The Pharmacotherapy of Anxiety Disorders

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KEY POINTS

- A variety of pharmacological agents are effective for the treatment of anxiety disorders.
- The SSRIs and SNRIs are first-line pharmacological agents for the treatment of anxiety disorders.
- Benzodiazepines are effective, rapidly acting and well-tolerated, but are associated with the risk of abuse and dependence, and lack efficacy for co-morbid depression.
- Anticonvulsants, atypical antipsychotics, adrenergic antagonists, and other agents also play role in the treatment of anxiety disorders.
- Many patients remain symptomatic despite standard treatments; this necessitates the creative use of available interventions (alone and in combination), and spurs the development of novel therapeutics.

OVERVIEW

As described elsewhere in this volume (Chapter 32), anxiety disorders are associated with both significant distress and dysfunction. In this chapter we will review the pharmacotherapy of panic disorder with or without co-morbid agoraphobia, generalized anxiety disorder (GAD), and social anxiety disorder (SAD); the treatment of posttraumatic stress disorder (PTSD) is discussed in Chapter 34, and obsessive-compulsive disorder (OCD) is discussed in Chapter 33. Table 41-1 includes dosing information and common side effects associated with the pharmacological agents commonly used for the treatment of anxiety, referred to in the following sections.

PANIC DISORDER AND AGORAPHOBIA

Pharmacotherapy of panic disorder is aimed at preventing panic attacks, diminishing anticipatory and generalized anxiety, reversing phobic avoidance, improving overall function and quality of life, and treating co-morbid conditions (such as depression). As for all anxiety disorders, the goal of pharmacotherapy is to reduce the patient’s distress and impairment to the point of remission, and/or to facilitate their participation, if necessary, in other forms of treatment (such as cognitive-behavioral therapy [CBT]).

Antidepressants

The selective reuptake inhibitors (SSRIs) and serotonin-norepinephrine serotonin reuptake inhibitors (SNRIs) have become first-line agents for the treatment of panic disorder as well as other anxiety disorders because of their broad spectrum of efficacy (including benefit for disorders commonly co-morbid with panic disorder, such as major depression), favorable side-effect profile, and lack of cardiotoxicity. Currently, paroxetine, both the immediate ([Paxil] and controlled-release formulations [Paxil-CR]), sertraline (Zoloft), fluoxetine (Prozac) and extended-release venlafaxine Effexor-XR are Food and Drug Administration (FDA)-approved for the treatment of panic disorder, though other SSRIs including citalopram (Celexa), and escitalopram (Lexapro),1 and fluvoxamine (Luvox)1 have also demonstrated anti-panic efficacy in both open and double-blind trials. A recently introduced SNRI, duloxetine (Cymbalta), has also been reported effective for panic disorder in case reports,3 and in an open-label trial4 though no randomized controlled trials (RCTs) are currently reported.

A recent meta-analysis on 50 clinical trials (yielding over 5,000 participants) confirmed that citalopram, paroxetine, fluoxetine, and venlafaxine were superior to placebo in the treatment of panic disorder.5 Finally, while the majority of data supporting the efficacy of pharmacological agents for panic disorder derive from short-term trials, several long-term studies have also demonstrated sustained efficacy over time.6

Because the SSRI/SNRIs have the potential to cause initial restlessness, insomnia, and increased anxiety, and because panic patients are commonly sensitive to somatic sensations, the starting doses should be low, typically half (or less) of the usual starting dose (e.g., fluoxetine 5 to 10 mg/d, sertraline 25 mg/d, paroxetine 10 mg/d [or 12.5 mg/d of the controlled-release formulation], controlled-release venlafaxine 37.5 mg/d), to minimize the early anxiogenic effect. Doses can usually begin to be raised, after about a week of acclimation, to achieve typical therapeutic levels, with further gradual titration based on clinical response and side effects, although even more gradual upward titration is sometimes necessary in particularly sensitive or somatically-focused individuals. Although the nature of the dose–response relationship for the SSRIs in panic is still being assessed, available data support doses for this indication in the typical antidepressant range, and sometimes higher, i.e., fluoxetine 20 to 40 mg/d, paroxetine 20 to 60 mg/d (25 to 72.5 mg/d of the controlled-release formulation), sertraline 100 to 200 mg/d, citalopram 20 to 60 mg/d, escitalopram 10 to 20 mg/d, fluvoxamine 150 to 250 mg/d, and controlled-release venlafaxine 75 to 225 mg/d (although some patients may respond at lower doses). In some cases of refractory panic, even higher doses may be clinically useful, although additional data examining such dosing is needed.

