Pharmacological Strategies for Generalized Anxiety Disorder

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Treatment approaches to GAD, a highly prevalent, chronic, debilitating, relapsing, and often underdiagnosed anxiety disorder.

Generalized anxiety disorder (GAD) is a highly prevalent, chronic, debilitating, relapsing, and often underdiagnosed anxiety disorder. Characterized by a waxing and waning episodic clinical course replete with periods of remission and relapse, GAD presents with excessive and pathological worry that is difficult to control. A diagnosis of GAD incorporates physical, psychological, and cognitive symptoms as well as potentially profound functional impairment.

The core symptom of excessive worry must be present for a minimum of 6 months and must occur in conjunction with at least 3 of 6 physiological arousal symptoms: restlessness, fatigue, muscle tension, irritability, concentration deficit, and sleep disturbance. The evolution of the diagnostic criteria from DSM-III through DSM-5 has seen changes only in the duration of the core worry component, which increased from a duration of 1 month in DSM-III to 6 months in DSM-IV and DSM-5.

The most commonly occurring anxiety disorder, GAD is unlike the other anxiety disorders. It is a disorder of adult onset, with the highest median age of onset of all the anxiety disorders—a pattern more consistent with MDD. The pathological worry is typically based on extant dangers with an overestimated likelihood that such dangers will realistically occur (eg, a loved one is kidnapped). This then rapidly devolves into generalized worry that pervades multiple life domains. For some patients, this leads to avoidant behavior, and activities or places with perceived danger are avoided. If it is not treated, the patient’s sphere of comfort may continue to constrict until daily activities become limited and normal function is impaired.

The close association of somatic complaints may complicate the diagnostic process, because patients with GAD generally present in primary care with a physical symptom seemingly unrelated to a mental health condition. Aside from the physical, psychological, and cognitive manifestations, social and occupational functioning are often impaired. The functional impairment sustained in GAD is comparable in magnitude to that of MDD. The robust association of GAD and psychiatric and physical comorbidity complicates the clinical course and is associated with reduced response and remission rates.

**General approach to treatment**

The diagnosis of GAD is initially made using DSM-5 criteria, which is generally coupled with the Hamilton Rating Scale for Anxiety (HAM-A) to assess severity, the Clinical Global Impression-Improvement (CGI-I) scale to assess overall improvement, and the Sheehan Disability Scale (SDS) to assess functionality.

Treatment response is defined as a 50% or greater improvement in HAM-A score and a “much improved” or “very much improved” rating on the CGI-I. Remission is defined as a HAM-A score of 7 or less, a CGI-I score of 1 (not ill at all), and an SDS score of 5 or less. Although at least half of the patients respond to treatment, remission is achieved by only about one-third to half of those who...
respond. Failure to remit fully confers a greater risk of relapse. Treatment phases are delineated into an acute and a long-term phase, with slight variations in treatment goals. Acutely, the goal is to improve the presenting anxiety symptoms. Once target symptoms are improved or resolved, the focus shifts to long-term, or maintenance, therapy, the goal of which is to completely resolve symptoms and return the patient to a premorbid level of social and occupational functionality (remission). Coupled with the goal of remission is relapse prevention. Characterized by alternating periods of remission and relapse, a critical therapeutic challenge in treating GAD is preventing relapse or recurrence of symptoms. Symptomatic remission typically precedes functional remission, which underscores the need for deliberately longer courses of treatment to truly achieve remission.

**Acute phase of treatment.** Customarily a single drug, generally an antidepressant, is initiated at a low dosage and is titrated according to clinical response and tolerability. A preliminary assessment of response can be gauged at 4 to 8 weeks. Patients who endorse some level of appreciable symptom resolution and are tolerant of the medication are considered to have achieved a durable remission. This is considered predictive of an eventual sustained remission that persists for several months beyond this acute treatment phase.

