Treatment-Refractory Generalized Anxiety Disorder

CME EDUCATIONAL OBJECTIVES

2. Explain treatment options available to patients who exhibit a partial response to standard pharmacotherapy for generalized anxiety disorder.
3. Explain treatment options available to patients who fail to respond to standard pharmacotherapy for generalized anxiety disorder.

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It has been reported that about half of patients with generalized anxiety disorder (GAD) do not respond adequately to standard pharmacological treatments, including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and imipramine, with or without a benzodiazepine. This article summarizes the literature on treatment-refractory GAD, which should assist clinicians in making relevant decisions.

Vladan Starcevic, MD, PhD; and Sean Hood, MD, MSc
DEFINING TREATMENT RESISTANCE

It has not been ascertained precisely at what point a GAD patient can be considered treatment-refractory. However, it is reasonable to assume that a patient is resistant to pharmacotherapy if he or she has not responded to 4 to 6 weeks of treatment with an adequate course of one of the SSRIs, SNRIs, and/or imipramine, administered in the maximum recommended or tolerated dose; response represents a 50% improvement in symptoms. In clinical practice, treatment resistance is not only related to the lack of effectiveness of medications but also to their adverse effects. Patients who cannot tolerate one or more standard pharmacological treatments for GAD are often considered treatment-resistant.

Complicating matters further is the lack of agreement on what constitutes an adequate medication trial for GAD. At times, there may be no need to wait 4 to 6 weeks to see whether a patient will respond. Some emerging evidence suggests that a lack of any improvement after only 2 weeks of treatment indicates a low likelihood of response after a full-length course of pharmacotherapy with that agent. Thus, in a patient with severe GAD who has not shown any signs of improvement after 2 weeks of treatment, perhaps another treatment strategy can be attempted.

Ultimately, it is up to clinicians to ascertain when the patient is considered refractory to the particular treatment.

Patients considered treatment refractory could be classified into two groups: those with some (partial) improvement and those who have not improved at all. There are few evidence-based guidelines about the next step for treatment-refractory patients. However, it is usually assumed that patients with partial response might continue treatment with the same medication, perhaps in a higher dose, or be considered for a treatment augmentation strategy. On the other hand, it is often thought that patients who fail to respond to one medication should be switched to another (see Sidebar, page 106).

PARTIAL RESPONSE TO STANDARD PHARMACOTHERAPY

Before any augmentation strategy is considered for partial responders, there are two options to consider. The first is to increase the dose of the medication, unless the patient has reached the maximum recommended or tolerated dose. There is some evidence to support this practice in GAD. For example, escitalopram 20 mg/day has been more efficacious than escitalopram 10 mg/day, and paroxetine 40 mg/day may produce better results than paroxetine 20 mg/day. Also, greater improvement in GAD may be achieved with higher doses (225 mg/day) of venlafaxine than with its lower ones (75 mg/day and 150 mg/day).

The other option is to continue medication treatment for several months, assuming the patient is able and willing. Incremental response to venlafaxine and improvement over the subsequent 3 to 6 months have been demonstrated in GAD patients who were initially only partly responsive.

The pharmacological treatment of GAD can be augmented with another medication or with psychological treatment.
Pharmacological Augmentation Strategies

Several augmentation strategies can be attempted, with varying degrees of supporting evidence. Adding a benzodiazepine to an antidepressant is common in clinical practice, usually when somatic symptoms of anxiety, tension, and insomnia are a prominent part in the clinical presentation. However, no studies demonstrate clearly the benefit of this.

Augmentation of an antidepressant with a hypnotic agent is also common. Insomnia is a frequent symptom of GAD and antidepressants, such as SSRIs and venlafaxine, may interfere with sleep.

One placebo-controlled study conducted in patients with insomnia and GAD investigated administration of escitalopram and eszopiclone, a nonbenzodiazepine hypnotic that acts as a gamma-aminobutyric acid (GABA) agonist. Escitalopram-treated patients who also received eszopiclone for 8 weeks significantly improved not only in terms of their sleep but also in their levels of anxiety, mood, and daytime functioning. There was no evidence of rebound insomnia after discontinuation of eszopiclone. Although this study was not a direct test of augmentation strategy, it demonstrated advantages of the treatment with an antidepressant and hypnotic.

A similar study with another hypnotic agent, zolpidem (extended release), added to escitalopram in GAD patients with insomnia, demonstrated significant improvements in sleep indices (albeit with one night of sleep deterioration upon discontinuation of zolpidem). However, no significant effects on anxiety symptoms were reported.