SSRI and SNRI administration may be associated with adverse effects that include sexual dysfunction, sleep disturbance, weight gain, headache, dose-dependent increases in blood pressure (with venlafaxine), gastrointestinal disturbance, potential risk of bleeding (with anticoagulants, aspirin or NSAIDs), and provocation of increased anxiety (particularly at initiation of therapy) that may make their administration problematic for some individuals.7,8 The SSRIs/SNRIs are usually administered in the morning (though for some individuals, agents such as paroxetine and others may be sedating and better tolerated with bedtime dosing); emergent sleep disruption can usually be managed by the addition of hypnotics. The typical 2–3 week lag in onset of therapeutic efficacy for the SSRI/SNRIs can be problematic for acutely distressed individuals. There is also an FDA class warning for risk of emergent suicidal thoughts and behaviors based on short-term studies that suggests close monitoring is advised for individuals age 24 or younger, with use balancing risk and
### TABLE 41-1A Dosing of selective Serotonin Reuptake Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose (mg/day)</th>
<th>Typical Dose Range (mg/day)</th>
<th>Limitations/Primary Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>10</td>
<td>20–40</td>
<td>Initial jitteriness, GI distress, sedation or insomnia, hypertension (venlafaxine), sexual dysfunction, urinary hesitation (duloxetine), discontinuation syndrome</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>30</td>
<td>60–90</td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>5–10</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10</td>
<td>20–80</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>50</td>
<td>150–300</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10</td>
<td>20–60</td>
<td></td>
</tr>
<tr>
<td>Paroxetine controlled release (Paxil-CR)</td>
<td>12.5</td>
<td>25–75</td>
<td></td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25</td>
<td>50–200</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine extended release (Effexor-XR)</td>
<td>37.5</td>
<td>75–225</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 41-1B Dosing of Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose (mg/day)</th>
<th>Typical Dose Range (mg/day)</th>
<th>Limitations/Primary Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic Antidepressants (TCAs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipramine (e.g., Tofranil)</td>
<td>10–25</td>
<td>100–300</td>
<td>Jitteriness, sedation, dry mouth, weight gain, cardiac conduction effects, orthostasis, variably anticholinergic</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>25</td>
<td>25–250</td>
<td></td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors (MAOIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine (e.g., Nardil)</td>
<td>15–30</td>
<td>45–90</td>
<td>Diet restrictions, hypertensive reactions, serotonin syndrome</td>
</tr>
<tr>
<td>Tranylcypromine (e.g., Parnate)</td>
<td>10</td>
<td>30–60</td>
<td></td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.25 QID</td>
<td>2–8</td>
<td>Sedation, discontinuation difficulties, potential for abuse, psychomotor and memory impairment, interdose rebound anxiety (for shorter-acting agents)</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25 at bedtime</td>
<td>1–5</td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5 TID</td>
<td>3–12</td>
<td></td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>15</td>
<td>30–60</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 41-1C Dosing of Other Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose (mg/day)</th>
<th>Typical Dose Range (mg/day)</th>
<th>Limitations/Primary Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>300</td>
<td>600–6,000</td>
<td>Light-headedness, sedation</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>200</td>
<td>300–600</td>
<td>Light-headedness, sedation</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>25</td>
<td>50–500</td>
<td>GI distress, rash (rare Stevens-Johnson)</td>
</tr>
<tr>
<td>Valproic acid (Valproate)</td>
<td>250</td>
<td>500–2,000</td>
<td>GI distress, sedation, weight gain (rare polycystic ovary disease, hepatotoxicity, pancreatitis)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>15</td>
<td>15–45</td>
<td>Extrapyramidal symptoms, metabolic syndrome, weight gain, sedation, akathisia, prolonged QTc, blood pressure changes, neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>2.5</td>
<td>5–15</td>
<td></td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>25</td>
<td>50–500</td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>0.25</td>
<td>0.5–3</td>
<td></td>
</tr>
<tr>
<td>Trifluoperazine (Stelazine)</td>
<td>2.5</td>
<td>2.5–40</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>20</td>
<td>40–160</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>25</td>
<td>50–100</td>
<td>Bradycardia, depression, hypotension, light-headedness, sedation; monotherapy efficacy limited to performance anxiety</td>
</tr>
<tr>
<td>Propranolol (Inderal)</td>
<td>10–20</td>
<td>10–160</td>
<td></td>
</tr>
<tr>
<td>Other Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buspirone (BuSpar)</td>
<td>5 TIB</td>
<td>15–60/day</td>
<td>Dysphoria; limited efficacy</td>
</tr>
</tbody>
</table>
clinical need. In addition, some data suggesting possibly dose-dependent QTc prolongation with citalopram in those aged 60 and up has led to recommendations to limit dose to 20 mg/day and EKG monitoring in some populations.

Although results from a recent meta-analysis of 50 trials suggest the following increasing order of effectiveness among SSRIs/SNRIs, citalopram, sertraline, paroxetine, fluoxetine, and venlafaxine, for panic symptoms, they found a different order for associated overall anxiety symptoms, and there is no clear evidence of a differential efficacy between agents in the SSRI or SNRI classes to guide selection. On the other hand, potentially relevant differences in their side-effect profiles (e.g., potential for weight gain and discontinuation-related symptomatology), differences in their potential for drug interactions, and the availability of generic formulations may be clinically relevant.10–12

Tricyclic Antidepressants (TCAs)

Imipramine (Tofranil) was the first pharmacological agent shown to be efficacious in panic disorder, and tricyclic antidepressants (TCAs) were typically the first-line, “gold standard” pharmacological agents for panic disorder until they were supplanted by the SSRIs, SNRIs, and benzodiazepines. Numerous, RCTs demonstrate the efficacy of imipramine and clomipramine for panic disorder, with supportive evidence for other TCAs.13,14 There is some evidence that clomipramine may have superior anti-panic properties when compared with the other TCAs, possibly related to its greater potency for serotonin uptake. The efficacy of the TCAs is comparable to that of the newer agents10–12 for panic disorder, but they are now used less frequently due to their greater side-effect burden, including associated anticholinergic effects, orthostasis, weight gain, cardiac conduction delays, and greater lethality in overdose. The side-effect profile of the TCAs is associated with a high drop-out rate (30%–70%) in most studies. The SSIS/SNIRIs appear to have a broader spectrum of efficacy than the TCAs, which are less efficacious for conditions such as SAD19 and, with the exception of the more serotonergic TCA, clomipramine, less effective for OCD. This is of particular importance as both SAD and OCD may present with co-morbid panic disorder.

Similar to recommendations for the use of the SSRIs/SNRIs, treatment with the TCAs should be initiated with lower doses (e.g., 10 mg/d for imipramine) to minimize the “activation syndrome” (including restlessness, jitteriness, palpitations, and increased anxiety) noted upon initiation of treatment. Typical antidepressant doses (e.g., 100–300 mg/d for imipramine) may ultimately be used to control the symptoms of panic disorder. In cases of poor response or intolerability to treatment with standard doses, use of TCA plasma levels, especially for imipramine, nortriptyline (Pamelor), and desipramine (Norpramin), may be informative.

