The Pharmacologic Treatment of Anxiety Disorders: A Review of Progress

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Anxiety disorders, as a group, are among the most common mental health conditions and frequently cause significant functional impairment. Both psychotherapeutic and pharmacologic techniques are recognized to be effective management strategies. This review provides a discussion of the major classes of psychotropic medications investigated in clinical trials of the following anxiety disorders: panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. Findings suggest that both selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are useful first-line agents for most of the anxiety disorders, particularly given the frequent comorbidity with mood disorders. Highly serotonergic agents are preferred for obsessive-compulsive disorder. Other antidepressants, such as tricyclic antidepressants or monoamine oxidase inhibitors, are generally reserved as second- and third-line strategies due to tolerability issues. Evidence for other agents, including anticonvulsants and atypical antipsychotics, suggests that they may have an adjunctive role to antidepressants in cases of treatment resistance, while azapirones have been used effectively for generalized anxiety disorder, and a substantial body of evidence supports benzodiazepine use in panic disorder and generalized anxiety disorder. Despite notable advances, many patients with anxiety disorders fail to adequately respond to existing pharmacologic treatments. Increased research attention should be focused on systematizing pharmacologic and combined pharmacologic-psychosocial strategies to address treatment resistance and developing novel treatments for anxiety disorders.

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Historically, the anxiety disorders have received relatively little research attention. Recent epidemiologic findings, though, point to their being the commonest class of mental illness[1] and frequently comorbid with other conditions, both medical and psychiatric. As such, there has been increased focus on the need to develop effective treatments, both pharmacologic and psychological, to provide symptom relief.

There are currently 6 primary anxiety disorders identified in the *DSM-IV-R*: panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and specific phobia. With the exception of specific phobia (for which exposure therapy or occasional as-needed benzodiazepine use has been found to be most helpful), both pharmacotherapy and psychological therapies have been used as effective treatments for the other anxiety disorders. Although a discussion of effective psychotherapies for anxiety disorders is beyond the scope of this review, the use of cognitive-behavioral therapy (CBT) is currently the gold standard in this regard.[2–5] Herein, we provide a review of different psychotropic medications used to treat anxiety disorders with an emphasis on evidence derived from randomized controlled trials (RCTs).

TRICYCLIC ANTIDEPRESSANTS

Different classes of psychotropic medications have been investigated for the treatment of anxiety disorders, with the most frequently investigated class being the antidepressants. The oldest among these, the tricyclic antidepressants (TCAs), have been used in psychiatry since the late 1950s. The TCAs, with their 3-ring molecular structure, work by inhibiting both serotonin and norepinephrine reuptake from the synaptic cleft.[6] TCAs have varying levels of evidence to support their use in different anxiety disorders.

In panic disorder, the 2 TCAs that have been most investigated are clomipramine and imipramine. Evidence from several RCTs indicates that either medication is more effective than placebo in the acute treatment of panic disorder[7–13] by reducing the number of panic attacks, decreasing anticipatory anxiety, and in some cases reducing the need for concurrent benzodiazepine use.[14] There is also additional support for the use of maintenance imipramine or clomipramine to decrease the risk of relapse.[15,16] Further, head-to-head comparison with other classes of antidepressants suggests that TCAs are as effective as newer agents such as sertraline and paroxetine[17–19] for panic disorder.

In the only double-blind placebo-controlled trial of a TCA in GAD, Rickels et al[20] found imipramine to be an effective anxiolytic, although its success was somewhat hampered by the higher reported rate of adverse effects compared to diazepam, the active comparator. In contrast to the evidence base that exists for TCAs and the other anxiety disorders, there are no placebo-controlled studies for these agents in social anxiety disorder. A small (N = 15) open trial[21] of imipramine

did not find this agent to be an effective treatment for social anxiety disorder.

TCAs have also been investigated in PTSD. Amitriptyline was found to be superior to placebo in one 8-week trial[22] in combat veterans, but the overall response rate in both groups was quite low by the end of the study (36% amitriptyline vs 28% placebo). However, desipramine, a TCA that works primarily by blocking norepinephrine reuptake, was not found to be particularly effective in a small 8-week double-blind crossover trial,[23] although the 4-week treatment periods may have been too brief to assess a beneficial effect. Two RCTs have compared imipramine to phenelzine (see "Monoamine Oxidase Inhibitors and Reversible Monoamine Oxidase Inhibitors").

The majority of controlled evidence investigating TCAs in OCD involves studies of clomipramine, a TCA with potent inhibition of serotonin reuptake. Clomipramine is the only TCA approved by the US Food and Drug Administration (FDA) for treatment of OCD. In one of the first published RCTs of TCAs in OCD,[24] clomipramine was found to be superior to placebo in ameliorating severity of OCD symptoms, while nortriptyline was not. The superiority of clomipramine over placebo has been confirmed in a number of trials of both acute-phase and continuation treatment.[25–27] Investigators have also explored the efficacy of brief courses of intravenous (IV) clomipramine. For instance, Fallon et al[28] found IV clomipramine significantly more efficacious than IV placebo in OCD patients who had failed a course of oral clomipramine. However, the more widespread use of IV clomipramine as a treatment has been limited by the need for close medical supervision and cardiac monitoring during administration (reviewed in Ravindran et al[29]). In blinded clinical trials, results of head-to-head comparisons of oral clomipramine with newer agents show similar efficacy between agents, but some authors suggest that the novel agents (fluvoxamine,[30–32] paroxetine,[33] venlafaxine[34]) may be more tolerable. Finally, Noorbala et al[35] investigated whether combining TCAs might provide additional benefit over monotherapy with clomipramine. Subjects were randomly assigned in a double-blind fashion to receive clomipramine in combination with nortriptyline or clomipramine plus placebo. While both groups improved over time, there was an advantage for the combination group in terms of both efficacy and onset of improvement.