The absence of a response at the initial 4- to 8-week follow-up visit or intolerance of adverse effects may prompt either a reevaluation of the diagnosis or an adjustment in medication. Reasonable interventions include increasing the dosage of medication (if the initial drug was tolerated but the clinical effect was not of the magnitude desired), switching to a different drug within the same pharmacological class (if there was some level of improvement but questionable tolerability), switching to a drug outside of the pharmacological class (if there was lack of response and/or poor tolerability), or augmenting the initial drug (if the dose of the initial drug was already optimized but the full therapeutic effect had not been achieved).

The acute treatment phase is now considered the most therapeutically sound time to use a benzodiazepine, which is representative of a shift in philosophy from when drug therapy options were more limited.

**Maintenance treatment.** On resolution of the presenting anxiety symptoms, it is recommended that treatment be continued beyond initial symptom resolution for 12 months to minimize the risk of relapse. If a benzodiazepine was initiated concomitantly with an antidepressant during the acute phase, it is generally tapered during the maintenance phase.

**Currently available pharmacotherapeutic options**

The arsenal of recommended pharmacotherapeutic interventions has grown meaningfully in the past decade. Drug classes that were experimental for the treatment of GAD 10 years ago have risen to first-line options, and newer, novel drug products are now beginning to amass a litany of literature that serves as an evidence base for clinical practice. Secondary to the proposed neurobiological basis for pathological worry and anxiety syndromes, drug therapies with evidence for clinical utility tend to target serotonin, norepinephrine, γ-aminobutyric acid (GABA), or combinations thereof. Internationally, the SSRIs, the SNRIs, and pregabalin are regarded as first-line options for GAD. US guidelines have not yet integrated pregabalin into the first-line tier, nor does the drug have FDA approval for this indication; however, it is considered an alternative therapy.

**SSRIs.** These drugs are thought to mitigate anxiety symptoms by inhibiting the reuptake of serotonin in the synaptic cleft. While the 2- to 4-week delay until onset of therapeutic effect may be discouraging and may impact patient compliance, significant reductions in “anxious mood” have been documented as early as week 1 in paroxetine trials. Remission rates in paroxetine responders at 32 weeks are as high as 73%, with only 11% relapsing, a statistic that demonstrates much improvement over the spontaneous remission rate of 20% to 25%.1

In patients with moderate to severe GAD, sertraline 50 to 100 mg/d has demonstrated superiority to placebo in improving HAM-A score. Clinical response criteria were met by 55% of patients in the sertraline group compared with 32% in the placebo group by week 12.2 Escitalopram has been evaluated for the long-term treatment of GAD and prevention of relapse. Davidson and colleagues3 reported significantly superior improvements in HAM-A total score, HAM-A somatic and psychic subscales, and quality-of-life measures for escitalopram at every time point starting at week 1. By week 4, 50% of patients in the escitalopram arm had responded, and by week 8, 68% fulfilled response criteria. Remission was achieved by 36% of patients who received escitalopram compared with 16% of patients who received placebo (P < .01). Pooled analyses further promulgate the sustained superior efficacy of escitalopram compared with placebo as early as week 1 with respect to HAM-A score and response and remission.4 The 24-week open-label extension study found that at 24 weeks, 92% of patients had responded and 60% of
patients had remitted. The adverse effects of SSRIs include weight gain, somnolence, GI sequelae, and agitation. Sexual dysfunction, often a presenting symptom in anxious patients, may be exacerbated or instigated. Another unfortunate pharmacological phenomenon of the SSRI class is its ability to cause agitation and jitteriness in the acute phase of treatment. This, coupled with the adverse-effect profile, might be responsible for early treatment failure with SSRIs.

SNRIs. These agents inhibit the reuptake of serotonin and norepinephrine, although the selectivity and balance with respect to the extent of inhibition are variable among the SNRIs. Superior efficacy in improving anxiety symptoms as evidenced by reduction in HAM-A total scores was seen with 75 to 225 mg of venlafaxine XR daily compared with placebo. In addition, venlafaxine’s efficacy in treating anxiety symptoms in patients with comorbid depression as well as those with pure GAD has made it a commonly prescribed first-line drug. The comorbidity of nonspecific somatic pain complaints is common in patients with GAD, and it negatively impacts quality of life, worsens outcomes, hampers symptom remission, and increases the risk of relapse. In a limited comparison of venlafaxine versus paroxetine, the improvement of HAM-A score and rates of response and remission did not differ between paroxetine and venlafaxine by week 8.