Monoamine Oxidase Inhibitors

Despite their reputation for efficacy, the monoamine oxidase inhibitors (MAOIs) have not been systematically studied in panic disorder as defined by the current nomenclature; there is, however, at least one study pre-dating the use of current diagnostic criteria that likely included panic-disordered patients and reported results consistent with efficacy for the MAOI phenelzine.16 Although clinical lore suggests that MAOIs may be particularly effective for patients with panic disorder refractory to other agents, there is actually no data to address this issue. Because of the need for careful dietary monitoring (including proscriptions against tyramine-containing foods and ingestion of sympathomimetic and other agents) to reduce the risks of hypertensive reactions and serotonin syndrome, the MAOIs are typically used after lack of response to safer and better tolerated agents.7,12 Use of MAOIs is also associated with a side-effect profile that includes insomnia, weight gain, orthostatic hypotension, and sexual disturbance.

Optimal doses for phenelzine range between 60 and 90 mg/d, while doses of tranylcypromine generally range between 30 and 60 mg/d. Though reversible inhibitors of monoamine oxidase (RIMAs) have in general a more benign side-effect profile and lower risk of hypertensive reactions than irreversible MAOIs (such as phenelzine), RCTs of brofaromine and of moclobemide in panic disorder report inconsistent efficacy; neither agent has become available in the US.23–27 A transdermal patch for the MAOI selegiline (that does not require dietary proscriptions at its lowest dose) became available in the US with an indication for treatment of depression; to date, systematic evaluation of its efficacy for panic or other anxiety disorders has not been reported.

Benzodiazepines

Despite guidelines28 for the use of antidepressants as first-line anti-panic agents, benzodiazepines are still commonly prescribed for the treatment of panic disorder.29,30 Two high-potency benzodiazepines, alprazolam (immediate and extended-release forms) and clonazepam, are FDA-approved for panic disorder; however, other benzodiazepines of varying potency, such as diazepam,30,31 adinazolam, and lorazepam,32 at roughly equipotent doses have also demonstrated anti-panic efficacy in RCTs. Benzodiazepines remain widely used for panic and other anxiety disorders, likely due to their effectiveness, tolerability, rapid onset-of-action, and ability to be used on an “as needed” basis for situational anxiety. It should be noted; however, that “as needed” dosing for monotherapy of panic disorder is rarely appropriate, as this strategy generally exposes the patient to the risks associated with benzodiazepine use without the benefit of adequate and sustained dosing to achieve and maintain comprehensive efficacy. Further, from a cognitive-behavioral perspective, “as needed” dosing engenders dependency on the medication as a safety cue and interferes with exposure to and mastery of avoided situations.

Despite their generally favorable tolerability, benzodiazepines may be associated with side effects that include sedation, ataxia, and memory impairment (particularly problematic in the elderly and those with prior cognitive impairment).31,32 Despite concerns that ongoing benzodiazepine administration will result in the development of tolerance (i.e., loss or therapeutic efficacy or dose escalation), available studies of their long-term use suggest that benzodiazepines remain generally effective for panic disorder over time,35–38 and do not lead to reports of significant dose escalation. Of interest, a recent randomized, naturalistic, parallel-group study, found that after 3 years of treatment, individuals receiving clonazepam were slightly better, and reported fewer side effects, than those receiving paroxetine.39,40 However, even after a relatively brief period of regular dosing, rapid discontinuation of benzodiazepines may result in significant withdrawal symptoms (including increased anxiety and agitation); for instance, in one study, over two-thirds of patients with panic disorder, discontinuing alprazolam, experienced a discontinuation syndrome.40 Discontinuation of longer-acting agents (such as clonazepam) may result in fewer and less intense withdrawal symptoms with an abrupt taper. Patients with a high level of sensitivity to somatic sensations may find withdrawal-related symptoms particularly distressing and a slow taper as well as the addition of CBT41 during discontinuation may be helpful to reduce distress associated with benzodiazepine discontinuation. A gradual taper is recommended for all patients treated with daily benzodiazepines for more
than a few weeks, to reduce the likelihood of withdrawal symptoms (including in rare cases, seizures). Though individuals with a predilection for substance abuse are at risk for abuse of benzodiazepines, those without this diathesis do not appear to share this risk. However, benzodiazepines and alcohol may negatively interact in combination, and the concomitant use of benzodiazepines in patients with current co-morbid alcohol abuse or dependence can be problematic (thus further supporting the use of antidepressants as first-line anti-panic agents in this population with co-morbid illness). In addition, given the high rates of co-morbid depression associated with panic disorder, it is worth noting that benzodiazepines are not in general effective for treatment of depression and may in fact induce or intensify depressive symptoms in those with co-morbid depression. A meta-analysis reported that, although benzodiazepines may be as effective as antidepressants on PD symptoms, they might be less so on depressive symptoms.

Although benzodiazepines are commonly prescribed for the treatment of panic disorder, benzodiazepine monotherapy has decreased somewhat. Treatment with a combination of an antidepressant and a benzodiazepine compared to an antidepressant alone results in acceleration of therapeutic effects as early as the first week, although by weeks 4 or 5 of treatment, combined treatment (whether maintained or tapered and discontinued) shows no advantage over monotherapy. Thus, the data suggest that co-administration improves the rapidity of response when co-initiated with antidepressants, but that ongoing use may not be necessary after the initial weeks of antidepressant pharmacotherapy. Recent data suggest some benefit of the augmentation with a benzodiazepine for individuals who remain symptomatic on antidepressant monotherapy.