The major limiting factors to the more widespread use of TCAs at this time are their side effect profile, which includes prominent anticholinergic and antiadrenergic effects such as sedation, constipation, dry mouth, orthostatic hypotension, and sexual dysfunction, and their well-documented risk of toxicity in overdose. These factors, along with the ready availability of other effective but more tolerable agents, have largely relegated TCAs to third- or fourth-line agents for use in treatment resistance. The exception is the use of clomipramine in OCD, for which it is largely regarded as the gold standard treatment. However, its side effect profile means that it is often only considered following a trial of a more tolerable serotonergic agent such as a selective serotonin reuptake inhibitor (SSRI).

MONOAMINE OXIDASE INHIBITORS AND REVERSIBLE MONOAMINE OXIDASE INHIBITORS

The monoamine oxidase inhibitors (MAOIs) are another older class of antidepressants that has been investigated for anxiety disorders. They work by irreversibly inhibiting the enzyme monoamine oxidase, which is responsible for the breakdown of monoamines such as serotonin and norepinephrine, resulting in a net increase in the availability of these neurotransmitters in the synapse. Both open and double-blind placebo-controlled studies support the use of MAOIs for panic disorder.[36,37]

While no double-blind placebo-controlled trials of MAOIs exist to support their use in GAD, there is a well-established evidence base for their use in social anxiety disorder. Phenelzine, in particular, has support for its efficacy from 4 double-blind placebo-controlled trials in which alprazolam,[38] atenolol,[39] moclobemide,[40] and most recently cognitive-behavioral group therapy[41] were used as active comparators.

The use of MAOIs in PTSD is more mixed. Two RCTs comparing phenelzine to imipramine and placebo for treatment of PTSD found both drugs to be superior to placebo,[42,43] with one of the trials[43] suggestive of a slight advantage for phenelzine over imipramine. However, Shestatzky et al[44] were unable to replicate these positive results for phenelzine in their 10-week double-blind crossover trial.

There is a single placebo-controlled trial[45] of MAOIs in OCD in which fluoxetine was compared to phenelzine. Fluoxetine was found to be significantly more efficacious overall than both phenelzine and placebo, although a subgroup of patients with symmetry obsessions showed response to phenelzine.

As with TCAs, the use of MAOIs is often reserved for third- or fourth-line management of anxiety disorders. This is due in part to the need to maintain a low-tyramine diet to decrease the risk of hypertensive crises, the risk of drug-drug interactions, and the side effect burden of these medications compared to newer more tolerable agents.

More recently, the use of reversible monoamine oxidase inhibitors (RIMAs) has also been investigated. The main advantage of these agents over their older counterparts is that their reversible inhibition of monoamine oxidase means that they are not subject to the same stringent dietary requirements of the MAOIs, nor do they require a 2-week washout period before switching to other antidepressant classes.

Moclobemide is a RIMA available in a number of countries worldwide, although it is not currently approved for use in the United States. Double-blind parallel-group studies[46,47] have found moclobemide to be as effective as both clomipramine and fluoxetine in the acute treatment of panic disorder and have provided support for the benefits of maintenance therapy with moclobemide up to 1 year. Results of studies

with moclobemide in social phobia are generally positive; a number of open and double-blind controlled trials found moclobemide to be an effective treatment for social anxiety disorder with comparable efficacy to phenelzine and citalopram,[40,48–51] not only for short-term treatment but also for maintenance.[40,52,53] Noyes et al[54] conducted a double-blind trial comparing 5 different fixed doses of moclobemide to placebo for 12 weeks. Although the authors observed a trend toward efficacy for the higher doses at the 8-week mark, by the end of the trial, response rates between all active drug groups and placebo were similar. To our knowledge, there are no placebo-controlled trials of moclobemide in GAD, OCD, or PTSD, although 2 small open trials do suggest a utility for moclobemide in PTSD.[55,56] Overall, moclobemide has been observed to be a well-tolerated medication, with insomnia, dizziness, nausea, and headaches among the commonest side effects.

Brofaromine, another RIMA with additional effects via inhibition of serotonin reuptake, has been investigated in scientific trials of anxiety. As with moclobemide, brofaromine has been shown in double-blind RCTs to be superior to placebo[57] and as effective as clomipramine[58] or fluvoxamine[59] for panic disorder. In the 3 placebo-controlled RCTs of brofaromine in social anxiety disorder, active drug was judged superior in all cases.[60–62] Trials of brofaromine in PTSD are mixed, with 1 multicenter RCT[63] suggesting that brofaromine is more effective than placebo in subjects with PTSD of greater than 1 year's duration, but a subsequent trial[64] unable to detect differences in outcome between groups. There are no RCTs of brofaromine for GAD or OCD. Sleep disturbance, dry mouth, dizziness, and nausea are commonly reported adverse effects of brofaromine.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The primary mechanism of action of the class of drugs known as selective serotonin reuptake inhibitors (SSRIs) is inhibition of reuptake at the presynaptic serotonin (5-HT) transporter pump, resulting in increased overall levels of brain 5-HT. There are currently 6 SSRIs available for clinical use: fluoxetine, sertraline, paroxetine (immediate release and controlled release formulations), fluvoxamine, citalopram, and, most recently, escitalopram. Although each SSRI may have different FDA indications for specific anxiety disorders, clinicians tend to treat them as having equal efficacy across the group. As a class, the SSRIs are considered first-line pharmacotherapy agents for each of the anxiety disorders due to their overall levels of efficacy, safety, and tolerability.

