First-Line Pharmacotherapy Approaches for Generalized Anxiety Disorder

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Many patients with generalized anxiety disorder (GAD) do not receive adequate treatment. Several classes of drugs, including benzodiazepines, azapirones, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, antihistamines, $\alpha_2\delta$ Ca++ channel modulators, and atypical antipsychotics are consistently beneficial in patients with GAD. Cognitive therapy is also effective as a first-line treatment. When individualizing treatment, drug dose ranges and side effect profiles need to be considered, as well as the patient's comorbid conditions. Doses may need to be reduced for elderly or medically ill patients or those taking other medications. Doses may need to be increased for refractory cases. Common comorbid conditions with GAD include depression, alcohol or drug abuse, social anxiety disorder, and panic disorder. In patients with significant depression, an antidepressant is more likely to succeed than a benzodiazepine. Generalized anxiety disorder is a chronic illness that requires long-term treatment. Remission is attainable but can take several months, and stopping medication increases the risk of relapse within the first year of initiating treatment.
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Several drug classes are consistently beneficial for generalized anxiety disorder (GAD), and cognitive therapy is also effective as a first-line treatment. Medications and doses should be selected to meet the needs of the individual patient, including comorbidities. Long-term treatment for GAD may be needed to prevent relapse and reach remission.

TREATMENT GOALS

When treating GAD, clinicians should try to remove the core psychic symptoms of the disorder (such as worry, tension, and irritability) and the somatic symptoms. Other goals are to reduce disability, treat comorbid conditions, improve quality of life, and achieve remission or "wellness."

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Unfortunately, few patients with GAD receive adequate treatment. According to a nationally representative survey of 3032 respondents in the United States,[1] guideline-concordant care was received by 35.2% of people with GAD in the primary care sector and 56.6% of those patients in the mental health care sector. Adequate treatment was defined as 4 or more medical or psychiatric doctor visits during 1 year and appropriate medication, or 8 visits to a psychiatrist or mental health specialist for psychotherapy without medication.

PHARMACOLOGIC TREATMENTS FOR GAD

Treatments With Established Efficacy

Efficacy for treatment of GAD has been established in randomized placebo-controlled clinical trials for drugs in several classes—benzodiazepines, azapirones, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), antihistamines, $\alpha_2\delta$ Ca++ channel modulators, and atypical antipsychotics. Despite established efficacy, many treatments that are effective for patients with GAD are not officially indicated for this purpose.

Antianxiety agents. Among anxiolytics, the benzodiazepines diazepam, alprazolam, and lorazepam and the azapirone buspirone have shown efficacy for GAD. Results from a 4-week double-blind trial[2] of buspirone and diazepam showed clear efficacy ($P < .001$) for both drugs relative to placebo. At endpoint, in the 212 patients who were evaluated, mean reductions in Hamilton Rating Scale for Anxiety (HAM-A) total scores were

FOR CLINICAL USE

- Several drug classes have proven efficacy for GAD, and selection and dose should be individualized.
- Antidepressants are more effective than other agents for GAD with comorbid depression.
- Cognitive-behavioral therapy appears to be beneficial; well-being therapy may produce further enhancement.
- Most patients with GAD require long-term treatment.

as follows: placebo 3.7, buspirone 9.7, and diazepam 11.5. The researchers reported that diazepam appeared more efficacious for somatic symptoms, while buspirone seemed more efficacious for cognitive and interpersonal problems.

The efficacy of buspirone and alprazolam was compared with placebo in a 6-week, double-blind randomized trial[3] in 94 outpatients. As measured by decreases in mean HAM-A total scores, both drugs were significantly ($P < .05$) more efficacious than placebo. Clinical improvement was evident in the first week in patients taking alprazolam, and improvement with buspirone was more gradual.

Antidepressants. Several antidepressants have proven efficacy for GAD. Extended-release (XR) venlafaxine, an SNRI, was the first antidepressant medication to receive U.S. Food and Drug Administration (FDA) approval for treating GAD. An 8-week study[4] of 349 adult outpatients with GAD examined the efficacy of venlafaxine XR in 75, 150, or 225 mg/d doses. At endpoint, the 225-mg dose was found to be significantly ($P = .03$) more efficacious than placebo in reducing HAM-A total scores.