Other Agents

The data addressing the potential efficacy of buspirone (a relatively weak reuptake inhibitor of norepinephrine [noradrenaline] and dopamine) for the treatment of panic disorder is mixed, with a small study of the immediate-release formulation administered at high doses demonstrating no benefit, but a more recent open-label study employing standard doses of the extended-release formulation suggesting potential benefit. Similarly, there is mixed support for the potential efficacy for panic disorder of another noradrenergic agent, reboxetine (with a meta-analysis reporting that this agent may be ineffective in treating both panic and anxiety symptoms in panic-disordered patients.

There is suggestive evidence from case reports that buspirone (an azapironine 5-HT1A partial agonist) may be useful as an adjunct to antidepressants and benzodiazepines and acutely, although not over the long term, to CBT for panic disorder, but appears ineffective as monotherapy.

Beta-blockers reduce the somatic symptoms of arousal associated with panic and anxiety, but may be more useful as augmentation for incomplete response rather than as initial monotherapy. Pindolol, a beta-blocker with partial antagonist effects at the 5-HT1A receptor, was effective in a small double-blind RCT of patients with panic disorder remaining symptomatic despite initial treatment.

Atypical antipsychotics, including olanzapine, risperidone, and aripiprazole, have demonstrated potential efficacy as monotherapy or as augmentation for the treatment of patients with panic disorder refractory to standard interventions in a number of small, open-label trials or case series. More recently, a randomized, single-blind comparison of low-dose risperidone to paroxetine in the treatment of panic attacks failed to show any significant difference. However, evidence for treatment-emergent weight gain, hyperlipidemia, and diabetes with some of the atypical agents, as well as the lack of large RCTs examining their efficacy and safety in panic disorder to date, do not support the routine first-line use of these agents for panic disorder, but rather consideration for patients whose panic disorder has not sufficiently responded to standard interventions.

On the basis of limited data, some anticonvulsants appear to have a potential role in the treatment of panic disorder, in individuals with co-morbid disorders (such as bipolar disorder and substance abuse), for which the use of antidepressants and benzodiazepines, respectively, are associated with additional risk. Small studies support the potential efficacy of valproic acid, but not carbamazepine for the treatment of panic disorder. Gabapentin did not demonstrate significant benefit compared to placebo for the overall sample of patients with panic disorder in a large RCT, but a post-hoc analysis found efficacy for those with at least moderate panic severity. Another related compound, the alpha, delta calcium channel antagonist pregabalin, has demonstrated utility for GAD, but there are no published reports to date in panic disorder.

GENERALIZED ANXIETY DISORDER

The pharmacotherapy of generalized anxiety disorder (GAD) is aimed at reducing or eliminating excessive and uncontrollable worry, somatic and cognitive symptoms associated with motor tension and autonomic arousal (e.g., muscle tension, restlessness, difficulty concentrating, disturbed sleep, fatigue, and irritability), and common co-morbidities (including depression) that comprise the syndrome. The anxiety characteristic of GAD is typically persistent and pervasive rather than episodic and situational. GAD severity, however, may worsen in response to situational stressors. Thus, while GAD pharmacotherapy is generally chronic, adjustments may be required in response to worsening during prolonged periods of stress.

Antidepressants

Selective serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

As is true for panic and the other anxiety disorders, the SSRIs and SNRIs are generally considered first-line agents for the treatment of GAD because of their favorable side-effect profile compared to older antidepressants (e.g., TCAs), lack of abuse or dependency liability compared to the benzodiazepines, and a broad spectrum of efficacy for common co-morbidities, such as depression. Similar to considerations for their use in individuals with panic disorder, SSRIs, SNRIs, and other antidepressants should be initiated in patients with GAD at half or less than the usual starting dose in order to minimize jitters and anxiety. Currently, the SSRIs paroxetine and escitalopram and the SNRIs (including the extended-release formulation of venlafaxine [Effexor-XR] and duloxetine [Cymbalta]) have received FDA approval for GAD; however, all agents in these classes including sertraline are likely effective for GAD without convincing evidence for significant divergence in efficacy between them, but with some differences in their side-effect profiles. Long-term trials with SSRIs and SNRIs demonstrate that continued treatment for 6 months is associated with significantly decreased rates of relapse relative to those who discontinued the drug following acute treatment: further, ongoing treatment appears associated with continued gains in the quality of improvement as evidenced by a greater proportion of individuals reaching remission over time.
Tricyclic Antidepressants

A number of studies have demonstrated the efficacy of the prototypic TCA imipramine for the treatment of GAD, with RCTs showing generally comparable efficacy but slower speed-of-onset relative to a benzodiazepine comparator,71 and a greater side-effect burden relative to an SSRI comparator.72

Benzodiazepines

Benzodiazepines have been widely used for the treatment of generalized anxiety for close to half a century. Although recent guidelines76 have emphasized the use of antidepressants for the treatment of anxiety states including GAD, particularly in the common scenario in which co-morbid depression is present. Benzodiazepines remain broadly prescribed, either as co-therapy or monotherapy for GAD, because of their ease of use, rapid and generally reliable anxiolytic effect, and relatively favorable side-effect profile.