A study by Rickels and colleagues evaluated the time to relapse by extending venlafaxine treatment to 6 and to 12 months in patients who had an initial response. After 12 months of treatment with venlafaxine, the relapse rate was 6.7% for the venlafaxine group and 32.3% for the placebo group. This study supports the use of venlafaxine for at least 12 months in patients who respond. The inhibition of serotonin and norepinephrine is more balanced with duloxetine than with venlafaxine. Its dual effect on anxiety symptoms and somatic pain resulted in 53% to 61% of treated patients who achieved symptomatic remission and approximately 47% who achieved functional remission. A second study of similar design also supported the superiority of duloxetine 60 to 120 mg compared with placebo in terms of HAM-A score improvement but did not observe a difference in rates of response, although the maintenance of response was superior to that of placebo. Early response to duloxetine within the first 2 weeks of therapy is predictive of a maintained response; therapy for 6 or more months is associated with functional remission and reduced risk of relapse. Duloxetine causes less sexual dysfunction than paroxetine. The adverse effects are similar in scope and magnitude to those of the SSRIs; however, the risk of clinically meaningful increases in blood pressure have also been documented, particularly with venlafaxine.

Benzodiazepines. The anxiolytic properties of the benzodiazepines are attributable to the modulation of the GABA receptor and enhancement of GABA’s inhibitory effects with subsequent inhibition of monoamine reuptake. Benzodiazepines are indicated for the short-term management of the acute phase of anxiety (first 2 to 4 weeks) and for any subsequent exacerbations of anxiety during stable treatment with an antidepressant. Their rapid onset of action and tolerability make them conducive to alleviating anxiety symptoms when immediate anxiolytic effects are necessary. Although more marked improvement is realized in the first 2 weeks of treatment with benzodiazepines, antidepressants consistently achieve the same efficacy and surpass it after 6 to 12 weeks of treatment. Although still a common practice, the use of benzodiazepines as long-term or as monotherapy is not recommended and is inconsistent with evidence-based guidelines. Benzodiazepines are most adept at alleviating somatic symptoms but have no effect, and may even have a somewhat detrimental effect, on the psychic symptoms of GAD.

TCAs. As a class, the TCAs have been limited by, and largely replaced as a result of, their adverse-effect profile. The anticholinergic and antidiurenergic effects, such as orthostasis, sexual dysfunction, sedation, and constipation, have markedly affected patient tolerability. The profound risk of toxicity in overdose coupled with these undesired effects has resulted in TCAs being replaced by newer, more tolerable, and possibly more effective drugs that are less toxic in overdose. Of the TCAs, imipramine has been the most compelling efficacy data relative to other drug therapies. In a landmark study by Rickels and colleagues, axiolytic effects of imipramine, trazodone, diazepam, and placebo were compared in nondepressed patients with GAD. Imipramine resulted in moderate to marked improvement between weeks 2 and 8 of therapy in 73% of patients, compared with 69% for trazodone, 66% for diazepam, and 44% for placebo.

Buspirone. This antianxiety agent is a partial agonist at the serotonin-1A receptors and a full agonist at the presynaptic serotonergic autoreceptors. Although buspirone’s effectiveness in treating GAD has been demonstrated inconsistently in several studies, its delayed onset of action, tolerability, and relative lack of efficacy with respect to most comorbid conditions (with the exception of MDD) has
resulted in buspirone being used primarily as adjunctive therapy. Its effectiveness is comparable to but slightly weaker than that of diazepam, clorazepate, lorazepam, and alprazolam, but it has a clearly slower onset of action.

A randomized controlled trial in GAD patients without comorbid MDD compared buspirone and venlafaxine with placebo and found that both active treatments were superior to placebo. Buspirone’s utility is mainly associated with its propensity to relieve the cognitive aspects, but it lacks long-term efficacy—particularly in managing the behavioral and somatic manifestations.