Duloxetine, another SNRI, was approved in 2007 for treatment of GAD. The efficacy of duloxetine was compared with placebo in 4 large trials.[5–8] Fixed doses of 20 mg/d, 60 mg/d, or 120 mg/d or flexible dosing were used in the trials. The study[5] that compared placebo, duloxetine 60 mg/d, and duloxetine 120 mg/d found significantly greater improvement for both doses ($P \leq .001$) on HAM-A total scores compared with placebo, and the difference was apparent by week 2. Three studies[6–8] used flexible doses of duloxetine (60–120 mg/d) and lasted 10 weeks, and 2 of these studies[7,8] compared duloxetine not only with placebo but also with venlafaxine. The active treatments all produced significantly greater improvements on HAM-A total scores compared with placebo ($P \leq .02$). Duloxetine also improved disability according to the Sheehan Disability Scale (SDS).[6] Separation from placebo was evident at week 1 for duloxetine and week 2 for venlafaxine.[7]

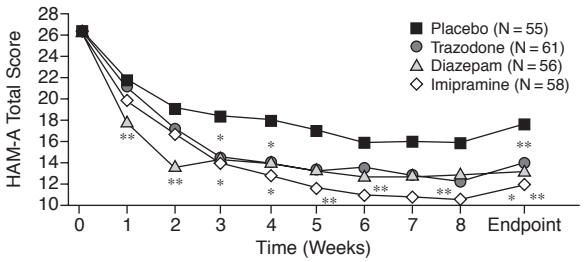
The immediate-release formulation of the SSRI paroxetine also has FDA approval for the treatment of GAD. Significant difference between mean HAM-A total scores for paroxetine and placebo was found ($P < .01$) in an 8-week randomized, double-blind trial[9] of 324 outpatients with GAD. The paroxetine group had experienced significant improvement in anxious mood by week 1 and in tension by week 3 ($P < .05$), both core symptoms of GAD. Another study[10] of paroxetine showed benefit for disability, one of the goals of treatment. Fixed doses of 20 mg/d and 40 mg/d were significantly more efficacious than placebo in improving family and social life and occupational functioning according to SDS scores ($P < .01$). No benefit was apparent for the higher dose of paroxetine over the lower dose.

Escitalopram was shown in several studies[11] to exceed the effects of placebo, and citalopram was effective in a geriatric population with GAD.[12]

Differences between antianxiety agents and antidepressants. Both benzodiazepines and antidepressants have advantages in the treatment of GAD, but differences exist between these classes. A comparison[13] between the benzodiazepine diazepam and the antidepressants trazodone and imipramine found that all drugs outperformed placebo (Figure 1) and that the benzodiazepine worked most quickly, but imipramine outperformed diazepam by the end of the study, with at least 1 measure showing a significant advantage for imipramine on psychic symptoms. Similarly, paroxetine was superior to a benzodiazepine in an 8-week study of 81 patients with GAD.[14] Although the SSRIs and SNRIs are the primary approaches for treating GAD, benzodiazepines are still widely used. Long-term benzodiazepine use needs to be monitored for dependence or tolerance.[8]

Antipsychotics. Although clinicians have believed for some time that both typical and atypical antipsychotics are useful for anxiety, none are approved for this use in the United States. An 8-week placebo-controlled study[15] examined the efficacy of quetiapine XR at doses of 50 mg/d, 150 mg/d, and 300 mg/d. After 8 weeks, HAM-A total scores were significantly improved for the 50-mg/d ($P = .001$) and 150-mg/d groups ($P < .001$) compared with placebo. Other studies[16,17] have also shown efficacy for quetiapine XR in this population, but more research on the long-term safety of atypical antipsychotics in GAD is

Figure 1. Placebo-Controlled Comparison of Imipramine, Trazodone, and Diazepam for the Treatment of GAD[a]



[a]Reprinted with permission from Rickels et al.[13]
*$P < .05$.
**$P < .01$.
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

Table 1. Dose Ranges for Medication in GAD[a]