Given their apparent equivalent efficacy, the selection of an appropriate benzodiazepine should be made by matching the pharmacokinetic properties of the agent with the situational parameters and patient’s clinical profile. Agents that are slowly metabolized and have multiple metabolites (such as diazepam and clorazepoxide) and those with long half-lives (such as clonazepam) may be easier to taper rapidly and are generally associated with fewer intra-dose breakthrough symptoms compared to shorter-acting and more rapidly metabolized agents (such as oxazepam or lorazepam); the latter agents may be better suited for brief intermittent anxiety or individuals likely to be slower metabolizers (e.g., the elderly or those with hepatic disease).77 The regular use of benzodiazepines for more than 2 or 3 weeks may be associated with physiological dependence and the potential for significant withdrawal symptoms with discontinuation. Discontinuation of benzodiazepines is best done with a gradual taper to minimize withdrawal symptoms. For some patients switching from a short-acting to a longer-acting agent (e.g., alprazolam to clonazepam) may facilitate discontinuation, although the available evidence suggests that differences in ease of discontinuation disappear during a slow as opposed to rapid taper. The addition of CBT during the tapering process may facilitate benzodiazepine discontinuation by giving the patient skills for the management of recurrent anxiety and withdrawal, and addressing concerns about their ability to function without benzodiazepines.48 There are few data supporting the utility of augmentation with agents such as anticonvulsants or antidepressants to facilitate discontinuation, although they may prove useful on a case-by-case basis. Moreover, the abuse liability of benzodiazepines may be problematic in individuals predisposed to substance abuse or dependence, although available evidence does not support concerns about dose escalation or therapeutic tolerance for the majority of individuals taking benzodiazepines.88 Pharmacodynamic interactions due to the co-administration of benzodiazepines with alcohol or other sedating agents, however, may be problematic because of the additive potential for CNS depression. In addition, benzodiazepines are less effective than antidepressants in the treatment of anxiety with significant co-morbid depression78 and in fact have the potential to worsen extant depression. Thus, benzodiazepines are not recommended as first-line treatment for GAD.

Buspirone

Buspirone is a 5-HT1A partial agonist belonging to the aza-pirone class that is FDA-approved for use in generalized anxiety, although it has demonstrated somewhat inconsistent effectiveness in clinical practice. However, case reports and small series suggest it may be useful as an adjunct to standard therapies for refractory panic and other anxiety disorders55,79 as well as depression;80 it may also have weak antidepressant effects at higher doses.81 Buspirone has a generally favorable side-effect profile, though a gradual onset of effect; the average therapeutic dose is in the range of 30–60 mg/d, typically administered as twice-a-day dosing. A review of the literature reporting on 36 trials involving aza-pirones, including buspirone, found no evidence for their superiority over antidepressants, and suggest they may be less effective than benzodiazepines.82

Anticonvulsants

The alpha-2 delta calcium channel antagonist pregabalin has received approval for the treatment of GAD in Europe, but not in the US. Pregabalin has demonstrated efficacy in seven large randomized placebo-controlled trials,83 including a number which showed efficacy of pregabalin for co-morbid depressive symptoms44–46 as well as studies showing a similar speed of therapeutic onset (as early as 1 week) to a benzodiazepine comparator.70,84 The typical therapeutic dose range for pregabalin is 300–600 mg/d, with the most common adverse events being somnolence and dizziness. Recent data suggest that while low doses of pregabalin are efficacious, there is additional benefit gained by increasing the dose up to 450 mg per day, but that beyond 450 mg, reduction in anxiety symptoms does not continue to improve. Gabapentin, a related compound, has also been suggested potentially effective for the treatment of GAD, though at the level of case reports rather than RCTs. The selective GABA reuptake inhibitor tiagabine demonstrated efficacy for the treatment of GAD in one randomized, placebo-controlled trial at doses of 4–16 mg/d,88 though a subsequent series of RCTs failed to confirm this initial observation and do not support the routine use of tiagabine as an anxiolytic.85,86

Antipsychotics

Conventional antipsychotics have long been used in clinical practice for the treatment of anxiety; in fact, based on a large placebo-controlled randomized trial of trifluoperazine (2–6 mg/d),89 the agent received an FDA indication for the short-term treatment of non-psychotic anxiety. However, concerns regarding the potential development of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) have limited the use of typical antipsychotics for the treatment of anxiety. More recently a number of atypical antipsychotics including olanzapine,92 risperidone,62–63 aripiprazole, and ziprasidone94 have demonstrated efficacy in RCTs, and case series and reports for the treatment of GAD,92 typically though not exclusively as augmentation in individuals refractory to standard interventions. In addition, five recent RCTs provide strong support for the efficacy of quetiapine (50 mg to 300 mg) monotherapy in the treatment of GAD.91–93 In particular, one of them showed that by day 4 of treatment, quetiapine was associated with significantly greater reduction in anxiety compared to escitalopram, though the difference was not significant by endpoint (week 8).92 In addition, the efficacy of the atypicals as mood stabilizers for bipolar disorder,95 their potential efficacy for refractory depression,96 and lack of abuse potential suggest they may prove useful for individuals with co-morbid anxiety, mood and substance use disorders, particularly those refractory to more standard interventions, though there is currently relatively little systematic data addressing this issue. Decisions regarding the use of the atypicals should involve consideration of their potential for significant adverse effects as well, including sedation, weight gain, and metabolic syndrome.
Other agents

Riluzole

The efficacy of riluzole, an anti-glutamatergic agent, traditionally used in the treatment of amyotrophic lateral sclerosis (ALS) was examined in individuals with GAD, in an 8-week, open-label, fixed-dose study of 100 mg/d. Riluzole appeared to be effective and generally well-tolerated; although its expense makes it unlikely that its use will be widely adopted, the report does suggest a potential role for anti-glutamatergic agents for the treatment of anxiety.

Chamomile

Chamomile as infusion has been commonly used for sleep for decades. Recently, one of its compounds, apigenin, which may have GABA-ergic actions, has been identified as a potential active agent. A small RCT (chamomile 220–1,100 mg, 1.2% apigenin vs. placebo) suggests that chamomile may be useful in the treatment of GAD.

Kava

Similarly, kava roots have been consumed throughout the Pacific Ocean cultures of Polynesia, as a drink with sedative and anesthetic properties. Although earlier reports were inconclusive, a recent RCT provides some support for the efficacy of its active agent kavalactones (120–240 mg) in the treatment of GAD.