Fluoxetine, paroxetine, and sertraline all carry FDA approvals for use in panic disorder, but all 6 SSRIs have been investigated in RCTs for this disorder. Overall, SSRIs are considered effective agents in the acute treatment of panic disorder, with 3 meta-analytic reviews[65–67] finding their efficacy and tolerability to be comparable to those of TCAs, although Bakker et al[66] suggested that there were significantly fewer dropouts in trials involving SSRIs relative to those investigating TCAs. Randomized controlled trials have also supported the use of SSRIs for maintenance therapy and relapse prevention in panic disorder.[15,47,68]

Two large, positive, double-blind placebo-controlled trials[69,70] have been reported that support paroxetine use for GAD, and head-to-head RCTs[71–73] in GAD have reported comparable efficacy among sertraline, escitalopram, and venlafaxine XR. A double-blind discontinuation study[74] concluded that paroxetine was an effective agent for preventing relapse in GAD, noting that twice as many paroxetine-treated patients achieved remission compared to those randomly assigned to placebo, and placebo-treated patients were 5 times more likely to relapse during the discontinuation taper. Similarly, positive results for sertraline have been reported for short-term treatment of GAD,[75,76] even in populations categorized as moderately to severely ill.[77] Escitalopram is the other SSRI with published reports of efficacy in GAD for both acute and long-term treatment[78–80] and, along with paroxetine, is officially indicated for GAD. There are no RCTs of citalopram, fluvoxamine, or fluoxetine as monotherapy for GAD.

As with the other anxiety disorders, multiple trials have been published supporting the use of various SSRIs for both acute and continuation treatment of social anxiety disorder, although only paroxetine and sertraline have been FDA-approved for this indication. A number of meta-analyses have confirmed the utility of SSRIs, finding them significantly superior to placebo with respect to both efficacy and improvement in psychosocial function.[81–85] While 1 meta-analytic review[81] found SSRIs to have greater effect sizes than the RIMAs, another[82] found them comparable to benzodiazepines, while yet another[83] was unable to find significant differences in efficacy between SSRIs and any of the other drug classes examined. However, when issues of tolerability were brought into the equation, the consensus was that SSRIs should be the preferred first-line treatment for social anxiety disorder.[83,84] The only exception to the above literature is the single RCT investigating fluoxetine for social anxiety disorder.[86] In this placebo-controlled trial, no significant outcome differences were detected between the active drug and placebo, although authors did report a higher-than-usual placebo response. Other trials comparing fluoxetine to psychological therapy and placebo have found different results.[87] There are no RCTs of citalopram for social anxiety disorder.

Two SSRIs, sertraline and paroxetine, have FDA indications for PTSD that follow positive results from several large multicenter acute-phase RCTs.[88–91] However, 2 subsequent, much smaller studies[92,93] that primarily studied military veterans were unable to find similar benefits for sertraline. Longer-term studies[94,95] have nevertheless found sertraline to be effective at maintaining acute-phase gains and preventing relapse. No RCTs of fluvoxamine or escitalopram in PTSD have been reported, but there is a single double-blind trial comparing citalopram to sertraline and placebo.[96] In that study, sertraline demonstrated a significant advantage for treating avoidance/numbing type symptoms, but no other

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outcome differences were noted between groups. Although a 2007 report published by the Institute of Medicine[296] concluded that there was insufficient evidence to support the efficacy of SSRIs in PTSD due to the moderate effect sizes (~0.5) seen in most pharmacotherapy trials, evidence from the above mentioned RCTs and meta-analyses,[97,98] taken with the frequent presence of comorbid depression in PTSD and prevalent nature of SSRI use, means that SSRIs will very likely continue to be a mainstay of PTSD treatment for the near future.

Several SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) carry official FDA indications for OCD, and as a class the SSRIs represent the first line of pharmacotherapeutic intervention for this disorder. Numerous large, well-controlled RCTs involving each SSRI have confirmed the efficacy of SSRIs for both acute-phase and continuation treatment of OCD.[99–113] A recent meta-analysis[114] noted that the efficacy of SSRIs relative to placebo could be seen between 6–13 weeks of treatment and further concluded that there were no within-class differences in efficacy. Trials of SSRIs in OCD have also underscored the importance of using doses in the upper end of the dosing spectrum for this population.[102,107,110,115] Although 3 earlier meta-analyses[116–118] comparing the effects of clomipramine to SSRIs for OCD found the TCA to be superior, results from all RCTs comparing the agents directly make the difference less clear. Nevertheless, despite the recognized efficacy of clomipramine for OCD, clinical guidelines generally recommend SSRIs as the first medication class to be tried because of the overall balance between efficacy and tolerability.[119–121]

Despite the prevalent use of SSRIs for anxiety disorders, concerns still exist about these medications. Common side effects upon initiation of these medications include nausea, dizziness, headaches, jitteriness, and both sleep and gastrointestinal disturbances—symptoms that are also commonly experienced as part of anxiety disorders and therefore often interpreted as a worsening of anxiety. As such, starting with lower than usual doses, gradual titration, and ongoing psychoeducation about side effects are necessary when using these medications in the anxiety disorder population. A discontinuation syndrome with SSRIs has also been documented and is more common with agents with a shorter half-life, such as paroxetine. Gradual tapering or switching to an SSRI with a long half-life, such as fluoxetine, may be helpful. There is also a risk of drug-drug interactions with SSRIs, particularly when they are combined with drugs that are also metabolized through the P450 enzyme system. Finally, there has been widespread recent media attention on the risk of increased suicidal ideation and behavior in youth started on these medications. This has resulted in a "black box warning" about use of these agents in children and people 24 years old or younger. Nevertheless, it has also been recognized that in more severe cases where there is also substantial functional impairment, the use of SSRIs may be appropriate and should be considered on the basis of clinical judgment.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

There are currently 4 serotonin-norepinephrine reuptake inhibitors (SNRIs) available for clinical use: venlafaxine extended release (ER), desvenlafaxine, duloxetine, and milnacipran. The majority of research investigating SNRIs for anxiety disorders is based on venlafaxine ER, as the latter 3 have only more recently become available. With respect to anxiety disorders, venlafaxine ER is indicated for the treatment of GAD, panic disorder, and social anxiety disorder, while duloxetine has also been approved for GAD. Along with SSRIs, SNRIs, specifically venlafaxine, are considered alternate first-line agents for the treatment of the anxiety disorders discussed here.