Drug Class	Drug	Dose Range, mg/d
Antidepressants		
SNRIs	Duloxetine[b]	30–120
	Venlafaxine-XR[b]	37.5–225
SSRIs	Escitalopram[b]	5–20
	Paroxetine[b]	10–50
	Sertraline	25–200
TCAs	Imipramine	25–300
Other antidepressants	Mirtazapine	15–45
	Trazodone	50–400
	Bupropion	100–400
Antianxiety agents		
Benzodiazepines	Alprazolam[b]	0.75–4
	Diazepam[b]	15–40
	Lorazepam[b]	2–6
Azapirones	Buspirone[b]	10–60
$\alpha_2\delta$ Calcium channel modulators	Pregabalin	150–600
Antihistamines	Hydroxyzine[b]	50–100
Antipsychotics		
Atypical	Quetiapine	50–150

[a]Adapted with permission from the International Psychopharmacology Algorithm Project (IPAP).[32] The IPAP algorithm is descriptive and not prescriptive.
[b]Indicated for treatment of GAD or related conditions by the US Food and Drug Administration.
Abbreviations: GAD = generalized anxiety disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, XR = extended release.

needed. Because the large quetiapine studies have so far only been presented as posters, it will also be essential to see fuller reports in the peer-reviewed literature. Ziprasidone,[18] risperidone,[19] and olanzapine[20] have also shown some benefit for patients with refractory GAD, but more research is needed.

Other medications. Other drugs have demonstrated efficacy in GAD in controlled trials and are emerging as treatment options. The $\alpha_2\delta$ Ca++ channel modulator pregabalin has shown greater efficacy than placebo in acute treatment; comparability to the active comparators alprazolam, lorazepam, and venlafaxine; onset of action in the first week; and maintenance of anxiolytic effect over 6 months.[21–24] The antihistamine hydroxyzine appears to be useful for GAD as well. Controlled studies[25,26] have demonstrated anxiolytic efficacy of hydroxyzine superior to placebo.

Treatments With Possible Efficacy

Bupropion,[27] mirtazapine,[28] and nefazodone[29,30] may all be useful second- or third-line options in GAD, but few data are available and the drugs have not been studied against placebo, although bupropion compared well against escitalopram and was superior on some measures. Larger and placebo-controlled studies are needed. The herbal supplement *Rhodiola rosea* has shown promise in a small open-label study.[31]

Dose Ranges

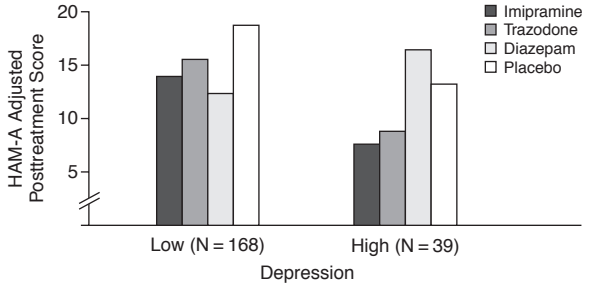
Some guidance on dose ranges for medications used for GAD treatment is available. Dose ranges for the main drugs that have been studied for GAD are listed in the International Psychopharmacology Algorithm Project (IPAP) algorithm for pharmacotherapy of GAD (Table 1).[32] The algorithm notes indicate a relatively wide dose range. When choosing a dose level, clinicians should start at the low end of the range and increase the dose until side effects become problematic, or improvement is seen. Some patients, including the elderly, the medically unwell, or those taking certain other medications, may need to be treated more cautiously. Conversely, healthy patients with treatment-refractory GAD may require higher doses. Clinicians should remember that, as shown in Table 1, many of the drugs listed in the IPAP algorithm for pharmacotherapy of GAD do not have FDA approval for treatment of GAD. The IPAP algorithm is descriptive and not prescriptive.

Comorbidity

Comorbid Axis I disorders are common in patients with GAD. In a study[33] of data from the U.S. National Comorbidity Survey (N = 8098), 90.4% of subjects with GAD were found to have a lifetime history of some other condition. In 8% of respondents, GAD occurred only during episodes of another disorder; in 9.6% of respondents, GAD was their only lifetime disorder; and in 12.2% of respondents, the onset of GAD preceded any other disorder. Major depression was the most commonly found comorbid condition, with a lifetime prevalence of 62.4%, followed by dysthymia (39.5%), alcohol abuse and dependence (37.6%), simple phobia (35.1), social anxiety disorder (34.4%), drug abuse and dependence (27.6%), and panic disorder (23.5%).

