to exert their anxiolytic action through modulation of the serotonin system, while monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCA), and serotonin and norepinephrine reuptake inhibitors (SNRIs) are thought to exert their anxiolytic action through modulation of both the serotonin and the norepinephrine system. Benzodiazepines are believed to have an immediate action on GABA receptors.

General Principles of Pharmacotherapy Approaches to Anxiety Disorders

First-line pharmacologic treatment for all anxiety disorders are antidepressants, including SSRIs and SNRIs, as well as less commonly used but comparably effective TCAs and MAOIs. When prescribing an antidepressant medication for anxiety, it is important to let the patient know that 4–8 weeks of treatment are typically needed to see the full effect of any given dose. Partial responses may be seen earlier but typically on the order of weeks, not days. Furthermore, because patients with anxiety disorders tend to experience increased perceived side effects to medications and frequent somatic symptoms, they may be particularly sensitive to the initiation side effects. There is thus some evidence that patients with PD and GAD may be more attuned to physiological changes (elevated anxiety sensitivity) [30] and thus perceive subtle changes in their bodies in response to medication more intensely and adversely. For this reason, the recommended titration schedules for patients with increased anxiety sensitivity [2, 5, 8], including those with full-blown or subthreshold PD, generally start lower (i.e., half dose) and proceed more slowly upward

compared to treating depression [27]. For instance, whereas the starting dose of sertraline may be 50 mg daily for depression, patients with anxiety usually benefit from starting at 25 mg. Although common in practice, the foregoing management has not been systematically studied [50]. Finally, treatment response and remission may also require higher doses compared to those used for treating depression.

When a patient completes an adequate therapeutic trial of a first-line agent with only an absent to partial response, no consensus algorithm exists to guide the next steps in pharmacologic treatment. Therapeutic options after one or multiple failed trials with SSRIs/SNRIs include adding an adjunctive treatment, switching to another SSRI/SNRI or switching to another class such as a TCA or an MAOI (Table 13.1).

Table 13.1 FDA-approved medications for anxiety disorders

Medication (brand) No generic available	Available PO dosage forms	Starting dosage (mg/day)	Target dose range (mg)	FDA-approved indications	Specific notes
Selective serotonin reuptake inhibitors					
Escitalopram (Lexapro)	5, 10, 20 mg tablets; 5 mg/5 ml solution	5–10	10–30	*GAD*	Few drug interactions
Sertraline (Zoloft)	25, 50, 100 mg tablets	25	50–200	*PD*, *SAD*, *PTSD*	Few drug interactions
Fluoxetine (Prozac)	10, 20, 40 mg capsules; 10, 20, 60 mg tablets; 90 mg weekly delayed-release capsules (equivalent to 20 mg/d); 20 mg/5 mL solution	10	20–80	*PD*	Very long elimination half-life CYP2D6 strong inhibitor Least weight gain Anecdotally more often activating
Paroxetine (Paxil)	10, 20, 30, 40 mg tablets; 7.5 mg capsules; 10 mg/5 mL solution	10	20–60	*PD*, *GAD*, *SAD*, *PTSD*	Anticholinergic and antihistaminergic side effects: sedation, dry mouth, weight gain Strong CYP2D6 inhibitor Difficult discontinuation – taper slowly
Paroxetine CR (Paxil CR)	12.5, 25, 37.5 mg tablets	12.5	25–75	*PD*, *GAD*, *SAD*, *PTSD*	Same as paroxetine

(continued)

Table 13.1 (continued)