Venlafaxine is an SNRI with a mechanism that involves differential reuptake of norepinephrine and serotonin at either end of its dose range. Large double-blind RCTs have been published examining the benefits of venlafaxine ER relative to placebo in the acute treatment of panic disorder. The first large trial[122] found that venlafaxine ER–treated subjects were not significantly more likely to be free from full-symptom panic attacks, but they were more likely to have overall decreased panic attack frequency, anticipatory anxiety, and avoidant behavior. A more recently published report[123] found no significant difference between venlafaxine ER and placebo on the primary outcome of freedom from panic attacks, although the active drug was significantly better on secondary outcomes. More favorable results have been seen in RCTs comparing venlafaxine to paroxetine. In these, venlafaxine ER dosed between 75–225 mg was found to be comparably efficacious and tolerable to paroxetine.[124,125] While these studies support the short-term treatment of panic disorder with venlafaxine ER, Ferguson and colleagues[126] published a report concluding that venlafaxine ER was significantly more effective than placebo in maintaining the gains of acute treatment and preventing relapse during a 6-month follow-up. Controlled investigations of the other SNRIs in panic disorder consist of 2 open trials of duloxetine[127] and milnacipran,[128] respectively.

The use of venlafaxine ER for short-term treatment of GAD is well established based on the results of several RCTs.[129–131] Head-to-head comparisons with different medication classes such as SSRIs[73,132] and pregabalin[133] report similar efficacy and tolerability. Longer-term studies[134,135] have also confirmed venlafaxine ER to be efficacious for relapse prevention. Similarly robust results have been found for duloxetine in GAD. Rynn et al[136] reported that duloxetine was superior to placebo not only on measures of efficacy but also with respect to improvement of functional impairment. In one comparison to venlafaxine,[137] both drugs were seen to be effective, but venlafaxine-treated subjects experienced a greater number of side effects during the tapering period. Another placebo-controlled trial[138] that compared duloxetine, dosed at either 20 or 60–120 mg/d, to venlafaxine found that all 3 active treatments were effective at treating psychic

anxiety, but only venlafaxine and high-dose duloxetine (60–120 mg) were more beneficial than placebo for somatic anxiety. Like venlafaxine, duloxetine has also been shown to be effective for relapse prevention[139] of GAD. There are no published trials of either desvenlafaxine or milnacipran for GAD to date.

With the exception of a case-study report of duloxetine, the only literature on SNRIs for social anxiety disorder consists of trials of venlafaxine ER. Two large double-blind RCTs[140,141] found venlafaxine to be significantly more effective than placebo, while 2 other placebo-controlled trials[142,143] involving head-to-head comparisons with paroxetine concluded that both active drugs were similarly effective and tolerable. In a large 6-month study, Stein et al[144] showed that both low-dose (75 mg) and high-dose (150–225 mg) venlafaxine ER were comparable and superior to placebo; the authors hypothesized that this could mean that the noradrenergic actions of venlafaxine—which are essentially nonexistent at the 75-mg dose—were not the ones responsible for therapeutic benefit in social anxiety disorder.

In a 12-week multicenter placebo-controlled trial, Davidson and colleagues[145] found venlafaxine ER to be well tolerated and comparable in efficacy to sertraline for acute treatment of PTSD. Extending these findings, a 6-month RCT showed that venlafaxine was superior to placebo in improving overall posttraumatic symptoms, with specific benefits to the avoidance/numbing and hyperarousal symptom clusters.[146] To date, no reports of controlled trials of PTSD involving the other SNRIs have been published.

Findings from controlled trials of venlafaxine ER in OCD are mixed. Although a small placebo-controlled RCT[147] failed to find evidence of its efficacy, it should be noted that the doses of venlafaxine used in the study were relatively low (up to 225 mg/d). However, authors of a larger double-blind parallel-group study[148] comparing venlafaxine ER to paroxetine concluded that both medications were similarly efficacious and tolerable for treatment of OCD. The authors subsequently assigned nonresponders from the original trial to switch to the alternate antidepressant for a further 12 weeks. In this case, 42% of the original nonresponders eventually converted to responders, but the effect was more noteworthy for those switched to paroxetine rather than to venlafaxine.[149] A double-blind comparison of venlafaxine to clomipramine found both medications to be equally effective, but venlafaxine-treated patients reported fewer treatment-emergent adverse effects.[34] There are no published reports of controlled trials in OCD involving the other SNRIs.

Overall, there is excellent controlled evidence to suggest that SNRIs, particularly venlafaxine, are effective and well-tolerated agents for the anxiety disorders discussed above. These are the main factors explaining why they are considered reasonable alternate first-line agents to SSRIs. One disadvantage often cited with the use of venlafaxine in particular is the potential not only for side effects but for the emergence of adverse events, similar to the SSRI discontinuation syndrome, during tapering periods or times of noncompliance. The use of SNRIs in anxiety disorders is more thoroughly discussed in a recent review.[150]

OTHER ANTIDEPRESSANTS

The use of alternate antidepressants with unique mechanisms of action has also been investigated for anxiety disorders, although the literature is sparser. Mirtazapine works presynaptically to inhibit the α_2 heteroreceptors on serotonergic neurons and the α_2-adrenergic autoreceptors. It also works to selectively block serotonergic 5-HT_2 and 5-HT_3 receptors on the postsynaptic neuron, as well as having potent antagonist effects at histaminic H_1 receptors.[151] Three open trials[152–154] suggested a utility for mirtazapine in the short-term treatment of panic disorder, and a double-blind parallel-group study[155] found it to be comparably efficacious to fluoxetine; however, all 4 studies used small samples. An open trial conducted by Van Veen et al[156] suggested that mirtazapine might be useful for treatment of social anxiety disorder. A single double-blind placebo-controlled RCT[157] did reinforce this idea, but the population studied was limited to females with social anxiety disorder. In the only RCT[158] of mirtazapine in PTSD, authors were able to demonstrate symptom improvement on a global measure of change, but on no other outcome variables. Twelve weeks of open-label mirtazapine followed by an 8-week discontinuation period indicated that mirtazapine was helpful for OCD,[159] but further controlled trials of mirtazapine monotherapy in OCD are lacking. A single-blind placebo-controlled study[160] suggested that combining mirtazapine and citalopram might accelerate treatment response in OCD relative to citalopram alone; however, there were no overall differences in responder rates by the end of the trial period. At this time, there are no RCTs of mirtazapine for GAD.