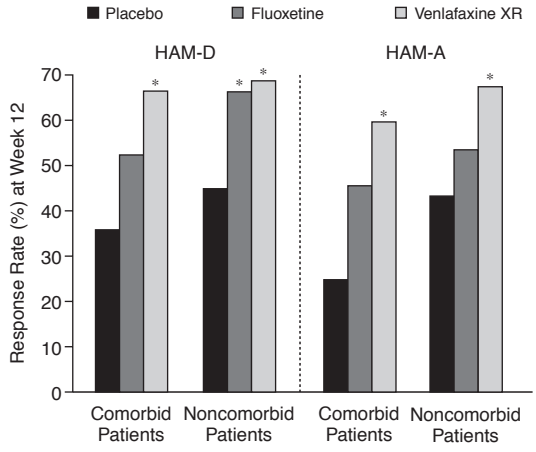
Failure to treat GAD with effective medication or other measures may put patients at higher risk for a depressive

Figure 2. Response Rates to Imipramine, Trazodone, Diazepam, or Placebo in 207 Patients With GAD and Low or High Levels of Depression[a]



[a]Adapted with permission from Rickels et al.[13] Low depression = 0–3 items endorsed on DSM-III depression checklist. High depression = 4 items endorsed on DSM-III depression checklist. In the low depression group, imipramine and diazepam show significantly more improvement than placebo ($P < .01$), with trazodone only at trend level ($P < .10$). In the high depression group, only 2 significant differences are present, between imipramine and trazodone vs diazepam ($P < .03$).
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety.

Figure 3. Response Rates to Fluoxetine and Venlafaxine XR in Depressed Patients With (n = 90) or Without (n = 269) Comorbid GAD[a]



[a]Reprinted with permission from Silverstone and Salinas.[35] Response defined as ≥ 50% reduction from baseline in HAM-D or HAM-A total score.
Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, XR = extended release.
*$P < .05$ vs placebo.

condition. A retrospective analysis[34] of data from the National Comorbidity Survey found that, among people with a diagnosis of GAD, those who had received psychopharmacologic treatment for GAD were less likely to develop major depressive disorder after the onset of GAD than those who had not received treatment (5.7% vs 18.9%). Subjects were not randomized, and it is possible that important differences between the groups led to prescription of a drug. Further studies of this relationship between GAD and depression are needed.

Pharmacologic Treatments for GAD and Comorbid Depression

Comorbidity is a critical factor in managing GAD and influences treatment choice. The efficacy of several medications for GAD and comorbid depression has been examined. Rickels and colleagues' placebo-controlled study[13] of the antidepressants imipramine and trazodone and the benzodiazepine diazepam in 230 patients with GAD found that the greater the depression, the less useful the benzodiazepine was relative to imipramine, which proved superior to diazepam in the comorbid group (Figure 2). This study suggests that, for GAD patients with significant depressive symptoms, an antidepressant drug is more likely to succeed than a benzodiazepine.

A retrospective study[35] analyzed response to treatment with venlafaxine XR or the SSRI fluoxetine in a double-blind, placebo-controlled study of patients with major depressive disorder with or without comorbid GAD. Venlafaxine XR appeared to be more effective for anxiety than placebo, whereas fluoxetine did not appear to be more effective than placebo (Figure 3).

Chromium picolinate may be effective for atypical depression with GAD. This dietary supplement was studied in an 8-week, double-blind, placebo-controlled, randomized, clinical trial[36] in 15 patients with atypical depression. In the sample, 87% (n = 13) also had comorbid GAD. Within this subsample, the chromium group achieved a 75% rate of remission, compared with 20% in the placebo group (effect size = 1.17). Respective response rates were 75% and 40% (effect size = 0.71), suggesting the value of further study for this intervention in GAD when comorbid with atypical depression (J.R.T.D., unpublished data, 2003).

RELAPSE PREVENTION AND REMISSION

Achieving remission may reduce the risk of relapse, but psychosocial problems may decrease the ability of the patient to achieve remission. In a 5-year study[37] of 167 patients with GAD, 27% of patients who achieved full remission experienced full relapse, whereas 39% of patients who achieved partial remission experienced full relapse. In the same study,[37] psychosocial problems were found to hinder remission. Poor relationships with spouses or relatives decreased the likelihood of remission, as did an overall dissatisfaction with life. Factors that were not associated with hindering remission included age at onset, friendship, gender, socioeconomic status, and general medical health.

Table 2. