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Management of treatment-resistant generalized anxiety disorder

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Abstract

Generalized anxiety disorder (GAD) is characterized by persistent and excessive worry. Around half of the patients treated for GAD will fail to respond to initial treatment. Treatment-resistant (or refractory) GAD is defined as failure to respond to at least 1 trial of antidepressant therapy at adequate dose and duration. Review of the literature indicates several potential medication classes and individual agents that can be used as augmentation strategies to treat residual symptoms when recommended therapy per clinical practice guidelines fails. A thorough literature search revealed 2 medication classes with the largest amount of data to support their use in treatment-resistant GAD treatment: gamma-aminobutyric acid–related agents and atypical antipsychotics. This article focuses on evidence-based recommendations for the use of these agents as adjunctive therapies for patients with treatment-resistant GAD. Different pharmacologic approaches to use these agents are demonstrated through 2 patient cases in which patients have failed first-line treatment options.

Keywords: generalized anxiety disorder, treatment-resistant, pregabalin, tiagabine, atypical antipsychotics

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Introduction

Generalized anxiety disorder (GAD) is classified under the umbrella of anxiety disorders within the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.[1] All anxiety disorders share characteristics of excessive fear and anxiety and differ from developmentally normal fear and anxiety by being excessive beyond appropriate periods. Diagnostic features of GAD included persistent and excessive anxiety and worry about various domains that the patient finds difficult to control. Symptoms of GAD also include feeling keyed up or on edge, fatigue, difficulty with concentration, irritability, muscle tension, and sleep disturbances. Symptoms must be present most days for a period of at least 6 months and cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (Table 1).[1] Evidence points towards neurochemical abnormalities in the gamma-aminobutyric (GABA)/ benzodiazepine (BZD), norepinephrine, and serotonin systems.[2]

Generalized anxiety disorder is the most common anxiety disorder seen in the primary care setting.[3] The 12-month prevalence of GAD is 2.9% among adults in the United States. Prevalence of the diagnosis tends to peak in middle age and decline over the course of aging.[4] Nonpharmacologic interventions for treatment of GAD include psychotherapies such as cognitive behavioral therapy or relaxation therapy. These psychotherapies can be used as first-line treatment choices or in combination with medication therapy.[5] Goals of therapy include decreasing core symptoms of the disorder, such as worry and distress, and improving overall function. A decrease in somatic symptoms such as fatigue and

Take Home Points:

1. Around 50% of the patients treated for generalized anxiety disorder (GAD) will not respond to first-line treatment such as antidepressant therapy. Treatment-resistant GAD (TR-GAD) is usually considered when a patient does not respond to at least 1 antidepressant at an adequate dose for an adequate duration.
2. While benzodiazepines have shown benefit in the short-term use of TR-GAD, long-term use is not recommended secondary to the potential for dependence, misuse, and correlation to cognitive decline.
3. Gamma-aminobutyric acid–related agents, such as the gabapentinoid pregabalin, have demonstrated efficacy in treating TR-GAD as adjunctive agents. Caution should be taken if using a gabapentinoid in a patient with respiratory compromise.
4. Atypical antipsychotics, such as quetiapine, risperidone, aripiprazole and ziprasidone, have demonstrated efficacy in the management of TR-GAD as adjunctive agents. Lower doses than those used in schizophrenia and bipolar disorder are typically needed for symptom improvement.

musculoskeletal complaints should also be achieved. Achieving symptom remission should enhance the patient's overall satisfaction in life.[6] First-line pharmacotherapy treatments approved by the Food and Drug Administration (FDA) for GAD include the selective serotonin reuptake inhibitors (SSRIs) escitalopram and paroxetine and the serotonin-norepinephrine reuptake inhibitors duloxetine and extended-release venlafaxine.[6] Other SSRIs have been shown effective in treating GAD and include fluoxetine, sertraline, and citalopram. Other FDA-labeled antidepressants such as vilazodone, mirtazapine, vortioxetine, and bupropion all have demonstrated varying degrees of efficacy in the treatment of GAD.[7] Other agents such as buspirone (FDA-approved for GAD) and antihistamines like hydroxyzine (FDA-approved for anxiety) have also demonstrated efficacy in the treatment of GAD and are considered reasonable second-line or third-line agents for management of the disorder.[3] Agents such as imipramine, a tricyclic antidepressant, are also considered second-line or third-line treatments secondary to their side effect profile when compared to preferred agents.[8]