In one controlled trial, adjunctive pregabalin was administered to partial SSRI or SNRI responders with GAD. Subjects who had not responded to a course of an SSRI/SNRI or benzodiazepine and who had only a partial response to a different SSRI/SNRI after 8 weeks of prospective open-label treatment were random assigned to 8 weeks of augmentation with pregabalin or placebo. The mean change in the scores on the HAM-A and in the HAM-A responder rate at week 8 was significantly greater for adjunctive pregabalin than for adjunctive placebo.

Augmentation with Antipsychotic Agents

Augmentation strategies with several second-generation antipsychotics — aripiprazole, quetiapine, risperidone, olanzapine, and ziprasidone — were tested in GAD (as the only diagnosis or co-occurring with other anxiety/depressive disorders).

All four studies with aripiprazole were open-label, with a small number of patients (maximum 23). Aripiprazole was added to antidepressant therapy for up to 9 weeks. Mean doses of aripiprazole were relatively low (10.5 mg/day to 16.9 mg/day). Results were encouraging, with improvement reported on various outcome measures. There is clearly a need to study this augmentation strategy under controlled conditions and in larger samples of patients.

The quetiapine augmentation was studied in two randomized controlled trials and one open-label study. The maximum number of patients was 58. Mean doses ranged from 120 mg/day to 386 mg/day, with augmentation treatment for up to 12 weeks. The results were favorable in two studies, whereas one study reported no statistically significant separation between quetiapine and placebo. Considering the positive results of a large placebo-controlled study of quetiapine as monotherapy for GAD, the role of quetiapine in treatment-refractory GAD deserves more attention.

Risperidone was used as an augmentation agent in two randomized, controlled trials and one open-label study for up to 8 weeks. The
number of patients was relatively low, except in one study conducted in 390 patients.\textsuperscript{23} Mean doses of risperidone ranged from 0.86 mg/day to 1.12 mg/day. Although the two studies reported favorable results of this augmentation strategy,\textsuperscript{20,22} the findings were negative in the largest study, which was a controlled trial, but lasted only for 4 weeks.\textsuperscript{21} These conflicting results obviously call for further research.

One randomized, placebo-controlled trial tested adding olanzapine to fluoxetine for 6 weeks in 21 patients with treatment-refractory GAD.\textsuperscript{23} The mean dose of olanzapine was 8.7 mg/day. The results were mixed: There was a significant decrease in the scores on the relevant scales in the olanzapine-treated group, but no significant difference in the proportion of patients achieving remission. The mean weight gain in patients receiving olanzapine was 11 lb.

One very small (13 patients), open-label, 7-week study of ziprasidone (mean dose: 40 mg/day) for refractory GAD showed encouraging results.\textsuperscript{24} In three patients, ziprasidone was added to a benzodiazepine, whereas in others, it was used as monotherapy. Further studies are needed to establish whether ziprasidone might be a useful treatment option in GAD.

Augmentation with Psychological Treatment

Considering the apparent popularity of combining medications with psychological therapies, including cognitive-behavioral therapy (CBT), it is a paradox that this combination for GAD has received so little attention from researchers. In fact, apart from specific phobia, GAD is the least studied anxiety disorder in this regard. This is partly related to the difficulties in designing combination treatment trials and interpreting their results.

There is only one controlled, short-term treatment study, conducted in 101 patients with GAD, that compared the efficacy of diazepam alone (15 mg/day), CBT alone, combination of CBT and diazepam, CBT plus pill placebo, and pill placebo.\textsuperscript{25} All active treatments were superior to placebo. Although combination treatment was associated with the best outcome, it was not significantly better than other active treatments. Patients who received CBT were more likely to maintain treatment gains than those treated only with diazepam. It is difficult to draw any firm conclusions from this study, but it may suggest that there is no advantage of combining CBT and diazepam and that it is not cost-effective to do so. It is also unclear whether there are any implications for treatment-refractory GAD.

Results of studies in other anxiety disorders similarly suggest a possible short-term advantage of combination treatments and loss of that advantage in the long run.\textsuperscript{26} This is presumably because of the various ways in which medications can interfere with CBT. It would be important to minimize interference by combining medications and CBT carefully.

Another important issue is sequencing of treatments. It is unclear whether commencing CBT and pharmacotherapy at the same time might offer some advantage over the usual practice of commencing treatment with one modality and then adding another in case of partial response.