Medication (brand) No generic available	Available PO dosage forms	Starting dosage (mg/day)	Target dose range (mg)	FDA-approved indications	Specific notes
Fluvoxamine (Luvox)	25, 50, 100 mg tablets; 100, 150 mg ER capsules	25	100–300	*SAD*	Many drug interactions CYP1A2 strong inhibitor – inhibits own metabolism, increases serum levels of clozapine, caffeine
SNRIs					
Venlafaxine XR (Effexor XR)	37.5, 75, 150 mg capsules; 37.5, 75, 150, 225 mg ER tablets (generic only, not FDA approved)	37.5	75–300	*PD*, *GAD*, *SAD*	Monitor BP for patients at doses ≥225 mg/day Difficult discontinuation – taper slowly
Duloxetine (Cymbalta)	20, 30, 40, 60 mg delayed-release capsules	20	30–90	*GAD*	FDA-approved for fibromyalgia and chronic pain
Azapirones					
Buspirone (Buspar)	5, 7.5, 10, 15, 30 mg tablets	5 BID – TID	10–20 BID – TID	*GAD*	No efficacy as monotherapy except in GAD
Benzodiazepines					
Lorazepam (Ativan)	0.5, 1, 2 mg tabs; 2 mg/1 mL solution	0.5 QD – TID	0.5–2 QD – TID	*"Anxiety disorders"*	
Clonazepam (Klonopin)	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5, 1, 2 mg ODT	0.25–0.5 BID	0.5–1 BID (max 4 daily)	*PD*	No proven increase efficacy advantage but increased side effects at doses >2 mg/day

Notes: The SSRI citalopram do not have FDA approval for any anxiety disorders but some efficacy data exist.

Specific Medications and Drug Classes Used in the Treatment of Anxiety Disorders

Selective Serotonin Reuptake Inhibitor (SSRIs) and Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

SSRIs and SNRIs are favored as first-line medications based on their broad spectrum of efficacy that can target multiple anxiety disorders as well as depression at the same time, their favorable side effect profile compared to older antidepressants, and a lack of risk of abuse and dependence compared to the benzodiazepines [4].

SSRIs and SNRIs are generally well tolerated, and severe adverse events are exceedingly rare. The common side effects of SSRIS/SNRIs are best separated into short-term adverse effects, which present on initiation and with dose increases, and usually remit within 1–3 weeks on a steady dose, and long-term adverse effects, which become evident weeks to months into treatment and do not fade over time. The most common short-term adverse effects are gastrointestinal, including dyspepsia, nausea, and loose stools. Patients may also experience activating side effects, which include motor restlessness, temporarily increased anxiety symptoms, and insomnia. Other typical short-term adverse effects include drowsiness and headaches.

The most common (and problematic) of the persistent adverse effects of antidepressants is sexual dysfunction. This can include diminished sexual desire and delay in or inability to achieve orgasm in both sexes, as well as erectile dysfunction in men. When sexual side effects emerge, they can have a major impact on patients' quality of life, medication adherence, and ability to tolerate an adequate dose for remission of symptoms [44]. Their prevalence is likely underestimated due to underreporting but has been estimated to range from 30% to 75% for SSRIs and SNRIs [14, 25, 26]. The usual strategies for managing adverse sexual effects include dose reduction, switching to a different SSRI/SNRI, or adding another drug to counteract the sexual dysfunction (although insufficient evidence is available to support any of the many drugs used as augmenting agents for sexual dysfunction) [55].

Another important sustained adverse effect of SSRIs is increased bleeding risk, which is imparted by the role of serotonin in inhibiting platelet aggregation. This is usually of minimal significance but may lead to clinically increased risk of bleeding if patients are simultaneously prescribed SSRIs/SNRIs with antiplatelet drugs such as aspirin and clopidogrel, or anticoagulants such as warfarin or the direct oral anticoagulants rivaroxaban, apixaban, and dabigatran.