BZD Use in GAD

Other agents historically used in the treatment of GAD include medications in the BZD class. Alprazolam, diazepam, and lorazepam all have demonstrated efficacy for the treatment of GAD, however their use is recommended as second-line therapy and for short duration use because of their known side effects, potential for dependence, and withdrawal issues.[8] Maximal duration of BZD use in clinical practice guidelines ranges from 2 to 8 weeks, followed by a slow taper. Despite these recommendations for short-term use, studies have found chronic, long-term BZD prescribing in anxiety patients, with rates as high as 83%.[9]

TABLE 1: The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition,[1] diagnostic criteria for generalized anxiety disorder

Criterion	Description
A	Excessive anxiety and worry, occurring more days than not for at least 6 mo, about a number of events or activities.
B	The individual finds it difficult to control the worry.
C	The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 mo): • Restlessness or feeling keyed up or on edge. • Being easily fatigued. • Difficulty concentrating or mind going blank. • Irritability. • Muscle tension. • Sleep disturbance.
D	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E	The disturbance is not attributable to the physiological effects of a substance or another medical condition.
F	The disturbance is not better explained by another mental disorder.

The discrepancy between guideline recommendations and observed clinical practice warrants further examination. Researchers have investigated the long-term use of BZDs in the treatment of anxiety disorders, however interpretation of the evidence can be difficult given the variability in duration and design. A systematic review[10] concluded that there was no significant differences in changes in Hamilton Anxiety Rating Scale (HAM-A), all-cause discontinuation, number of panic attacks, and side effects between BZDs and antidepressants after 8 weeks of acute treatment. The review also points out that, given the limited amount of evidence, further investigation of the long-term effectiveness and safety of BZDs is warranted. Some correlate low dropout rates in these studies to efficacy, despite results that showed that BZDs did not separate from placebo in effectiveness measures such as HAM-A.[11] A 2014 review[12] of clinical practice guidelines investigated the recommendation for short-term or long-term use of BZDs in GAD. In this review BZDs were

recommended for short-term treatment of GAD, either until the effects of the concomitantly started antidepressant were apparent, or for use during an unexpected crisis or period of time where increased anxiety was identified. Long-term use of BZDs was only recommended for patients with a lack of treatment response or intolerance to first-line antidepressant and psychological intervention.

Opposition of long-term use of BZDs is largely driven by safety concerns, namely discontinuation and withdrawal symptoms, misuse, and cognitive impairment.[11] While the anxiolytic effect of BZDs is observed with short term use (ie, <4 weeks), use beyond that can cause rebound anxiety.[13] Rebound symptoms appear after medication termination and are the opposite of the effects of the medication (ie, worsening anxiety, restlessness). These symptoms may be severe enough to cause the patient to return to using the medication, mistaking the rebound symptoms for symptoms of their anxiety disorder.[14] When contemplating long-term BZD use, consideration should be given to their effects on cognition and development of cognitive impairment. Patient populations identified to be at high risk for cognitive changes are those who require high doses of BZDs, males, elderly, those with concurrent substance use disorders, or those taking medications with anticholinergic properties. Visuospatial impairments appear to have been most specifically linked to long-term use. Changes in psychomotor function, motor speed, sustained attention, and verbal memory appeared to be unassociated with long-term BZD use. After cessation of the BZD, patients have demonstrated recovery in cognitive domains, however some impairment can still persist when compared with control groups.[15] Given the potential for cognitive effects to occur, along with other concerns such as dependence and withdrawal effects, a risk versus benefit analysis and conversation with the patient should occur when deciding if long-term BZD use is appropriate for treatment.