LACK OF RESPONSE TO STANDARD PHARMACOTHERAPY

In patients showing no or minimal response to standard pharmacological agents for GAD, the diagnosis should be reassessed and co-occurring conditions should be checked. Medication adherence issues may also need to be addressed. Ultimately, monotherapy with several other medications could be considered.

There is varying evidence to support using pregabalin, buspirone, hydroxyzine, benzodiazepines, and several antidepressants (trazodone, mirtazapine, bupropion, agomelatine), antipsychotics (quetiapine, trifluoperazin), and anticonvulsants (valproate, tiagabine). The choice of pharmacological agent in this situation depends not only on the efficacy in GAD, speed of therapeutic action, and efficacy against depressive symptoms and depression (see Table, page 108) but also on adverse effects, tolerability, dependence propensity, and safety in overdose.

A number of other medications and herbal medicines have been preliminarily investigated as potential monotherapy for GAD. Most of these agents are available only in some countries or remain unlicensed for wider use, and they will not be discussed in this article. Furthermore, there is conflicting, unconvincing, or little evidence that these agents (abecarnil, gepirone, riluzole, tandospirone, lesopitron, kava kava, passionflower extract, valerian) are useful in GAD. Some evidence suggests that a few other agents (opipramol, ginkgo biloba extract) may have a potential value in the treatment of GAD, which calls for further studies.
**Pregabalin**

Although it is a structural analogue of the inhibitory neurotransmitter GABA, pregabalin has no clinically significant effects at GABA receptors, nor does it exhibit functional activity at serotonin, dopamine or norepinephrine receptor sites. It binds with high affinity to the alpha2delta subunit of brain voltage-gated calcium channels, decreasing calcium-dependent presynaptic vesicle docking, which in turn decreases the release of neurotransmitters including glutamate, norepinephrine, and substance P that are known to be implicated in clinical anxiety states. As pregabalin has a high oral bioavailability, rapid onset of action, no significant protein binding and no known drug interactions, it is a potential anxiolytic compound of interest.

Results of a series of studies of short-term and long-term GAD treatment with pregabalin are now available. Pregabalin at doses of 150 to 600 mg/day in patients with GAD was statistically superior to placebo in five studies of adults and in one study of older adults. It was well tolerated; dizziness, weight gain, somnolence, headache, dry mouth, amblyopia, and diarrhea were the most frequently reported adverse effects, especially at the highest dose. Although some drug “likeability” was reported in recreational drug users, analysis of the long-term dataset provided no evidence of craving, misuse, or dependence. One 6-month relapse prevention study showed that pregabalin 450 mg/day was superior to placebo, albeit with a significant proportion (36%) of patients discontinuing pregabalin. Limitations of the evidence base supporting pregabalin as a therapy for GAD include uncertain efficacy in reducing depressive symptoms of greater than mild severity, lack of direct comparison studies with SSRIs, and availability/licensing/cost issues in some jurisdictions. Further (ideally, industry-independent) studies would be welcome in clarifying the role of this potentially useful medication.

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**TABLE:**

Comparisons Between Pharmacological Agents Used as Monotherapy in Patients with Treatment-Refractory GAD

<table>
<thead>
<tr>
<th>Short-term Efficacy in GAD</th>
<th>Long-term Efficacy</th>
<th>Efficacy in Preventing Relapse</th>
<th>Speed of Therapeutic action</th>
<th>Efficacy against Depressive Symptoms/Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin A</td>
<td>B</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Buspirone A</td>
<td>?</td>
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<td>0</td>
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<tr>
<td>Hydroxyzine A</td>
<td>?</td>
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<tr>
<td>Benzodiazepines A</td>
<td>?</td>
<td>?</td>
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<td><strong>Antidepressants</strong></td>
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<tr>
<td>Trazodone B</td>
<td>?</td>
<td>?</td>
<td>0</td>
<td>++</td>
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<tr>
<td>Mirtazapine C</td>
<td>?</td>
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<td>Bupropion C</td>
<td>?</td>
<td>?</td>
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<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Quetiapine A</td>
<td>B</td>
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<td>Trifluoperazine B</td>
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<td>+/++</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<tr>
<td>Valproate B</td>
<td>?</td>
<td>?</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Tiagabine D</td>
<td>?</td>
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<td>0/+</td>
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</tbody>
</table>

1. Levels of evidence
   - A = At least 2 randomized, double-blind, placebo-controlled studies showing efficacy
   - B = 1 randomized, double-blind, placebo-controlled study showing efficacy
   - C = Efficacy based on open-label or non-placebo-controlled studies
   - D = Questionable efficacy