SOCIAL ANXIETY DISORDER

The pharmacotherapy of social anxiety disorder (SAD) is aimed at reducing the patient’s anticipatory anxiety prior to and distress during social interaction and performance situations, reducing avoidance of social and performance situations, and improving associated impairments in quality of life and function.

Selective serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

Selective serotonin and SNRIs have become first-line pharmacotherapy for the treatment of SAD because of their greater efficacy for this condition, broad-spectrum effects for other anxiety disorders, efficacy for co-morbid depression in contrast to the benzodiazepines, better tolerability than the TCAs, more favorable safety profile than the monoamine oxidase inhibitors (MAOIs), and lack of abuse potential. Currently, the SSRIs paroxetine and sertraline as well as the SNRI venlafaxine (extended-release) have FDA-approved indications for SAD, though available evidence suggests that other agents from these classes, including fluvoxamine, citalopram, and escitalopram, may be effective. Regarding fluvoxamine, the reported study results have been mixed. Finally, some recent data suggest the efficacy of the SNRI duloxetine for the treatment of SAD as well. A meta-analysis of the efficacy of second-generation antidepressants in SAD suggests that escitalopram, paroxetine, sertraline, and venlafaxine produced significantly more responders than placebo and that there were no differences in terms of efficacy among them.

As noted, individuals with SAD are at increased risk for alcohol and other substance abuse, which may in some cases reflect an attempt to “self medicate” anxiety in social situations. A small, randomized placebo-controlled study in individuals with SAD and active alcohol use disorders suggested that treatment with the SSRI paroxetine decreased the anxiety and may have reduced the alcohol use as well.

Treatment with the SSRIs and SNRIs for SAD is typically initiated at low doses (e.g., paroxetine 10 mg/d, sertraline 25 mg/d, venlafaxine-extended release 37.5 mg/d) and titrated up against therapeutic response and tolerability (e.g., paroxetine 20–60 mg/d, sertraline 50–200 mg/d, and venlafaxine 75–225 mg/d). There is usually a therapeutic lag in efficacy of 2–3 weeks following initiation of SSRI/SNRI therapy for SAD, although full response can occur over weeks to months, particularly when social anxiety-related avoidance is present, and a return to avoided situations should be encouraged alongside pharmacotherapy to both assess and optimize outcomes. Typical treatment-emergent adverse effects include nausea, headache, dizziness, sedation, increased anxiety, and sexual dysfunction.

Beta-blockers

Beta-blockers, including propranolol (Inderal) and atenolol (Tenormin) are effective for the treatment of non-generalized social anxiety (i.e., “performance anxiety”) about public speaking or other performance situations. Beta-blockers blunt the symptoms of physiological arousal associated with anxiety or fear, such as tachycardia and tremor, which are often the focus of an individual’s apprehension in performance situations and lead to an escalating cycle of arousal, agitation, and further elevations in social anxiety. Beta-blockers are effective for the treatment of performance anxiety, at least in part by blocking these physiological symptoms of arousal, interrupting the escalating fear cycle, and thus mitigating the individual’s escalating concern and focus on their anxiety.

Though effective for physiological symptoms of arousal, beta-blockers are not as effective as reducing the emotional and cognitive aspects of social anxiety and thus are not first-line agents for generalized SAD. Results from a double-blind, placebo-controlled study of the beta-blocker atenolol and the MAOI phenelzine found the beta-blocker ineffective for individuals with generalized social anxiety.

Beta-blockers (e.g., propranolol [10–80 mg/d] or atenolol [50–150 mg/d]) are typically administered “as needed” 1–2 hours before a performance situation. The use of beta-blockers may be associated with orthostatic hypotension, lightheadedness, bradycardia, sedation, and nausea. Atenolol is less lipophilic and thus less centrally active than propranolol, and, therefore, may be less sedating. In practice, it is best to administer a “test dose” of the beta-blocker prior to use in an actual performance-related event in order to establish the tolerability of an effective dose and minimize disruptive side effects during a performance that could further increase anxiety.

Monoamine Oxidase Inhibitors

Before they were supplanted by the SSRIs and SNRIs, the MAOIs were the “gold-standard” pharmacological treatment for SAD. Interest in their use in SAD grew in part from initial observations of their efficacy for the atypical subtype of depression characterized in part by marked sensitivity to rejection, and they were subsequently demonstrated effective in RCTs in SAD.

Though clearly effective, the use of MAOIs is associated with troubling side effects including orthostatic hypotension, paresthesias, weight gain, and sexual dysfunction, as well as the need for careful attention to diet and use of concomitant medication because of the risk of potentially fatal hypertensive reactions and serotonin syndrome if the proscriptions are violated. Concerns about the use of MAOIs may have contributed in part to the under-recognition and treatment of SAD that existed until demonstration of the efficacy of the generally safer and easier-to-use SSRIs and SNRIs for this syndrome.
Among the MAOIs, phenelzine has been the best studied for SAD, although tranylcypromine also appears effective. In a study comparing cognitive-behavioral group therapy (CBGT), phenelzine, an educational-supportive group, and a placebo for the treatment of SAD (n=133), 77% of patients taking phenelzine, were responders at 12 weeks compared to 41% of those in the placebo group (p < 0.005). Phenelzine appeared to be more effective than CBGT on some measures during acute treatment, but the psychosocial intervention resulted in better maintenance of benefit after treatment discontinuation.

Phenelzine is typically initiated at 15 mg PO BID, and is less likely than reuptake inhibitors (such as the TCAs, SSRIs, or SNRIs) to exacerbate anxiety during initiation of treatment. The usual therapeutic dose range of phenelzine is 60 to 90 mg/d, with some refractory patients responding to higher doses. Careful attention to adherence to a diet free of tyramine-containing foods and avoidance of sympathomimetic and other serotonergic drugs is important to avoid the risk of hyperensive or serotonergic crisis, and assessment of the ability of an individual patient to maintain these restrictions is a critical component of the risk–benefit analysis of MAOI usage.