While a host of pharmacologic agents are available to treat GAD, it is estimated that as many as half of the patients treated will not respond adequately to selected therapy. Although there is not one recognized definition, treatment-resistant GAD (TR-GAD) can be defined when a patient does not respond to at least one antidepressant at an adequate dose for an adequate duration.[7] Given that anxiety disorders often take longer to observe a treatment response compared to the treatment of depression, an adequate duration of at least 8 weeks of treatment is warranted before considering the treatment a failure. If a first-line agent is not effective, another first-line agent can be tried. Clinical practice guidelines offer several second-line and third-line therapies to treat GAD (Table 2). However, because there is a high partial or nonresponse rate in GAD treatment, augmentation strategies have been studied to guide pharmacologic therapy to help achieve the goal of remission in these difficult-to-treat patients. The remainder of this review will focus on some of these augmentation strategies.

Case 1

A 63-year-old with a history significant for GAD presented to the psychiatrist for evaluation after failed treatment of anxiety symptoms by the primary care provider for the past 8 months. Chief complaints included excessive anxiety and worry most days of the week. The reported anxiety was accompanied by feelings of fatigue, irritability, muscle tension, and difficulty with sleep. Both monotherapy with paroxetine and extended-release venlafaxine, optimized to maximum dosage were tried and tolerated to help alleviate these symptoms. Residual symptoms were still reported with extended-release venlafaxine after 16 weeks of treatment. At that time buspirone was added and titrated to maximum tolerated dose, however prominent symptoms that interfere with daily functioning continued to be reported. Per review of records, cognitive behavioral therapy sessions were attended regularly, and all homework was completed thoroughly and in a timely manner. The physical exam and all laboratory values and vital signs were within normal limits. Other known medical conditions included hypertension and diabetes mellitus, both of which were controlled. There were no known allergies to medications.

GABA-Related Agents

Pregabalin

The GABA analogue pregabalin has demonstrated efficacy as both monotherapy and as an adjunctive intervention for TR-GAD.[7] Pregabalin exerts its anxiolytic effects by potently binding to the alpha2-delta subunit of the voltage-gated N-and P/Q-type calcium channels in central nervous system (CNS) tissue.[18] This causes a decrease in presynaptic calcium currents which modulates the release of neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide from excited neurons. Unlike BZDs, pregabalin does not exacerbate GABA-mediated responses nor does it affect GABA reuptake or GABA transaminase inhibition.[8,18]

The efficacy of pregabalin as an adjunctive treatment in TR-GAD has been studied in randomized, double-blind, placebo-controlled trials.[19,20] Studies were 8 weeks in length and used the HAM-A as the primary endpoint for measuring anxiety refractory to treatment with antidepressants. Results from these trials show clinical response compared to placebo[19] or usual care[20] by week 1 and the addition of pregabalin as an augmenting agent was associated with significantly higher benefit in anxiety outcomes. A potential benefit of using pregabalin may be

TABLE 2: Summary of current generalized anxiety disorder treatment guidelines

Guideline	Intervention Level			
	Process	First Line	Second Line	Third Line
BAP[16]	Systematic review and expert opinion/ clinical experience	Psy: CBT or applied relaxation SSRI: citalopram, escitalopram, paroxetine, sertraline SNRI[a]: duloxetine, venlafaxine Pregabalin[a] Treatment period: 12 wk	Switch to another EBT (includes: agomelatine, quetiapine, BZD, imipramine, hydroxyzine, trazodone) Consider combination of EBTs Pregabalin augmentation Combination drug treatment and CBT	BZD after non-response to SSRI, SNRI, pregabalin and buspirone
Canadian Clinical Practice Guidelines[8]	Systematic review and consensus process	Psy: CBT SSRI: escitalopam, sertraline paroxetine; paroxetine CR SNRI: duloxetine, venlafaxine XR Agomelatine Pregabalin	BZD (short-term): alprazolam, bromazepam, diazepam, lorazepam Bupropion XL Buspirone Hydroxyzine Imipramine Quetiapine XR Vortioxetine 2nd line adjunctive therapy: pregabaline	SSRI: citalopram, fluoxetine Divalproex Mirtazapine Trazodone 3rd line adjunctive therapy: aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone
NICE[17]	Systematic review and expert testimony; considers costs	Psy: CBT or applied relaxation SSRI: sertraline	Alternative SSRI or SNRI Pregabalin[b]	