Hyponatremia has been reported in association with SSRIs/SNRIs, usually caused by pathologic release of antidiuretic hormone from the hypothalamus, which leads to free water retention and dilution of serum sodium levels. The most feared of adverse effects is serotonin syndrome, which can occur if these drugs are coprescribed with other medications that act on serotonin receptors or increase levels of serotonin in the brain and body (i.e., other antidepressants, especially MAOIs,

certain antibiotics such as linezolid, pain medications such as tramadol and meperidine, illicit drugs such as MDMA and cocaine, and some herbal remedies such as St. John's wort). Serotonin syndrome is a clinical syndrome that falls along a spectrum of severity, but in its most recognizable and fulminant form, it may include some or all of high fever and altered mental status which may include agitation, sweating, tremor, hyperreflexia and clonus, myoclonus, dilated pupils, and diarrhea. The main treatment is promptly recognizing and removing all serotonin-modulating agents.

One of the most controversial "side effects" of the use of SSRIs is the association that has been observed between SSRIs and a slight increased incidence of suicidal ideation and behavior in younger patients across randomized controlled trials. This has led to the addition of a "black box warning" by the U.S. Food and Drug Administration (FDA) in 2004 regarding increased risk of suicidal ideation and behavior (attempts) with SSRI/SNRI therapy in children and adolescents, which was extended in 2006 to include the population of young adults from 18 to 24 years. A proposed mechanism for the connection with suicidal behavior is that the activating effects of antidepressants precede relief of symptoms of the underlying disorder, leaving patients who have already contemplated suicide or self-harm with more energy and motivation to engage in such action. Reviews in adult populations aged 25 and older have failed to find an increased rate of completed suicides in patients on antidepressants compared to placebo [53]. Consensus opinions on this topic have noted that risk–benefit analysis favors the use of antidepressants, because untreated depression and anxiety place people at higher risk of suicide [17, 48]. However, response to antidepressants in any individual patient is unpredictable, and thus patients should be closely monitored, especially during initiation of treatment.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have demonstrated efficacy in the treatment of PD and were widely used for this indication before the arrival of SSRIs, SNRIs, and benzodiazepines. Imipramine (the prototypical TCA) has the strongest and most randomized controlled trial evidence, but studies have also shown efficacy for clomipramine – possibly superior to imipramine [32] – and preliminary evidence for desipramine [23, 45]. Though they are generally as efficacious as newer antidepressant medications, TCAs are used less often most importantly due to risk of lethality in overdose caused by fatal cardiac arrhythmias and anticholinergic poisoning. Another reason TCAs have fallen out of favor is a broad side effect burden caused by their effects on numerous drug receptors, which includes anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision, tachycardia and cognitive effects), with other side effects including sedation, orthostatic hypotension, weight gain, and cardiac conduction problems. This has led to a high dropout rate of between 30% and 70% in most RCTs [3, 28]. Another factor that has favored newer

medications over TCAs is that the available evidence base supports TCAs in a narrower range of anxiety disorders when compared to SSRIs/SNRIs and benzodiazepines. TCAs have failed to show comparable efficacy to SSRIs/SNRIs for the treatment of SAD. For GAD, imipramine has trials supporting it as comparable in efficacy to both SSRIs and benzodiazepines, but with greater side effect burden than the former and slower onset of effect than the latter.

Monoamine Oxidase Inhibitors

The MAOIs (particularly phenelzine and tranylcypromine) were once considered the treatment of choice for pharmacologic treatment of SAD based on evidence of strong efficacy in randomized controlled trials, until they were overtaken by the SSRIs and SNRIs. Often intolerable side effects and an unfavorable safety profile are the major reasons why MAOIs were largely replaced by SSRIs and SNRIs for treatment of this disorder [9]. Common MAOI side effects include orthostatic hypotension, paresthesia, weight gain, and sexual dysfunction. Unlike those who take newer agents, patients taking MAOIs also need to strictly adhere to dietary restrictions disallowing foods such as aged cheeses and beers which contain tyramine that, in sufficient amounts, can interact with MAOIs and lead to fatal hypertensive crises. Furthermore, drug interactions with MAOIs are a significant safety concern. Taking other drugs that affect serotonin, norepinephrine, and dopamine, or their associated receptors, in conjunction with MAOIs may precipitate serotonin syndrome or dangerous hypertension [57].