2. Comparative advantage
   - ++ = Clear advantage
   - + = Some/possible advantage
   - 0 = Lack of advantage
   - ? = Insufficient information/lack of data

Source: Starcevic V.
Buspirone

Buspirone, an azapirone derivative and a 5-HT_{1A} partial agonist, is a non-sedating anxiolytic that does not cause dependence.\(^5\) In studies of GAD patients reviewed by Mitte et al.,\(^8\) buspirone demonstrated efficacy superior to placebo,\(^39,41\) comparable to benzodiazepines,\(^31-47\) but inferior to hydroxyzine\(^48\) and venlafaxine XR.\(^40\)

A recent study demonstrated comparable efficacy for buspirone 10 to 15 mg/day and sertraline 50 to 100 mg/day in an elderly GAD population.\(^49\) However, buspirone is not considered first-line therapy. It has a relatively slow onset of action, variable tolerability, lack of benefit against co-occurring depressive disorders,\(^38\) and lack of efficacy in recent benzodiazepine users\(^60\) (unless benzodiazepines are discontinued very gradually,\(^41\) ideally at least a month before initiation of buspirone treatment\(^40\)).

Buspirone remains a useful option in non-depressed, benzodiazepine-naive GAD patients and those with alcohol or cognitive problems.\(^51\) Treatment often starts at a dose of 5 mg three times daily, gradually titrating up to 60 mg/day, while monitoring for common side effects, including nausea, insomnia, headache, or agitation.

Hydroxyzine

The H1 histamine receptor antagonist hydroxyzine has been found to be particularly efficacious in treating GAD symptoms of insomnia and muscle tension, and has evidence of efficacy in studies of GAD patients lasting up to 12 weeks.\(^48,52,53\) Doses as low as 50 mg/day may be efficacious. However, because of its lack of efficacy in treating commonly co-occurring depressive symptoms and potential for oversedation, hydroxyzine is usually reserved as a second-line option.

Benzodiazepines

Benzodiazepines have historically been the main pharmacological agents in treating GAD and chronic anxiety states. In the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III), diagnosis of GAD included motor and autonomic symptoms of anxiety, and not surprisingly, benzodiazepines proved efficacious in subjects with GAD based on the DSM-III criteria.

In subsequent DSM iterations, the cognitive concept of worry has been increasingly emphasized in GAD. This shift parallels the rise of SSRIs as first-line anxiolytics and the move away from benzodiazepines. There is a solid evidence base\(^38\) supporting short-term use of benzodiazepines in GAD as monotherapy, including diazepam,\(^54,55\) lorazepam\(^28,29,33\) and alprazolam,\(^31,33,55\) especially in patients with prominent somatic complaints.\(^56\) However, benzodiazepines are generally reserved as second-line therapies because of the availability of alternatives with less potential for dependence, no motor impairment, and efficacy in frequently co-occurring depressive states.

Alternative Antidepressant Monotherapy

The efficacy in GAD of trazodone, a 5-HT_{2A} receptor antagonist and a less potent serotonin reuptake inhibitor, was compared with that of imipramine and diazepam in one large, placebo-controlled 8-week trial.\(^50\) The mean maximum dose of trazodone was 255 mg/day. Although the efficacy was most consistently demonstrated for imipramine, a comparable percentage of trazodone-treated patients were reported to exhibit moderate to marked improvement. The main drawback of trazodone is its sedative effect.

Mirtazapine is the noradrenergic and specific serotonergic antidepressant that enhances central noradrenergic and serotonergic neurotransmission. Its efficacy in GAD has been reported in one open-label study of 44 patients.\(^57\) Mirtazapine was administered in a fixed dose (30 mg/day) for 12 weeks. At the end of the trial, almost 80% of the patients were classified as responders. The onset of efficacy tended to be early, in the first week of treatment. The most common adverse effects of mirtazapine were sedation and weight gain.

Bupropion has a different mechanism of action from antidepressants effective in GAD. It is a norepinephrine and dopamine reuptake inhibitor. One 12-week randomized, double-blind study in 32 patients with GAD compared efficacy of fixed-dose bupropion extended-release (300 mg/day) and fixed-dose escitalopram (20 mg/day).\(^58\) Patients treated with bupropion improved significantly more than those treated with escitalopram in terms of anxiety and self-efficacy. No increase in anxiety and no agitation were reported in the bupropion-treated group. These findings call for larger placebo-controlled studies.