BAP = British Association of Psychopharmacology; BZD = benzodiazepine; CBT = cognitive behavior therapy; CR = extended release; EBT = evidence-based therapy; NICE = National Institute for Health and Care Excellence; Psy = psychotherapy; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; XL = extended release; XR = extended release.

[a]If SSRIs are not suitable.

[b]If SSRI/SNRI not tolerated.

this quick time to effect as demonstrated in these studies, compared to the delayed effect of trialing another antidepressant medication.[7] Treatment with pregabalin was associated with significantly greater improvement compared to placebo in 3 out of 7 assessment timepoints (weeks 1, 3, and 4). Mean reduction in HAM-A total scores over the 8-week period were –7.6 for pregabalin versus –6.4 for placebo ($P < .05$).[19] Doses varied between 150 and 600 mg/d. Treatment with pregabalin was generally well-tolerated within this dose range. Studies of pregabalin for use in GAD indicate that serious side effects are rare. Mild side effects include dizziness, somnolence, and dry mouth. Side effects were observed to be correlated to dose, as patients who discontinued secondary to adverse effects tended to be taking higher doses.[21]

Although literature indicates a large number needed to harm for the use of pregabalin in TR-GAD, it should be noted that in December 2019 the FDA[22] issued a drug safety communication regarding the use of gabapentinoids (gabapentin and pregabalin). Several data sources, including case reports (reported to the FDA or published in the medical literature), observational studies, clinical trials, and animal studies, were reviewed by the FDA and showed that serious breathing difficulties can occur when gabapentinoids, including pregabalin, are taken by patients with preexisting respiratory risk factors. The warning specifies preexisting risk factors as medical conditions such as chronic obstructive pulmonary disease, as well as in combination with medications such as opioid pain medication or other medications that depress the CNS. Other medications that can depress the CNS are antianxiety medications, such as BZDs, antidepressants, and antihistamines. Given that these medications can be used in the treatment of TR-GAD, caution should be used if pregabalin is selected as an augmenting agent. Prescribers should use caution if initiating a gabapentinoid in combination with a CNS depressant to start at the lowest possible dose and monitor for symptoms of respiratory depression.[22] Additional caution should also be noted for rising concern of the abuse and misuse of gabapentinoids. A recent published analysis[23] of the FDA Adverse Events Reporting System revealed more than

600 cases of gabapentinoid abuse over a 4-year time period.

Tiagabine

Tiagabine is a GABA-reuptake inhibitor and exerts its action on the presynaptic GABA transporter-1.[7] Inhibition of the GABA reuptake pump allows for higher concentrations of GABA, which can potentiate GABA receptor activity. The pharmacodynamic effect of tiagabine is similar to BZDs, which can be used to treat GAD.[24] While results from double-blind placebo-controlled trials have produced mixed results, open label studies have found tiagabine to be effective and well tolerated in the treatment of TR-GAD.[7] Augmentation doses reported in open label studies range from 10 to 16 mg/d given in divided doses. Clinical improvement, if seen, was observed within 2 months of therapy.[24] Tiagabine was generally well tolerated with common adverse effects reported to be similar to those of pregabalin, which include dizziness, headache, nausea, fatigue, and somnolence.[7]

Case 1 is an example of a patient with GAD which is considered treatment-resistant, given failure of symptom remission after adequate trials of recommended first-line antidepressants, in this case paroxetine and extended-release venlafaxine, as well as augmentation with buspirone. Even though the patient notes some relief of symptoms, they still occur to a point of functional interference. While agents such as BZDs could be considered for treatment, there is limited data to support their long-term use and clinical efficacy in GAD. An argument could be made for short-term use of BZDs, however, given the partial response to current therapy with extended-release venlafaxine, long-term augmentation to control symptoms is likely needed for this patient. Known safety risks of long-term use of BZDs limit the feasibility for use in this patient. Additionally, given the age of this patient, additional concern is warranted when considering long-term use and the risk for cognitive impairment.

The GABA-related agents, such as pregabalin, could be considered for augmentation to help alleviate symptoms in this case. Although tiagabine has some evidence for use, the relative amount of data for use of pregabalin compared to tiagabine makes pregabalin the preferred choice. Although there are safety concerns for pregabalin as well, the patient does not have any known risk factors outside of the use of the prescribed antidepressant agent, as mentioned in the FDA drug safety communication, that would make pregabalin a less preferred agent. The FDA drug safety communication classifies antidepressants as *CNS depressants*, thus the rationale for extra precautions when combining them with pregabalin, or another gabapentinoid. The risk of combining an antidepressant (such as venlafaxine) could be argued as lower, compared to selecting an agent such as a BZD for reasons stated above. An additional benefit of selecting pregabalin in this case for augmentation is the relatively quick onset of symptom remission. As noted above, symptom remission was seen as quickly as within the first week. This quick response time is likely preferable compared to the time it may take to switch to another antidepressant agent and wait for an effect.

Case 2

After stabilization at an outside hospital, a 32-year-old with GAD was admitted to an inpatient psychiatric treatment facility after a suicide attempt via overdose on lorazepam. Despite multiple trials of recommended antidepressants as well as augmenting therapies including buspirone and long-term lorazepam, minimal remission of anxiety symptoms had been observed since starting treatment for GAD in the patient's mid-20s. Engagement with both cognitive behavioral therapy and relaxation therapy, in addition to pharmacologic treatment was noted in the medical record. Primary symptoms reported include excessive worry as well as somatic symptoms, primarily muscle tension and inability to sleep, which led to the suicide attempt. No other psychiatric diagnoses were noted. Physical exam, laboratory values, and vital signs were all within normal limits. Since the suicide attempt and subsequent stabilization, home doses of escitalopram 20 mg by mouth daily and buspirone 20 mg by mouth 3 times daily were restarted. Lorazepam was not restarted. There were no known allergies to medications.

Atypical Antipsychotics

The exact mechanism of action of atypical antipsychotics in the treatment of GAD is unknown. Proposed mechanisms include antagonism at the 5-HT_{2A} receptors, as well as partial agonism at the 5-HT1A receptors. Modulation of histamine receptors may also contribute to the efficacy of these agents in treating GAD. Additionally, the active metabolite of quetiapine, norquetiapine, is a norepinephrine reuptake inhibitor. The atypical antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all have been examined as augmentation options in the treatment of TR-GAD.[6]

Aripiprazole

Aripiprazole is a partial dopamine type 2 (D_2) and serotonin type 1A (5-HT_{1A}) receptor agonist that binds to dopamine type 3 and serotonin type 2A (5-HT_{2A}) receptors.[7] One open-label study[25] examined the use of aripiprazole as an augmenting agent in patients with GAD who had an inadequate response despite an adequate dose and duration of their SSRI. Doses ranged from 7.5 to

30 mg/d. Aripiprazole improved the mean (± SD) baseline Clinical Global Impression - Severity (CGI-S) score from 5.4 ± 0.5 to 3.8 ± 1.3 ($P < .001$). Fifty-nine percent of the patients (10/17) were rated as demonstrating a full response, defined as a significant mean change in CGI-S score from baseline to endpoint and Clinical Global Impression - Improvement (CGI-I) score of ≤2 (much improved or very much improved). Five of the 17 patients reported having no adverse effects. Adverse effects that were reported included lightheadedness and jaw clenching. Two patients reported weight gain as a primary adverse effect at the end of the 12-week trial.[25] Another open-label study[26] looked at aripiprazole as an augmenting agent over a 6-week period in 9 patients with TR-GAD. The mean dose of aripiprazole used at the end of the study was 13.9 mg/d. Addition of aripiprazole to current regimen in this study showed improvement in the HAM-A with the baseline mean of 26.2 to 14.2 ($P < .0001$). Five patients were deemed HAM-A responders (≥50% reduction) and 1 was a remitter (HAM-A <10). One patient terminated the study secondary to akathisia. Side effects reported as mild to moderate included headache, nausea, dizziness, tiredness, blurred vision, weight gain, and increased anxiety. An open-label study[27] of adjunctive aripiprazole in 23 patients with either GAD or panic disorder found that augmentation was associated with a significant reduction in CGI-S scores. Similar to other augmentation studies, patients remained symptomatic despite treatment with an adequate dose of an anxiolytic agent for at least 8 weeks. Aripiprazole was initiated at 2.5 mg/d and flexibly titrated up to a maximum dose of 30 mg/d. Mean aripiprazole dose at endpoint was 10.5 ± 4.95 mg/d. In addition to the primary outcome of CGI-S score, a subgroup analysis of the GAD patients showed significant improvement in HAM-A scores (23.5 ± 3.5 to 16.8 ± 6.3; $P \leq .01$). Augmentation with aripiprazole was generally well tolerated, common adverse effects were fatigue, insomnia, and jitteriness. Mean weight gain was 1.1 ± 1.9 kg in this 8-week study.

Olanzapine

Olanzapine has potent, mixed effects at serotonin type 2 (5-HT_2) and D_2 dopamine receptors. One randomized controlled trial[28] of 24 patients with TR-GAD investigated olanzapine augmentation in patients treated with the SSRI fluoxetine. Treatment with olanzapine augmentation (n = 12) compared to placebo (n = 12) demonstrated a decrease in mean HAM-A scores (± SD) from 17.4 ± 6.5 to 10.4 ± 6.4 in the olanzapine treated group, compared to 22.6 ± 5.2 to 18.7 ± 9.2 in the placebo group ($P = .4$). Authors[28] note that while reduction in HAM-A scores were not statistically different when compared to placebo, the change in score was in the expected direction and achieved an effect size of 0.58, indicating that a larger study may find greater reduction in HAM-A with olanzapine use. The mean dose of olanzapine used in augmentation of fluoxetine 20 mg/d was 8.7 ± 7.1 mg/d. Most adverse events reported were mild to moderate in severity, however 4 patients in the olanzapine arm did discontinue the study secondary to sedation. For those who completed the study, average weight gain on olanzapine was 5.0 ± 2.2 kg (range 0.9 to 7.2 kg) compared to –0.3 ± 1.1 kg with placebo after 6 weeks of olanzapine therapy.