Beta Blockers

Beta-adrenergic blockers are a class of medications which are usually prescribed as antihypertensive and heart failure drugs but have also been used off-label as sympatholytic agents to manage short-term anxiety reactions about specific events [20]. Beta-blockers have not been shown to decrease psychological anxiety; however, they can decrease the intensity of physical anxiety manifestations, which might serve to reduce the secondary anxiety about others perceiving and judging physical signs of nervousness. As such they have been used for performance anxiety [13]. The usual agent is propranolol 10–40 mg given 30 minutes to 1 hour before the performance situation. A reasonable approach for finding the right dose is measuring resting heart rate at the time of peak effect (~1 hour) and titrating the dose to a resting heart rate of roughly 60 beats per minute. Higher doses have been studied but have been associated with greater incidence of adverse effects. The duration of effect is short, on the order of a few hours. Atenolol has also been demonstrated to be helpful for this purpose but is used less commonly. Propranolol has a theoretical benefit of readily crossing the blood–brain barrier, although its anxiolytic effect is

thought to be mostly mediated by its peripheral sympathetic nervous system blocking effects. Adverse effects may include lightheadedness, bradycardia, and hypotension. Caution should be used for patients with significant obstructive lung disease (asthma or chronic obstructive pulmonary disease), as blockade of the beta-2 receptor causes bronchoconstriction.

Benzodiazepines

Benzodiazepines are a very effective class of medications for treatment of the immediate symptoms of anxiety and, in select cases, for long-term suppression of panic attacks and management of the symptoms of SAD and GAD. These medications continue to be widely prescribed, although over the last several decades considerable controversy has arisen due to concerns about potential for misuse and long-term dependence even among those using them appropriately, long-term cognitive effects, and potential for fatal respiratory depression when used in combination with opioids, alcohol, or other sedating drugs [7, 15].

While an approach that combines medication with cognitive behavioral therapy (CBT; see Chap. 12) may produce the most successful treatment outcomes, overreliance on PRN anxiolytics, particularly fast-acting benzodiazepines, can interfere with engagement and successful unlearning of avoidant behaviors that perpetuate anxiety. Taking a powerful and fast acting anxiety quelling medication can be considered an avoidance behavior, even if it used to enable a person to face an anxiety inducing stimulus, because they will be prevented from feeling the associated anxiety and then extinguishing that same anxiety through repeated exposures. Thus, if used in an inappropriate fashion by a patient who is also engaged in CBT, benzodiazepines may undermine the very mechanism by which the psychotherapy works [35, 36].

In terms of adverse effects, benzodiazepines on their own are generally very well tolerated but can cause sedation, dizziness, gait problems, and cognitive slowing [56]. Tolerance tends to develop to the sedating/hypnotic effects of the drugs, but when used properly their anxiolytic benefits should be sustained, and studies have not demonstrated a consistent pattern of dose escalation over time. However, they can be associated with chemical dependence, meaning when they are stopped or reduced significantly, the patient may notice "rebound" symptoms, including a worsening of underlying anxiety and insomnia. Abrupt cessation of benzodiazepines from high doses can lead to a life-threatening withdrawal syndrome which may include alterations in consciousness or confusion, seizures, and hemodynamic instability [51]. Agents with longer clearance half-lives such as clonazepam and diazepam carry less risk of life-threatening withdrawal than agents with short half-lives such as alprazolam.

Patients who misuse or abuse benzodiazepines usually have abused other substances as well. Thus, they should not be started in anyone with a substantial history of substance abuse.