Agomelatine is an agonist at melatonin (MT_{1} and MT_{2}) receptors and an antagonist at 5-HT_{2C} receptors, with confirmed antidepressant effects. A randomized, double-blind, placebo-controlled study was conducted in 121 GAD patients for 12 weeks. Agomelatine was administered at 25 mg/day for 2 weeks with an optional increase to 50 mg/day thereafter.\(^59\) Agomelatine was superior to placebo on all outcome measures. The potential advantages of agomelatine include its favorable effects on somatic and cognitive symptoms of GAD, efficacy in improving sleep, and very good tolerability with no sexual dysfunction.

Antipsychotic Monotherapy

Quetiapine, a second-generation antipsychotic, has been investigated as a monotherapy in a series of phase 3 trials of acute primary GAD,\(^19,60,61\) in addition to a monotherapy trial in elderly patients\(^62\) and a 1-year maintenance trial.\(^63\) All these trials investigated the
efficacy of quetiapine’s extended-release formulation (quetiapine XR).

In one monotherapy study, quetiapine XR was used in fixed doses (50 mg/day and 150 mg/day) and compared with a fixed dose of paroxetine (20 mg/day) for 8 weeks. Quetiapine XR was superior to placebo and as efficacious as paroxetine. The dose of 150 mg/day achieved better results than the dose of 50 mg/day. A possible advantage of quetiapine XR over paroxetine was a lower frequency of sexual side effects and its early significant separation from placebo (after 4 days of treatment), suggesting a quick onset of action. The sedative properties of quetiapine XR may represent a disadvantage, but this medication was generally well tolerated.

In another monotherapy trial, quetiapine XR separated from placebo at doses of 50 mg/day or 150 mg/day, but not 300 mg/day, on the HAM-A scores; the efficacious doses were generally well tolerated.

The third monotherapy study compared quetiapine XR at 50 mg/day and 150 mg/day with escitalopram 10 mg/day and placebo. Both quetiapine XR doses were effective in improving GAD symptoms by day 4 (earlier than escitalopram), and quetiapine XR 150 mg/day significantly improved response and remission rates based on HAM-A scores. Quetiapine XR at doses of 50 mg/day to 300 mg/day was also efficacious in the monotherapy trial in elderly patients, while the 52-week time-to-event extension of a 12-week, open-label stabilization trial found that quetiapine XR at an average dose of 162.8 mg/day significantly reduced the risk of anxiety symptom recurrence in patients with GAD. Thus, quetiapine XR appears to be a promising pharmacotherapy option for treatment-refractory GAD at doses at or around 150 mg/day.

The first-generation antipsychotic, trifluoperazine, was efficacious in one large, double-blind, placebo-controlled trial in patients with moderate to severe GAD. The trial lasted only 4 weeks, but trifluoperazine was consistently superior to placebo on all outcome measures and at all points of comparison.

**Anticonvulsant Monotherapy**

One randomized, double-blind, placebo-controlled study examined the efficacy of valproate (1,500 mg/day) in 80 male GAD patients who were rated at least moderately anxious. The subsequent course of action depends on the clinical presentation of particular patients.

Compared with the group that received placebo, a significantly greater proportion of the valproate-treated patients responded after 6 weeks. These findings need to be replicated, but they are interesting in view of efficacy of valproate in treatment of other anxiety disorders, especially panic disorder.

Tiagabine is an anticonvulsant acting as a selective GABA reuptake inhibitor, which has been used with some success in various anxiety disorders and found to be efficacious in GAD in one open-label study. The efficacy of tiagabine in GAD was subsequently investigated in three large, randomized, placebo-controlled, 10-week trials. One was a fixed-dose study (4, 8, and 12 mg/day) and two were flexible-dose trials (4 to 16 mg/day). Across all three studies, patients receiving tiagabine did not fare significantly better than those in the placebo group. However, in the two flexible-dose trials, patients who completed 10 weeks of treatment demonstrated significantly greater improvement compared with patients receiving placebo. This suggests that tiagabine might still be a viable option for some GAD patients.

**CONCLUSION**

Patients with treatment-refractory GAD represent a challenge. Many promising pharmacological strategies have been used in the management of these patients, and pharmacotherapy can be combined with psychological treatments, such as CBT.

Although clinicians are not likely to use instruments, such as HAM-A, in their busy practice to determine whether a patient has exhibited full, partial, or negligible response, they should still be able to establish this on the basis of their comprehensive but routine assessment. The subsequent course of action depends on the clinical presentation of particular patients and characteristics of medications that are considered, either as augmentation agents or as alternative monotherapy.

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