Bupropion, a norepinephrine and dopamine reuptake blocker, has mixed findings from open trials in panic disorder,[161,162] but lacks data from placebo-controlled RCTs to make definitive conclusions. A single RCT[163] comparing bupropion extended release to escitalopram found both agents to effectively treat GAD, but no RCTs exist to support bupropion treatment of social anxiety disorder. On the basis of the results of 2 controlled trials,[164,165] bupropion was not found to be an effective treatment for PTSD. There are no controlled trials of bupropion in OCD, but in 1 open-label study,[166] it was not found to be particularly useful.

Nefazodone is an older antidepressant hypothesized to work via both antagonism of postsynaptic serotonin 5-HT_{2A} receptors and modest inhibition of presynaptic serotonin and norepinephrine reuptake. Positive findings from 3 small open trials[167–169] suggest a potential benefit for nefazodone in panic disorder, but no RCTs have confirmed this. Similarly, Hedges and colleagues[170] found promising results in the only open trial of nefazodone in GAD. By contrast, Van Ameringen et al[171] demonstrated that nefazodone was not an effective treatment for generalized social anxiety disorder in their placebo-controlled study. Two controlled studies[172,173]

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of nefazodone in PTSD found it to be superior to placebo and as effective as sertraline. There are no controlled trials of nefazodone in OCD. Despite the potential utility of nefazodone in various anxiety disorders, worries about possible hepatotoxicity caused this drug to be withdrawn from the market in several countries. Although it is still available in the United States, these health concerns have likely contributed to the decline in research of this drug.

While the mechanism of action of trazodone is not entirely clear, it is thought to work similarly to nefazodone through weak reuptake inhibition of serotonin and norepinephrine and antagonism of 5-HT_{2A} receptors. Although a small (N = 11) single-blind trial[174] found trazodone to be helpful for panic disorder, Charney et al[175] found that it was neither well tolerated nor effective in their double-blind RCT comparing trazodone to imipramine and alprazolam. A double-blind placebo-controlled RCT of trazodone, imipramine, and diazepam for GAD found all active treatments to be helpful, with a slight superiority for both antidepressant agents.[20] In their small double-blind placebo-controlled trial, Pigott et al[176] did not find trazodone to be a useful agent for treatment of OCD.

ANTICONVULSANTS

Nonbenzodiazepine drugs with anticonvulsant activity are commonly used in the treatment of different psychiatric illnesses. On the basis of the hypothesis that clinical anxiety results from excessive neuronal activation of fear circuits, it has been theorized that anticonvulsant drugs may potentially reduce this excitation in a similar fashion to the way in which they decrease epileptic burst firing.[177] These drugs often differ significantly from each other with respect to chemical structure, and, further, their mechanisms of anxiolytic action are frequently poorly understood. Nevertheless, researchers have investigated their use in the different anxiety disorders with varying results. There are only 2 double-blind placebo-controlled trials of anticonvulsants in panic disorder, both with limited success. In the first RCT, which examined gabapentin compared to placebo for panic disorder, Pande et al[178] were unable to find an overall difference between treatment groups, but a post hoc analysis suggested that gabapentin had an advantage for treatment of the subgroup with more severe illness at baseline. More recently, Zwanzger and colleagues[179] were unable to detect differences in outcome between groups receiving tiagabine or placebo for 4 weeks. In an earlier controlled open trial,[180] carbamazepine was similarly found to display a lack of benefit for panic disorder. In contrast to these negative trials in patients with panic disorder, positive open trials and case series of valproate,[181,182] vigabatrin,[183] and levetiracetam[184] have been published but lack more controlled evidence to substantiate the findings.

For GAD, pregabalin has the greatest amount of support, with 6 positive double-blind placebo-controlled RCTs published. The first 4 of the trials focused on optimal dosing of the drug for the short-term treatment of GAD.[185–188] With the exception of 1 study,[185] all investigated doses of pregabalin (200–600 mg/d) were superior to placebo at decreasing overall anxiety (somatic and psychic), and improvements were frequently observed as early as the first week. Three[185,186,188] of the 4 trials used a benzodiazepine as an active comparator, and pregabalin was found similarly efficacious to these agents in these studies. In 2006, Montgomery et al[133] conducted a placebo-controlled trial comparing venlafaxine to 2 different doses of pregabalin in patients with moderate to severe GAD. All 3 active treatment groups showed significant improvement, with pregabalin showing a slightly earlier time to response than venlafaxine. Continuation treatment with pregabalin has also been shown to be an effective strategy at preventing relapse in GAD.[189] Tiagabine, a γ-aminobutyric acid (GABA) reuptake inhibitor with anticonvulsant properties, has had mixed results in GAD. A 10-week open trial[297] that randomly assigned patients to treatment with either tiagabine or paroxetine found that both drugs were well tolerated and similarly effective in reducing anxiety symptoms. However, Pollack and colleagues[190] failed to find a difference between tiagabine and placebo on the primary outcome analyses of their multicenter 8-week double-blind RCT. In a double-blind trial of males with GAD,[191] 68% of subjects receiving valproate were deemed responders compared to only 16% of those receiving placebo. Riluzole, a glutamate modulator, showed some promise as a treatment of GAD when results from an open trial[192] indicated that 80% of completers responded and 53% remitted, but further investigation is needed.

A variety of anticonvulsants have been investigated as potential treatments for social anxiety disorder. Although there was initial promise for levetiracetam,[193] 1 small and 1 large placebo-controlled trial[194,195] have since found it ineffective. Double-blind RCTs have also shown support for gabapentin[196] and for high-dose pregabalin (600 mg/d), although low-dose pregabalin (150 mg/d) was found to be no better than placebo.[197] Although there is a lack of controlled evidence, results of open trials indicate that valproate,[198] topiramate,[199] and tiagabine[200] may also be useful in social anxiety disorder.

Few controlled trials of anticonvulsants have been published in PTSD. A small pilot study[201] did find lamotrigine monotherapy to be helpful. A subsequent RCT[202] of topiramate monotherapy was similarly positive, but a double-blind study[203] of topiramate augmentation in patients with PTSD was unable to find such a benefit, although the elevated attrition rates in the latter study might have affected results. A large multicenter RCT[298] failed to find tiagabine to be an effective treatment for PTSD, and 2 negative RCTs of valproate in adult PTSD have now been published.[204,205]

There are no controlled studies of anticonvulsant monotherapy for OCD and only limited literature on augmentation with anticonvulsants. In a study by Onder et al,[206] subjects with OCD were randomly assigned to receive either fluoxetine alone or fluoxetine and gabapentin. Results showed that the combination treatment seemed to accelerate response,

although there were no statistical differences in outcome at endpoint. Case reports and a retrospective case series suggest a possible role for topiramate[207,208] and lamotrigine[209] in OCD, but no controlled trials have been published to date.

With the exception of pregabalin for GAD, the paucity of double-blind trials and the frequently mixed results would suggest that anticonvulsant monotherapy be largely reserved for cases of treatment resistance or possibly as augmentation of a more established first-line agent in the treatment of anxiety disorders.

ATYPICAL ANTIPSYCHOTICS

The introduction of the atypical antipsychotics into the psychiatric pharmacopoeia during the 1990s transformed the management of schizophrenia. That these drugs also had serotonergic properties and could be used to successfully augment antidepressant effects in mood disorders led to interest in uncovering a possible additional role for anxiety disorders. In their small (N = 10) open-label trial of olanzapine monotherapy in patients with treatment-refractory panic disorder, Hollifield et al[210] found that patients experienced a significant decrease in anticipatory anxiety by study end, with 50% of participants free of panic attacks. In a subsequent open trial[211] of SSRI augmentation with low-dose olanzapine in a similar population, 82% of subjects were deemed responders by study end, with a 58% remission rate in those who completed the trial. Risperidone monotherapy was compared to paroxetine in a recent randomized, rater-blinded study.[212] Both groups showed similar improvement, but a post hoc analysis suggested that risperidone might work slightly faster. Placebo-controlled studies of atypical antipsychotics in panic disorder are lacking.

In GAD, controlled evidence for atypical antipsychotics has so far been limited to augmentation studies. Olanzapine augmentation of fluoxetine resulted in a significantly greater proportion of responders than placebo, but the olanzapine-treated group also gained significantly more weight.[213] A double-blind RCT[214] of low-dose risperidone augmentation resulted in significantly greater reductions of both psychic and overall anxiety in the treatment group, but responder rates were not statistically different. A more recent double-blind RCT[215] also failed to find a difference between low-dose risperidone augmentation and placebo on primary endpoints, although post hoc analyses suggested a possible role for risperidone in subjects with more severe GAD. Despite the promising results of an open-label study of quetiapine augmentation[216] in treatment-refractory GAD, Simon and colleagues[217] were unable to find benefits to quetiapine augmentation of paroxetine CR in a placebo-controlled RCT. Open-label augmentation with aripiprazole, an atypical antipsychotic with partial agonism at both the D_2 and 5-HT_{1A} receptors, resulted in significant improvement in a small group of patients with refractory GAD and secondary depression diagnoses.[218] However, the authors were unable to determine whether the overall benefits were due to improvement of anxious or depressive symptoms. A small open trial[219] of ziprasidone augmentation has also shown promising results, but replication of the results in a larger controlled trial is needed.

A double-blind RCT[220] of olanzapine monotherapy for social anxiety disorder resulted in significantly better clinical outcome than placebo. Although weight gain was minimal and similar between groups, subjects receiving olanzapine had greater complaints of dry mouth and drowsiness. Authors of a small open trial[221] of quetiapine monotherapy in social anxiety disorder reported positive findings, but results of a subsequent RCT[222] failed to distinguish between active treatment and placebo on primary outcomes.

Controlled evidence of atypical antipsychotics in PTSD largely consists of augmentation trials, but with conflicting results. Of the trials investigating augmentation with risperidone, 3 trials[223–225] found the drug to benefit the reexperiencing or hyperarousal symptom clusters, but no improvements were seen in the avoidance/numbing cluster. Hamner et al[226] found risperidone specifically helpful for psychotic but not overall posttraumatic symptoms. Similarly, Rothbaum et al[227] was unable to find benefits for risperidone augmentation for overall posttraumatic symptoms or even individual symptom clusters. In contrast, the single RCT[228] of olanzapine augmentation showed significant reductions in overall scores of PTSD measures as well as improvements in sleep and depression. However, authors were concerned about the mean weight gain of 13 lb in subjects treated with olanzapine. Monotherapy with risperidone was investigated in an RCT[229] of women with PTSD, with the results showing benefit on the primary outcome measure (total score on the Treatment Outcomes Post-traumatic Stress Disorder Scale-8) but none of the secondary measures. Results of the single RCT[230] of olanzapine monotherapy for PTSD failed to demonstrate a beneficial effect, but that study was small and possibly underpowered.

Virtually all published trials of atypical antipsychotics in OCD consist of augmentation studies in patients who have not responded to a course of SSRIs, and results are mixed. While authors of several placebo-controlled RCTs found evidence to support augmentation with olanzapine,[231] risperidone,[232,233] and quetiapine,[234,235] other investigators failed to find these atypical antipsychotics efficacious for this purpose.[236–239] Head-to-head comparisons involving these agents have also been studied. A single-blind trial conducted by Maina et al[240] compared olanzapine and risperidone augmentation in subjects resistant to serotonin reuptake inhibitors. Both agents were found to be equally effective at reducing obsessive-compulsive symptoms, but the adverse event reports differed between groups, with the main complaints being amenorrhea in the risperidone group and weight gain in the olanzapine group. A double-blind placebo-controlled crossover trial comparing risperidone and haloperidol augmentation found them to be equally effective at treating obsessions, although risperidone was significantly better at improving depressive symptoms and was generally better tolerated.[241] Using findings from the above studies, a

recent meta-analysis by Bloch and colleagues[242] concluded that augmentation with atypical antipsychotics could be a helpful strategy for treatment-resistant OCD. Benefits were most evident with risperidone, but evidence was inconclusive for both olanzapine and quetiapine. A single pilot trial[243] of atypical antipsychotic monotherapy has been published using open-label aripiprazole, one of the newest atypical antipsychotics. Treatment with aripiprazole resulted in significant improvement in compulsive symptoms, and overall improvement showed a trend toward significance ($P = .06$). However, the results need to be replicated with a larger population under controlled conditions. An open-label study[244] of aripiprazole augmentation in a population with treatment-resistant OCD also showed promising results.

It is clear that the evidence base of atypical antipsychotics for anxiety disorders is still quite sparse. There is an urgent need for larger and more definitive trials to validate the common clinical strategy of augmenting antidepressants with these agents when managing anxiety disorders. Further, the worrisome side effect burden of these agents, which often includes substantial weight gain and other metabolic sequelae, also needs to be addressed in these studies to develop better ways of managing it, particularly since these side effects may have a considerable effect on both general medical health and compliance.

AZAPIRONES

Buspirone is a psychotropic medication that exerts its anxiolytic effect via partial agonism of the 5-HT_{1A} receptor. Buspirone is currently the only one of its class (the azapirones) to have regulatory approval in the United States, where it is indicated for the treatment of anxiety that would come closest to what we would currently define as GAD. However, published trials of buspirone for other anxiety disorders also exist. Findings for buspirone in panic disorder are generally unfavorable. Two randomized placebo-controlled trials have been published comparing buspirone to imipramine. In one,[245,] no significant differences were found between all 3 groups, while the other[246] found that only imipramine was superior to placebo. Similarly, a randomized head-to-head comparison of buspirone and clorazepate found the latter agent to be significantly more efficacious.[247]

There are several RCTs of buspirone in GAD. The vast majority of these are head-to-head or placebo-controlled trials comparing buspirone to benzodiazepines. Buspirone was generally found to be as efficacious and tolerable as the benzodiazepines. In the only RCT[129] comparing buspirone to a newer antidepressant, both venlafaxine and buspirone were found to be superior to be placebo, although venlafaxine demonstrated greater efficacy on one anxiety measure.

There are conflicting findings on the efficacy of buspirone in social anxiety disorder. Modest efficacy was found by Schneier and colleagues[248] in their 12-week open trial, but in a double-blind RCT, van Vliet et al[249] were unable to find outcome differences between buspirone and placebo.

A positive preliminary open trial[250] in PTSD suggested a possible role for buspirone in this disorder, but no RCTs have been published to substantiate this.

Controlled trials of buspirone in OCD also demonstrate mixed findings. While an early open trial[251] of buspirone monotherapy failed to demonstrate benefit for any of the 14 patients enrolled, a double-blind RCT[252] comparing buspirone to clomipramine found both agents to be similarly effective at improving obsessive-compulsive symptoms. Buspirone augmentation in patients with insufficient response to serotonin reuptake inhibitors has also been studied. Two open trials[253,254] of buspirone augmentation of an SSRI showed promising results, but subsequent findings from both open and double-blind trials failed to support this practice.[255–257]

While tolerability and low potential for dependence are advantages over benzodiazepine use, buspirone can often take a few weeks to show clinical effect. Further, its limited efficacy for anxiety disorders means that it is mainly relegated to use for uncomplicated GAD. However, since GAD is commonly comorbid with other anxiety and mood disorders, even here other antidepressants are the preferred first choice.

BENZODIAZEPINES

The benzodiazepines have been a mainstay of anxiety disorder treatment for many years. These drugs work by binding to a specific site on the GABA-A receptor, resulting in an enhanced effect of the inhibitory neurotransmitter GABA. Benzodiazepines have many properties including anxiolytic, anticonvulsant, muscle-relaxant, and sedative actions. The multiple benzodiazepines are usually classified by their elimination half-life into short-, intermediate-, and long-acting. Their tolerability and rapid onset of effect have contributed to their continued use in the anxiety disorders.

Several RCTs of benzodiazepines in panic disorder have been published supporting their use (reviewed in the American Psychiatric Association Practice Guidelines for the Treatment of Patients With Panic Disorder[258]). Alprazolam, a short-acting benzodiazepine, was the first medication to receive regulatory approval by the FDA for the treatment of panic disorder following the results of 2 large multicenter studies.[259,260] Not only has alprazolam been found to be significantly superior to placebo and comparable in efficacy to imipramine, but clinical improvement was also seen sooner with alprazolam than with imipramine.[260] Other studies have confirmed the utility of alprazolam for panic disorder[261–266] in reducing frequency of panic attacks, phobic avoidance, and anticipatory anxiety, as well as maintaining gains during continuation treatment.[267–269] Studies have also validated the utility of clonazepam, the other benzodiazepine FDA-approved for use in panic disorder,[264,270–272] as well as diazepam[261,273,274] and lorazepam.[275,276] Overall, meta-analytic comparisons of the different drug classes used in panic disorder found that benzodiazepines had similar

effect sizes compared to either SSRIs or TCAs.[67,277] There has also been interest in combining benzodiazepines with other agents to assess whether this affects response. Two trials[278,279] showed that coadministration of a benzodiazepine and SSRI conferred an earlier benefit compared to an SSRI alone, although this advantage was not sustained by trial end.

As with panic disorder, studies of benzodiazepines in GAD are numerous, and, as a result, alprazolam has been approved by the FDA for use in this disorder. One meta-analytic review[280] of pharmacologic agents used in GAD found benzodiazepines to be as effective as the azapirones, although compliance was noted to be greater with the benzodiazepines. A more recent meta-analysis[281] showed moderate effect sizes for benzodiazepines that were comparable to those of SSRIs and venlafaxine.

Three controlled trials of benzodiazepine monotherapy, all involving clonazepam, have been reported for social anxiety disorder. The first 2 trials[282,283] concluded that clonazepam was significantly superior to placebo in the acute treatment of social anxiety disorder. Connor et al[284] found that responders to 6 months' treatment with clonazepam were significantly less likely to relapse compared to those who switched to placebo, suggesting that continuation treatment with clonazepam is a safe and effective strategy for social anxiety disorder.

Limited evidence for benzodiazepine use in PTSD exists. In 1 double-blind crossover study,[285] alprazolam was helpful for nonspecific anxiety but not specific posttraumatic stress symptoms, while Cates et al[286] failed to find evidence that clonazepam was helpful to treat sleep disturbance in PTSD. Findings of 2 studies[287,288] investigating whether benzodiazepine administration in the aftermath of trauma might prevent PTSD development were negative, with investigators even suggesting the possibility of deleterious effects. Given the paucity of effective pharmacotherapies for PTSD, the use of benzodiazepines—which are so effective in the other fear-based anxiety disorders such as panic disorder and the phobias—in PTSD should be further explored with large-scale controlled studies.

Reports of controlled trials of benzodiazepines in OCD are few. A double-blind multiple crossover study[289] comparing psychotropic medications with different mechanisms found both clonazepam and clomipramine to be significantly superior to the control medication. The authors noted that the benefits of clonazepam over the other medications were seen within the first 3 weeks of its use. In contrast, a placebo-controlled RCT[290] failed to demonstrate the superiority of clonazepam over placebo with respect to either rates of response or degree of symptom improvement. Similarly, in a double-blind placebo-controlled RCT[291] of clonazepam augmentation of sertraline, no differences were detected between groups.

Enthusiasm for benzodiazepine use in anxiety disorder has waned in the face of several factors. Although these medications are often tolerated well and have the ability to provide rapid and effective relief of symptoms, clinicians are often concerned about more severe adverse effects such as oversedation, cognitive impairment, and psychomotor incoordination. Benzodiazepines are dangerous in overdose, and individuals discontinuing benzodiazepine use may experience uncomfortable withdrawal symptoms. Further, 2 of the most cited reasons for a general reluctance to use benzodiazepines are the risk of tolerance and dependence in long-term use. While this is certainly a risk, longer-term follow-up studies of patients receiving clonazepam or alprazolam for panic disorder showed little evidence of tolerance, while noting that a majority of patients maintained their treatment gains.[267,269,292,293] That being said, one population in whom it would be prudent to exercise more care is individuals with a history of substance abuse. Although not specifically prohibited in these cases, benzodiazepine use should be undertaken only after a frank discussion about the risks with an emphasis on the need for careful monitoring. Overall, benzodiazepines represent a valuable treatment option for anxiety, particularly for panic disorder, GAD, and, in some cases, social anxiety disorder. However, benzodiazepines are often overlooked in favor of other conventional agents for other reasons. Anxiety disorders are frequently comorbid with other psychiatric illnesses, particularly depressive disorders. Since benzodiazepines have no recognized antidepressant effects, the use of a conventional antidepressant agent in these cases is more appropriate. A popular strategy for using benzodiazepines in anxiety disorders is short-term use during initiation of an antidepressant agent, as these may take time to display therapeutic benefit. Not only does this coadministration have the benefit of providing some initial symptom relief, but it may also attenuate some of the more agitating side effects that can be seen when starting an antidepressant. Once patients are stabilized on treatment with antidepressants, clinicians will often opt to taper the benzodiazepine.

DISCUSSION

The pharmacologic management of anxiety disorders has made great progress over the last few decades; however, large gaps continue to exist in the literature and in practical implementation of the evidence. A number of clinical trials involving SSRIs have, by and large, been well powered and well replicated, but pilot studies or open trials involving other medication classes need to be replicated and investigated in larger populations to validate findings. There are a large number of augmentation studies with atypical antipsychotics for OCD, although, even here, the findings are not generally conclusive. With the exception of this instance, augmentation and combination studies of pharmacologic agents to systematically identify next-step strategies for cases of treatment resistance are generally few and far between. More recently, investigators[294,295] have been attempting to address this deficit.

There has also been an increased effort to delineate specific neurobiological dysfunctions underlying the different

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anxiety disorders in the hope that this may help clinicians to better target symptoms with the appropriate pharmacologic agents and may also be of use in developing new drugs. Genetics and neuroimaging are 2 streams of research that will be of critical importance in extending this field further.

Although developing more effective psychotropic drugs would be helpful, it is also important to be open to using more novel therapies, such as repetitive transcranial magnetic stimulation, that could be employed either on their own or in combination with existing pharmacotherapeutic agents. Despite the gaps in the literature, findings from the above studies have provided invaluable information to clinicians, aiding them to more effectively provide symptom relief and improved quality of life for patients suffering from this often debilitating group of illnesses.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), atenolol (Tenormin and others), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), diazepam (Diastat, Valium, and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), levetiracetam (Keppra and others), lorazepam (Ativan and others), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), pregabalin (Lyrica), quetiapine (Seroquel), riluzole (Rilutek and others), risperidone (Risperdal and others), sertraline (Zoloft and others), tiagabine (Gabitril), topiramate (Topamax and others), trazodone (Oleptro and others), valproate (Depacon and others), venlafaxine (Effexor and others), vigabatrin (Sabril), ziprasidone (Geodon).

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