One of the most common uses of benzodiazepines in anxiety disorders is for short-term relief of anxiety during initiation and titration of an antidepressant. This can be especially useful to counteract the activating effects which often present in patients with anxiety starting SSRI/SNRI therapy, and to temporize anxiety symptoms during the prolonged interval required for the antidepressants to demonstrate a therapeutic effect [18]. There is no consensus on whether benzodiazepines used in this fashion should be given on a standing or as-needed (PRN) basis. Factors favoring standing dosage include more controlled drug exposure throughout the day and less behavioral reinforcement from pill taking. More sparing use of PRN medication poses less risk of physical dependence in longer-term use and would be appropriate especially in the more transitory situational anxiety. In the case of prescribing standing benzodiazepines, a long-acting medication should be used such as clonazepam, which can be dosed twice daily or sometimes daily [39]. In either case, the lowest dose required to achieve a therapeutic effect should be employed, and the length of therapy should be relatively brief (a few weeks to about 2 months), especially if used in a standing fashion or if the patient ends up using PRN meds on a daily or almost daily basis. The benzodiazepine should be tapered over the course of at least a few weeks to avoid rebound anxiety and withdrawal symptoms. The longer a patient has been regularly taking benzodiazepines, the longer the planned taper should be in order to reduce associated discomfort.

In the right patient, long-term/indefinite use of benzodiazepines may indeed be appropriate. For instance, many patients suffer from disabling residual symptoms despite multiple adequate trials of first-line agents (SSRIs/SNRIs) and psychotherapy. Furthermore, since patients with anxiety disorders often require higher doses of antidepressant to fully remit, they may be limited from titrating these drugs to the maximally effective dose by problematic adverse effects such as sexual dysfunction. In these case, relatively low doses of benzodiazepines may help them achieve full remission as an augmenting agent [40, 46].

Other Agents

Buspirone

Buspirone (Buspar) is an agent that has moderate evidence from randomized controlled trials of being helpful for GAD, either as a monotherapy or as an adjunct to other first-line treatments. Although the exact mechanism of buspirone's anxiolytic effect is unclear, it is thought to be mediated by its agonist activity at 5HT-1A receptors as well as mild antagonism at D2 receptors. Advantages to this medication include minimal long-term side effect burden, notably no significant sexual side effects. Like SSRIs/SNRIs, buspirone has a delayed onset of anxiolytic effect. Unlike the antidepressants, buspirone is not effective as a monotherapy for depression, PD, or SAD and has very sparse evidence for its use as an adjunct in these

disorders. Typical effective dosing ranges from 20 to 30 mg total daily but can be as high as 60 mg.

Anticonvulsants

Pregabalin (*Lyrica*) has numerous randomized controlled trials supporting its efficacy in GAD [6] and has an official indication for use in GAD in the European Union, but not in the USA. As with duloxetine, this medication would be a good choice for patients with comorbid chronic pain syndromes such as fibromyalgia. Pregabalin is an anticonvulsant medication categorized as a GABA analog but does not achieve anxiolytic effects via action on GABA receptors. Rather, its proposed mechanism of action is via binding to the alpha-2-delta subunit of voltage-gated calcium channels on neurons in the central nervous system, leading to an overall inhibitory downstream effect. Commonly observed side effects include sedation, dizziness, headache, fatigue, visual changes, dry mouth, weight gain, and peripheral edema. Gabapentin, a drug closely related to pregabalin, is often used for GAD and other anxiety disorders, although there is limited randomized controlled trial data to support its use, except in SAD. The available evidence suggests high doses are needed for efficacy. In a key study showing benefit of gabapentin for SAD, more than 60% of the patients who achieved a positive response took the maximum daily dose of 3600 mg [37]. Pregabalin and gabapentin are C-5-controlled substances regulated by the U.S. Drug Enforcement Administration because of some abuse potential, although the risk is thought to be much lower than for benzodiazepines.