Interest in the reversible inhibitors of MAO, (RIMAs) was stimulated by the significant safety concerns attendant to the administration of the irreversible MAOIs, such as phenelzine. Because they can be displaced from MAO when a substrate (such as tyramine) is presented, the RIMAs do not carry with them the need for strict dietary prohibitions and the risk of hypertensive crisis and serotonin syndrome associated with the irreversible MAOIs. Unfortunately, while some clinical trials have reported positive results with RIMAs (such as moclobemide and brofaromine) for SAD, others have not. Further, while moclobemide is available in some countries, it is generally not perceived as effective as standard MAOIs and is not available in the US. There are no systematic data available to date regarding the efficacy of the selegiline transdermal patch for the treatment of SAD.

**Benzodiazepines**

Although benzodiazepines are commonly used for many anxiety disorders (including SAD) there are relatively few systematic data addressing their use for this indication. However, the available data do suggest efficacy for these agents with response noted as soon as early as 2 weeks in non-depressed individuals with SAD. Benzodiazepines may also help enhance response to an antidepressant; results from a randomized, double-blind placebo-controlled study demonstrated that the addition of clonazepam 1–2 mg/d to flexibly dosed paroxetine (20–40 mg/d) resulted in greater improvement than paroxetine alone in generalized SAD.

As noted, benzodiazepines have the advantage of a relatively rapid onset of effect, a favorable side-effect profile, and efficacy on an as-needed basis for situational anxiety. The use of benzodiazepines, however, may be associated with treatment-emergent adverse effects (including sedation, ataxia, and cognitive and psychomotor impairment), as well as the development of physiological dependence with regular use. Further, they are generally not effective for depression that commonly presents as co-morbid with SAD, and may worsen it. Their potential for abuse in those with a diagnosis or a history of alcohol or substance abuse, and their potential negative interaction with concurrent alcohol use, is relevant given the increased rates of alcohol and substance use amongst social phobics. Benzodiazepines are initiated at low dose (e.g., clonazepam 0.25–0.5 mg qHS) to minimize emergent adverse effects (such as sedation) and then titrated up as tolerated to therapeutic doses (e.g., clonazepam 1–4 mg/d or its equivalent).

For maintenance treatment, in order to optimize a continuous anxiolytic effect, longer-acting benzodiazepines (such as clonazepam) are associated with less inter-dose rebound anxiety than shorter-acting agents and are generally preferred, whereas a shorter-acting agent with a more rapid onset of effect (such as alprazolam or lorazepam) may be more appropriate if used on an as-needed basis for performance situations. Mono-therapy with as-needed dosing of benzodiazepines alone is not, however, recommended for “performance only” social anxiety disorder, and as-needed benzodiazepine use may interfere with the reduction of social anxiety and related avoidance with cognitive behavioral treatments.

**Other medications**

Although TCAs are useful for a number of anxiety disorders including panic disorder, PTSD, GAD, and, in the case of clomipramine, OCD, results from open and double-blind placebo-controlled trials suggest they are not effective for the treatment of SAD. Small open trials have suggested the efficacy of bupropion in SAD. Although the noradrenergic and serotonergic antidepressant mirtazapine has been reported to be effective for SAD in open-label studies, as well as in a RCT conducted specifically in women, a recent randomized placebo-controlled trial failed to replicate these results in a sample (n=60) including adults of both genders. Available evidence does not support the use of buspirone as a monotherapy for the treatment of SAD, although one report suggests that it may have a role as an adjunct for patients incompletely responsive to SSRI therapy. Small studies and case series suggest the potential efficacy of atypical antipsychotics, including olanzapine, risperidone, and quetiapine for the treatment of SAD, but their use is generally reserved for patients remaining symptomatic despite more standard interventions. A number of anticonvulsants have demonstrated potential efficacy for the treatment of SAD. Gabapentin, a GABA (alpha-2 delta calcium channel antagonist), demonstrated efficacy for SAD in a double-blind, placebo-controlled, parallel-group trial with doses of ranging from 900 to 3,600 mg daily, with most patients receiving greater than 2,100 mg/d. A related compound, pregabalin, currently indicated for the treatment of neuropathic pain and as adjunctive treatment for partial seizures, also demonstrated efficacy for the treatment of SAD at a dose of 600 mg/d, although the side-effect burden at this higher dose was significant. Valproic acid, an anticonvulsant mood-stabilizer, was reported effective for SAD, in an open trial with flexible dosing of 500–2,500 mg/d. Levetiracetam demonstrated promising potential for the treatment of SAD in open trial, but recent RCT data failed to show any efficacy over placebo. An open-label trial suggests the potential efficacy of topiramate and tiagabine for the treatment of SAD; however, to date, no RCTs have confirmed these findings.

Though the adjunctive use of pindolol, a beta-blocker with 5-HT1A autoreceptor antagonist properties, has in some, but not all, studies accelerated or augmented response to antidepressants for depression, it was ineffective in one placebo-controlled randomized augmentation trial in social phobics. Other medications, such as the pre-synaptic adrenergic agonist clonidine and the 5-HT1A receptor ondansetron, have been reported helpful for social anxiety in case reports, but there are few systematic data following up on these observations.