Risperidone

Risperidone has potent effects at serotonergic, as well as dopaminergic, receptors with its modulation of the serotonin system being theorized as the mechanism by which it exerts its anxiolytic effects.[29,30] In 1 open-label study,[29] 30 patients with panic disorder, social anxiety disorder, or GAD refractory to initial pharmacotherapy with adequate antidepressant trial of at least 8 weeks received risperidone augmentation. Doses of risperidone ranged from 0.25 to 3 mg/d and resulted in an average decrease in HAM-A of 6.75 points ($P = .0005$). Common adverse effects reported were sedation, increased appetite, and dizziness. Five patients discontinued risperidone because of adverse effects. An additional double-blind, placebo-controlled study[30] evaluated the use of risperidone in patients who continued to experience GAD symptoms, despite anxiolytic or antidepressant treatment for at least 4 weeks. Patients were initiated on once daily risperidone or placebo. Doses started at 0.5 mg/d and were titrated to 1.5 mg/d based on tolerability and response. The primary outcome measure was change from baseline to endpoint on the HAM-A total score after 5 weeks of therapy. Thirty-nine patients were included in the study, 19 of which received at least 1 dose of risperidone. Adjunctive risperidone was found significantly more effective than placebo in reducing anxiety as evidence by change in total HAM-A score (–9.8 ± 5.5 vs –6.2 ± 4.9; $P = .034$). In this 5-week investigation, risperidone was reported as being well tolerated, but 3 patients did discontinue the study secondary to adverse effects. Mostly commonly reported events were dizziness, somnolence, and blurred vision. No patients required adjunctive treatment with anticholinergic agents. Mean changes in weight between the groups was not statistically significant.

Ziprasidone

Ziprasidone is an atypical antipsychotic whose mechanism is mediated through the combination of D_2 and 5-HT_2 antagonism. Additionally ziprasidone has moderate affinity for histamine 1 receptors.[31] Its serotonergic properties are what may make it useful in the treatment of GAD.[32] Ziprasidone's use in TR-GAD was investigated in an open-label pilot study[32] of patients with GAD who had HAM-A scores ≥16 after 8 weeks of treatment with at least 1 first-line antianxiety agent. Patients were randomized to receive ziprasidone monotherapy for 7 weeks, starting at

20 mg/d and titrating based on response up to 80 mg/d. Thirteen patients were enrolled, and treatment with ziprasidone showed that 54% of the patients receiving ziprasidone responded (reduction in HAM-A $\geq$50%) and 38% of the patients receiving ziprasidone remitted (HAM-A $<$7). Although this was a small pilot study, results indicate that ziprasidone may be useful in the treatment of TR-GAD. Adverse effects included sedation, difficulty concentrating, dizziness, and insomnia. The QTc change from baseline to end point was 1.7 milliseconds. A placebo-controlled, double-blind 8-week study[33] investigated the use of ziprasidone in 62 patients with TR-GAD. In this randomized study, 41 received ziprasidone as augmentation or monotherapy. Mean doses of ziprasidone ranged from 50.24 mg/d to 62.86 mg/d. HAM-A total scores in the intent to treat population (n = 57) did not show statistical significance (P = .22); however, in the medication augmented group a trend towards significance was noted. Common adverse effects reported with ziprasidone use included drowsiness, stimulation, insomnia, and dry mouth. Administration of ziprasidone with food is recommend as absorption is increased up to 2-fold in the presence of food.[31] In both these studies[32,33] it was not assessed if ziprasidone was administered with food.

Quetiapine

Quetiapine, and its active metabolite norquetiapine, have moderate to high affinity for D_2 and 5-HT_2 receptors. Norquetiapine is also a potent inhibitor of the norepinephrine transporter.[34] Quetiapine exists in both immediate release and extended-release formulations. Efficacy and tolerability of the extended-release preparation as monotherapy in GAD has been demonstrated in randomized, double-blind, placebo-controlled and active comparator-controlled trials.[34] In TR-GAD, safety and efficacy has been evaluated with immediate release quetiapine as an augmenting agent. In 1 randomized, placebo-controlled study,[35] 20 patients with GAD who had failed treatment with an adequate trial of an SSRI for 8 weeks were randomized to receive augmentation with quetiapine or placebo in addition to their current therapy. Individual doses of quetiapine were not reported, but patients were initiated at 25 mg/d and titrated weekly up to a maximum of 150 mg/d. At end point, the quetiapine group showed a statistically significant improvement over placebo on the HAM-A. Number of responders was higher in quetiapine group compared to placebo but did not reach statistical significance (60% vs 30%; P = .37). This was also true with regards to remitters (40% vs 20%; P = .63). As serotonergic effects of quetiapine appear to start at 150 mg/d, the maximum dose used (150 mg/d) may have limited the observed. No patient discontinued the trial because of side effects or lack of compliance. Another flexible-dose, open-label pilot trial[36] investigated the use of quetiapine as an adjunctive pharmacology in patients with GAD who had not achieved remission following at least 8 weeks of an adequate and stable dose of traditional therapy. Forty patients received adjunctive doses of quetiapine immediate release, in addition to their current medication. The dose range of quetiapine for those who completed the study was 25 to 800 mg/d (mean dose 386 mg/d). Adjunctive quetiapine significantly reduced the HAM-A scores as early as week 1 and achieved statistical significance by week 12 with a mean decrease of –20.6 in the HAM-A score (P $<$ .001). No serious adverse effects were reported during the course of the study, with the most commonly reported adverse effects of sedation and dry mouth. Seven patients withdrew because of adverse effects.