Newer or novel modalities. Pregabalin is a branched-chain amino acid and GABA analogue. The antinociceptive, antiseizure, and potentially anxiolytic properties of pregabalin—mediated through binding to the α2δ subunit of voltage-gated calcium channels within the CNS. Its action involves decreasing calcium influx at the presynaptic channel and subsequent inhibition of norepinephrine and glutamate.

Two similarly designed randomized, placebo-controlled, double-blind studies evaluated the efficacy of pregabalin versus lorazepam for the treatment of GAD. The pregabalin groups and the lorazepam group all experienced greater reductions in HAM-A score by week 4 compared with placebo, with no observed statistically significant differences among the active-treatment groups. Pregabalin at its highest study dose (600 mg) produced reductions in the psychic and somatic anxiety HAM-A subscale scores that were statistically superior to those produced with placebo, whereas lorazepam produced reductions that reached statistical significance versus placebo with respect to only the somatic subscale. The improvements in HAM-A score produced by the active-treatment groups were apparent by week 1 of the study. The relative efficacy and early onset of effect of pregabalin versus commonly used benzodiazepines may represent a new therapeutic intervention for GAD as both a monotherapy (after failure of an initial monotherapy) and as an augmentation strategy. Pregabalin is renally excreted and therefore poses a low risk of drug-drug interactions, lacks withdrawal or physical dependence risk, is associated with minimal adverse effects (dizziness, weight gain, insomnia), and is safe and well tolerated. A potential role for pregabalin may be in patients who are tapering off long-term benzodiazepine monotherapy for GAD.

Agomelatine is a novel compound that acts as an agonist of melatonergic (MT1, MT2) receptors and an antagonist of serotonergic (serotonin-2C) receptors. The antidepressant and anxiolytic effects of agomelatine appear to be mediated through the synergistic action at these receptors rather than through either one independently.

A 12-week, randomized, placebo-controlled study evaluated 25 to 50 mg of agomelatine used daily as monotherapy for GAD. Agomelatine was associated with a larger decrease in HAM-A score that persisted through study end. Responder rate in the agomelatine group separated from placebo by week 2 and persisted through week 12. By study end, remission rates were statistically significantly higher in the agomelatine group than in the placebo group. Subjective sleep parameters also improved to a greater extent in the agomelatine group. The most commonly reported adverse effects associated with agomelatine were dizziness and nausea.

A longer-term, randomized, placebo-controlled relapse prevention study enrolled patients who had responded to an initial 16-week open-label treatment with agomelatine into a 26-week double-blind maintenance period, during which time to relapse was assessed. Patients either remained in the agomelatine group or were switched to placebo during the blinded maintenance phase. During this phase, 19.5% of patients in the agomelatine arm relapsed compared with 30.7% in the placebo arm (P = .046). The risk of relapse over time was reduced by 41.8% for the agomelatine group (hazard ratio = 0.582). The reduced risk of relapse was achieved in the severely ill group as well.

Discontinuation of agomelatine did not precipitate withdrawal or discontinuation effects.

A 12-week international, multicenter, randomized, double-blind, placebo-controlled, active-comparator, parallel group study evaluated the efficacy of 25 to 50 mg of agomelatine daily compared with that of placebo or 10 to 20 mg of escitalopram daily. Both agomelatine and escitalopram were statistically superior to placebo in the reduction of HAM-A score by study end as well as in response rate and remission rate. This was also observed in the severely ill subset and was more pronounced in this group than in the full analysis set. Agomelatine has been established as a possible therapy for patients who endorse psychic and somatic symptoms and for patients who are considered more severely ill. It may be useful for treating patients for whom there is concern about drug interactions, dependence, or intolerance of adverse effects, since none of these issues are associated with agomelatine.

Vortioxetine is a multimodal antidepressant with potential anxiolytic effects. It acts as an inhibitor of...
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Serotonin reuptake by antagonizing the serotonin-3, serotonin-7, and serotonin-1D receptors, agonizing the serotonin-1A receptor, partially agonizing the serotonin-1B receptor, and inhibiting the serotonin transporter. Vortioxetine’s activity at multiple receptors results in modulation of the serotonergic, noradrenergic, dopaminergic, and histaminic systems, which results in antidepressant effects.