Antipsychotics

The efficacy of antipsychotic agents has also been studied with regard to treating anxiety. The typical antipsychotic trifluoperazine was unique in receiving an FDA indication for the treatment of nonpsychotic anxiety in doses ranging from 2 to 6 mg/day. Thioridazine had significant evidence for use in GAD but was withdrawn from the market worldwide due to excessive risk of cardiac arrhythmias. Quetiapine has numerous trials supporting its efficacy as a monotherapy in GAD, particularly at total daily doses of 150 mg or higher [24, 31]. Quetiapine may prove especially useful in a population with comorbid bipolar disorder and GAD, given the drug's demonstrated antimanic properties and efficacy in the prevention and acute treatment of bipolar depression [16, 54]. Despite abundant evidence of anxiolytic efficacy of neuroleptics, their adoption has been limited by concerns about the development of extrapyramidal symptoms and tardive dyskinesia in the case of first-generation drugs and weight gain and metabolic dysfunction in the case of second-generation drugs. Thus, antipsychotics should be reserved for patients with the most refractory anxiety, and prescribers should extensively counsel patients about the attendant risks and benefits.

Psychopharmacologic Approach to Specific Anxiety Disorders

Panic Disorder

Panic disorder is a syndrome marked by anxiety and pathological avoidance related to recurrent panic attacks, which are short-lived episodes of intense fear accompanied by very uncomfortable physical symptoms. At least some of the panic attacks must have occurred without a specific trigger. Patients may avoid a variety of situations they have mentally associated with the onset of panic attacks, and thus the avoidance may generalize to multiple important domains of life and significantly impair functioning. Treatment is focused first on reducing frequency and severity of panic attacks and, in the longer term, undoing patterns of learned avoidant behavior. Although some patients may attain full remission with psychotherapy with or without medication, for many, PD remains a relapsing–remitting chronic disorder for which the symptomatology varies considerably throughout time. Patients may be able to taper off medications slowly after a period of at least a year of sustained remission on a stable dose, and may maintain remission after cessation of pharmacotherapy. However, for many, indefinite treatment with medications may be needed.

Several SSRIs/SNRIs have FDA indications for panic disorder, including the SSRIs fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil/Paxil CR) and the SNRI venlafaxine (Effexor, extended release formulation only). However, the effectiveness of other agents has been demonstrated in multiple randomized controlled trials, including escitalopram (Lexapro), citalopram (Celexa), and fluvoxamine (Luvox) among the SSRIs. Duloxetine (Cymbalta) has preliminary evidence only at this time [49] but theoretically should be similarly effective given the demonstrated efficacy of the similar SNRI venlafaxine. Prescribing duloxetine for PD would be a reasonable choice in patients with comorbid chronic musculoskeletal pain, diabetic neuropathic pain, or fibromyalgia, as it carries the FDA indication for these conditions. As stated previously, patients with panic disorder are particularly sensitive to the activating effects or "jitteriness" associated with starting and uptitrating antidepressants, so low doses with slower titration are essential. Recommended starting doses per day are about half of those used in depression: 25 mg for sertraline, 10 mg for fluoxetine, 10 mg/12.5 mg for paroxetine/paroxetine CR, 37.5 mg for venlafaxine XR, 5 mg for escitalopram, 10 mg for citalopram, and 50 mg for fluvoxamine. Sometimes patients may even benefit from starting at half of the above doses.

Benzodiazepines are highly effective medications for the short-term treatment of panic attacks and valuable because of their relatively rapid onset of anxiolytic effect compared to antidepressants, as well as their favorable adverse effect profile compared to other second- and third-line agents, such as tricyclic antidepressants and MAOIs. However, as mentioned before, for patients engaged in CBT – which is the psychotherapeutic modality with the strongest evidence base for panic disorder – benzodiazepines may interfere with the essential process of learning that the physi-