**CONCLUSIONS AND FUTURE DIRECTIONS**

The increased recognition of the prevalence, early-onset, chronicity, and morbid impact of the anxiety disorders has spurred development efforts to find more effective and better-tolerated pharmacotherapies for this condition. Though the SSRIs/SNRIs...
and benzodiazepines have demonstrated efficacy and favorable tolerability compared to older classes of agents, many patients remain symptomatic despite standard treatment; only a minority remit. In addition to creative uses of available agents alone and in combination, a variety of other pharmacological agents with novel mechanisms of actions, including corticotropin releasing factor (CRF) antagonists, neurokinin (NK)-substance P antagonists, metabolotropic glutamate receptor agonists, GABA-ergic agents and receptor modulators, and compounds with a variety of effects on serotonin, noradrenergic, and dopaminergic receptors and their subtypes are in various stages of development. In addition, specific agents targeting ways to enhance outcomes with cognitive-behavioral therapy for anxiety disorders, such as the NMDA receptor antagonist d-cycloserine, remain an active area of translational research.\textsuperscript{158,159} These efforts may provide more effective and better-tolerated agents for the treatment of anxiety in the future.

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REFERENCES


more gradual upward titration is sometimes necessary in particular sensitive individuals. Although the nature of the dose-response relationship for the SSRIs in panic is still being assessed, doses for this indication are in the typical antidepressant range, and sometimes higher, that is, fluoxetine 20 to 40 mg/day, paroxetine 20 to 60 mg/day (25 to 72.5 mg/day of the controlled-release formulation), sertraline 100 to 200 mg/day, citalopram 20 to 60 mg/day, escitalopram 10 to 20 mg/day, fluvoxamine 150 to 250 mg/day, and controlled-release venlafaxine 75 to 225 mg/day (although some patients may respond at lower doses).

Q2 The answer is: True.

Imipramine (Tofranil) was the first pharmacological agent shown to be efficacious in panic disorder. Until it was supplanted by the SSRIs, SNRIs, and benzodiazepines, the tricyclic antidepressants (TCAs) were typically the first-line, “gold standard” pharmacological agents for panic disorder. Numerous, randomized controlled trials (RCTs) demonstrate the efficacy of imipramine and clomipramine for panic disorder, with supportive evidence for other TCAs. There is some evidence that clomipramine may have superior anti-panic properties when compared with the other TCAs, possibly related to its greater potency for serotonergic uptake. The efficacy of the TCAs is comparable to that of the newer agents for panic disorder, but they are now used less frequently due to their greater side effect burden, including associated anticholinergic effects, orthostasis, weight gain, cardiac conduction delays, and greater lethality in overdose. The side-effect profile of the TCAs is associated with a high dropout rate (30% to 70%) in most studies. The SSRIs/SNRIs appear to have a broader spectrum of efficacy than the TCAs (which are less efficacious for conditions such as social phobia and obsessive-compulsive disorder [OCD]) with the exception of clomipramine, which may present with co-morbid panic disorder.

Similar to recommendations for the use of the SSRIs and SNRIs, treatment with the TCAs should be initiated with lower doses (e.g., 10 mg/day for imipramine) to minimize the “activation syndrome” (involving restlessness, jitteriness, palpitations, and increased anxiety) noted on initiation of treatment. Typical antidepressant doses (e.g., 100 to 300 mg/day for imipramine) may ultimately be used to control the symptoms of panic disorder. In cases of poor response or intolerability to treatment with standard doses, use of TCA plasma levels, especially for imipramine, nortriptyline (Pamelor), and desipramine (Norpramin), may be informative.

Q3 The answer is: False.

Despite their reputation for efficacy, the MAOIs have not been systematically studied in panic disorder as defined by the current nomenclature; there is, however, at least one study providing the use of current diagnostic criteria that likely included panic-disordered patients and reported results consistent with efficacy for the MAOI phenelzine. Although clinical lore suggests that MAOIs may be particularly effective for patients with panic disorder refractory to other agents, there are actually no data to address this issue.

Because of the need for careful dietary monitoring (including proscriptions against tyramine-containing foods and ingestion of sympathomimetic and other agents) to reduce the risks of hypertensive reactions and serotonin syndrome, the MAOIs are typically used after failure with safer and better-tolerated agents. Use of MAOIs is further associated with a side-effect profile that includes insomnia, weight gain, orthostatic hypotension, and sexual disturbance.
Q4 **The answer is: Clonazepam.**

Benzodiazepines remain widely used for panic and other anxiety disorders, likely due to their effectiveness, tolerability, rapid onset of action, and ability to be used on an “as-needed” basis for situational anxiety.

Despite their generally favorable tolerability, benzodiazepine administration is associated with side effects that include sedation, ataxia, and memory impairment (particularly problematic in the elderly and those with prior cognitive impairment). However, even after a relatively brief period of regular dosing, rapid discontinuation of benzodiazepines may result in significant withdrawal symptoms; for instance, over two-thirds of patients with panic disorder who discontinued alprazolam experienced a discontinuation syndrome (involving increased anxiety and agitation). Discontinuation of longer-acting agents (such as clonazepam) may result in fewer and less intense withdrawal symptoms with an abrupt taper. Patients with a high level of sensitivity to somatic sensations may find withdrawal-related symptoms particularly distressing, and a slow taper as well as the addition of cognitive-behavioral therapy (CBT) during discontinuation may be helpful to reduce distress associated with benzodiazepine discontinuation.

A gradual taper is recommended for all patients treated with daily benzodiazepines for more than a few weeks, to reduce the likelihood of withdrawal symptoms, including, in rare cases, seizures.

Q5 **The answer is: Beta-blockers.**

Beta-blockers reduce the somatic symptoms of arousal associated with panic and anxiety, but may be more useful as augmentation for incomplete response rather than as initial monotherapy. Recently, pindolol, a beta-blocker with partial antagonist effects at the 5-HT1A receptor, was effective in a small double-blind randomized controlled trial (RCT) of patients with panic disorder remaining symptomatic despite initial treatment.