A 12-week relapse prevention study suggested that 5 or 10 mg of vortioxetine daily was efficacious in preventing relapse compared with placebo, and it was well tolerated. The most recent study, a randomized, double-blind, fixed-dose study, compared 2.5 and 10 mg of vortioxetine daily with placebo and found that there was no meaningful difference among any of the study arms. Atypical antipsychotics differ from typical antipsychotics with respect to their ability to antagonize the serotonin-2A receptor and with their partial agonism of the serotonin-1A receptor. Modulating the serotonin-1A receptor yields the anxiolytic effects, while antagonism of the serotonin-2A receptor minimizes the development of extrapyramidal effects. The atypical antipsychotics, particularly olanzapine, risperidone, and aripiprazole, also have high affinity for histamine receptors, which further augments their sedative and anxiolytic effects.

Aripiprazole was evaluated in 4 open-label studies involving patients with treatment-resistant disease who were not adequately controlled with SSRI monotherapy. A retrospective analysis reported that at the end of 12 weeks, 59% of patients were considered “improved” or “very much improved” in terms of CGI-I, which equates to a response. Numerous patients experienced an early (weeks 1 to 5) as well as sustained response to augmentation with 15 and 30 mg of aripiprazole daily. Weight gain, sedation, and insomnia were among the most frequently reported adverse events. Additional studies also supported the use of adjunctive aripiprazole, citing statistically significant improvements in HAM-A and CGI-I scores and appreciable rates of treatment response. Sedation, insomnia, and significant weight gain were observed in all 4 studies. Adjunctive risperidone has improved the clinical picture in patients with either treatment-refractory GAD or residual anxiety symptoms. The separation from placebo occurs as early as week 2 of therapy with respect to statistically significant reductions in HAM-A score. Patients with more severe residual anxiety symptoms derived the most benefit; the magnitude of score improvement was greater for these patients than for patients with less serious symptoms at baseline. Adverse effects most frequently observed include weight gain, headache, and increased appetite. Evidence suggests that monotherapy with extended-release quetiapine yields clinically and statistically significant improvements in HAM-A score and improved rates of remission compared with placebo. Three 10-week, multicenter, double-blind, placebo-controlled studies found that the reductions in HAM-A scores were statistically different from placebo for all active arms, with meaningful separation from placebo as early as week 1. Some improvements occurred as early as day 4. Somnolence, dizziness, and fatigue were reported more frequently in the active arms, yet sexual function improved slightly in the quetiapine groups. Patients with MDD frequently endorse comorbid anxiety, and the addition of quetiapine to SSRIs or venlafaxine was shown to improve HAM-A score by week 2 and improve rates of response and remission. Quetiapine also has been shown to decrease symptom recurrence and improve sleep quality in patients during maintenance treatment. Evidence supporting the use of quetiapine as adjunctive therapy in patients who are classified as nonresponders or partial responders is inconsistent at best and is not currently recommended.

Clinical challenges
Medications prescribed for GAD, although relatively effective, are associated with adverse effects and are frequently discontinued by patients after an inappropriately brief duration. Premature discontinuation of medication or unrealistic expectations can result in ineffective treatment and the retention of residual symptoms. The presence of residual symptoms increases the likelihood of a relapse. The first step in maximizing the effects of drug therapy is to provide patient education, specifically concentrating on adverse effects and when to expect them to arise, the expected delay in therapeutic effect when using antidepressants, and the importance of adhering to the regimen until an appropriate interval at which the efficacy and tolerability can be assessed. When a patient experiences lack of success with an initial monotherapy, additional medications can be used adjunctively to augment the first. This is becoming increasingly more common with the advent of anticonvulsants and antipsychotics being integrated into the treatment schema, particularly in treatment-resistant patients. Fortunately, there is momentum in developing newer, novel drugs in the hopes of mitigating some of the issues experienced with our current armamentarium.
**Disclosures:**

*Dr Reinhold is Associate Professor of Clinical Pharmacy in the department of pharmacy practice/pharmacy administration at the Philadelphia College of Pharmacy. She reports no conflicts of interest concerning the subject matter of this article.*

**References:**


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