ological symptoms of panic are safe. It follows that scheduled dosing is generally preferred in the use of benzodiazepines for panic disorder. Among the benzodiazepines, clonazepam has the most evidence for efficacy in PD. This medication has been shown to be well-tolerated and have sustained efficacy without significant dose escalation with long-term use [21, 33]. The dose may occasionally be given once daily at night or in the morning, but typically twice-daily dosing is best: The typical starting dose is 0.5–1 mg per day of clonazepam, and the studied therapeutic dosing range is 1–4 mg daily, but doses greater than 2 mg have been associated with higher rates of adverse effects. Lorazepam and diazepam have been studied and used to good effect in anxiety disorders including panic disorder, but do not carry specific indications for this use and require more frequent dosing due to their short duration of action (usually TID to QID). Alprazolam (Xanax, Xanax XR) is the other medication with FDA approval specific to PD. Due to its very rapid onset of effect and short duration of action, alprazolam is very effective as an acute abortive agent for panic attacks. However, the aforementioned pharmacokinetic properties can also produce a euphoric effect that is highly reinforcing and more conducive to misuse and abuse. If used on a standing basis, the short half-life and duration of action of alprazolam necessitate dosing it three to four times per day, and treatment may still be complicated by inter-dose anxiety or rebound symptoms. Alprazolam XR (Xanax XR) is an extended-release version of the drug with a smoother onset of action which can be dosed twice or sometimes once a day, similarly to clonazepam. Nevertheless, this medication is infrequently used in clinical practice.

There are number of other second-, third-, and fourth-line agents which have evidence for efficacy in PD, including TCAs, MAOIs, atypical antidepressants, anticonvulsants, and some second-generation antipsychotics (preliminary or mixed evidence), but if these drugs are being considered, the patient should be referred to a board-certified psychiatrist. TCAs, particularly clomipramine and imipramine, have been shown to be quite effective as treatments for panic disorder. Their use is limited by toxicity in overdose (usually secondary to lethal cardiac arrhythmias) even in relatively small amounts and a broad and problematic side effect profile which includes significant sedation, dry mouth, urinary retention, orthostatic hypotension, cardiac effects, and weight gain. Phenelzine, a hydrazine MAOI, has the strongest evidence among this class of drugs for efficacy in PD.

Social Anxiety Disorder

SAD is marked by recurrent disproportionate fear of social situations in which a person anticipates scrutiny from others, leading them to either avoid the distressing situations or to endure them with severe anxiety symptoms.

The pharmacological treatment of SAD aims to reduce anticipatory anxiety and distress, as well as avoidance behavior associated with social interaction and

performance situations. The most effective medications for social anxiety are antidepressants, benzodiazepines, and, in the case of performance-only anxiety, beta-adrenergic blockers. Other medications including anticonvulsants and MAOIs have been studied and shown to be effective in this population, but this chapter will primarily focus only on the aforementioned first-line drugs.

Sertraline, paroxetine (both regular and CR formulations), and venlafaxine carry FDA indications for use in SAD among the first-line treatments of SSRIs and SNRIs. Empirical data also support the use of escitalopram, citalopram, and fluvoxamine for SAD. All of these SSRIs/SNRIs show efficacy in the usual antidepressant ranges of dosing (see Table 13.1). The high-potency benzodiazepines alprazolam and clonazepam are also useful in SAD. However, monotherapy with benzodiazepines on a PRN basis is not advised unless the anxiety is related to only a very circumscribed set of circumstances, and potential cognitive dulling or mild-to-moderate impairment of motor coordination caused by the medication would not interfere with the patient's ability to function safely and effectively in the fear-inducing situation. For reasons stated elsewhere in this chapter, clonazepam is generally a preferred agent among the benzodiazepines, and the usual dosing for SAD is 0.5–1 mg daily in two divided doses. For performance-only-type SAD, beta-blockers have shown to be quite helpful. They are thought to suppress the distressing physical symptoms of anxiety caused by excessive sympathetic nervous system activity, such as palpitations, sweating, and tremor. Pregabalin has been found to be effective in doses ranging from 150 to 600 mg daily in two to three divided doses, although the best balance of efficacy and adverse effects has been demonstrated between 300 and 450 mg daily. Some data suggest that pregabalin may be efficacious in SAD at a high daily dose of 600 mg/day [38].