One limitation in the use of atypical antipsychotics for the use in the treatment of TR-GAD is the incomplete evaluation of these medications on metabolic adverse effects. Many trials did not evaluate lipid panels or fasting glucose measurements, therefore the metabolic effects of these agents on patients when used for the treatment of GAD is largely unknown.[5] Many of these studies are short in duration (6-8 weeks) and therefore the long-term effect of these agents when used as adjunctive therapy in TR-GAD has still not been elucidated.

Case 2 illustrates a patient who has failed many monotherapy and adjunctive therapy options in the treatment of GAD. Continuation of the BZDs as a treatment option would not be recommended given the inefficacy of the agent to treat anxiety symptoms, risk of long-term effects, and perhaps most importantly safety concerns given the patient's history of overdose requiring hospitalization. While augmentation options including the aforementioned GABA-related agents could be considered, atypical antipsychotics would also be a treatment option for this patient to help reduce symptoms. Several atypical antipsychotics have been investigated and found efficacious as augmentation to recommended antidepressant therapy to improve residual symptoms. An agent should be selected based on patient-specific factors including side effect profile and potential drug-drug interaction. Efficacy of these agents has been shown in short-term trials ranging from 5 to 8 weeks in duration. It is unknown if therapy for these agents should be continued indefinitely if symptom remission is achieved. Given the known adverse effects of these agents such as metabolic syndrome and their potential for extrapyramidal symptoms, usefulness should continually be evaluated and assessed for discontinuation or dose reduction. Although studies discussed did not demonstrate these effects to be significant, the short duration may be a limiting factor in observing their development. Given the lack of long-term data on the use of atypical antipsychotics in TR-GAD, their use should routinely be evaluated for continued inclusion in a patient's treatment regimen.

Dosing of these agents is also variable among studies. In general, doses of atypical antipsychotics seem to be less than those typically used in schizophrenia and bipolar disorder, and more in line with doses used for augmentation in the treatment of depression. If an atypical antipsychotic is selected as an augmenting agent, initiation at a low starting dose with titration based on clinical response is recommended. In instance of patient case 2, an agent such as quetiapine, initiated at 25 mg/d and titrated at weekly intervals to response could be considered for therapy in addition to the escitalopram. Choice of another atypical antipsychotic discussed above would also be appropriate. Additionally, the patient should be monitored for metabolic events such as weight gain and blood pressure, lipid, or blood glucose changes.

Conclusion

Treatment-resistant GAD can be defined as the failure of 1 antidepressant at adequate dose and duration. Although there is an armamentarium of agents that have been studied in the treatment of GAD, and current published treatment guidelines provide substantial guidance on treatment pathways, about 50% of the patients with GAD still do not respond adequately to selected treatment. Given the high nonresponse or failure rate of treatment, alternative, off-label agents should be considered to help treat patients. Considerations to GABA-related agents such as pregabalin and tiagabine, as well as atypical antipsychotics such as aripiprazole, olanzapine, risperidone, ziprasidone, and quetiapine should be given. Although limited, data has been presented to support trials of these agents in this difficult-to-treat population.

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