Generalized Anxiety Disorder

GAD is characterized by persistent excessive worries and anxiety about multiple aspects of life, accompanied by several autonomic hyperarousal symptoms such as poor sleep, irritability, concentration difficulties, restlessness, easy fatigability, and muscle tension. GAD is frequently comorbid with MDD, especially in women.

As with PD and SAD, the treatment of choice for GAD is SSRIs/SNRIs. Several of these antidepressants have FDA approval in the USA for treatment of GAD. These include SSRIs paroxetine and escitalopram and SNRIs venlafaxine and duloxetine. As with other anxiety disorders, any of the medications in the same class may have treatment benefits for GAD, and the best treatment for any given patient depends on their clinical response to the medications and whether or not they experience problematic idiosyncratic adverse effects. If there are comorbid psychiatric and nonpsychiatric conditions, then it may be helpful to choose a first-line agent that can address both. For instance, because GAD tends to co-occur with somatic syndromes such as chronic pain and fibromyalgia, it would be reasonable to pursue treatment

with duloxetine first, because this drug has FDA approval for these conditions as well. Considerations for dosing and titration of SSRIs/SNRIs are very similar to those for those for PD.

Although it does not have FDA approval for GAD, the relatively new multimodal "SSRI-plus" antidepressant Vilazodone (*Viibryd*) theoretically should be useful and has preliminary evidence of efficacy for GAD. Vilazodone acts both as an SSRI and as a 5HT-1A partial agonist and thus shares properties of both SSRIs and buspirone. A meta-analysis of three randomized controlled trials of Vilazodone showed efficacy for GAD at doses between 20 and 40 mg daily, albeit with a small effect size and nontrivial dropout due to adverse effects [58]. To date, there is insufficient data to establish Vilazodone as a first-line treatment for GAD.

Pregabalin is approved for treatment of GAD in Europe but does not carry FDA approval for this indication in the USA to date. Dosing is similar to that employed for SAD, as discussed in the previous section. Post hoc analysis of several trials also supports efficacy for treating depressive symptoms associated with GAD using pregabalin [52].

In appropriate patients, usually those who have had inadequate responses or intolerable adverse effects to multiple trials of SSRIs/SNRIs and buspirone, maintenance benzodiazepines remain useful as either monotherapy or adjunctive treatment for GAD. There is no evidence for differential efficacy between the various benzodiazepines for GAD, but generally maintenance treatment with longer half-life agents such as clonazepam and diazepam is preferable because these are associated with less pill-taking and reduced risk of inter-dose anxiety. The principles discussed regarding benzodiazepine prescribing in previous sections apply to GAD as well, namely, avoiding prescribing in those with active or recent substance use problems and starting low and titrating to the lowest dose needed for acceptable symptom management.

Conclusions and Future Directions

While a variety of agents are effective for the treatment of anxiety disorders, SSRIs and SNRIs are the consensus first-line medications given their efficacy and tolerability. Although benzodiazepines are effective, rapidly acting, and relatively well tolerated, their lack of efficacy for comorbid depression and concerns about risk of abuse and dependence limits their use. Antipsychotic, anticonvulsant, and adrenergic antagonist agents may play a role in the pharmacological management of anxiety disorders but should not be considered as first-line strategies. Despite the number of treatments available, many patients with anxiety disorders only partially respond despite extensive trials and combinations of medications. Thus, drugs with novel mechanisms of action targeting various brain receptors and neuronal circuits are currently under investigation. A number of studies have examined the efficacy of oxytocin, a neuropeptide involved in affiliation behaviors, to decrease anxiety, with inconclusive data [11]. Finally, recent advances in the understanding of the role of

the endocannabinoid system in emotion regulation have paved the way to preclinical and clinical studies currently underway examining the therapeutic effects of inhibiting fatty acid amide hydrolase (FAAH), an enzyme involved in deactivating this pathway [29]. Clearly, more research examining the role of these stress pathways and neurotransmitter systems is warranted.

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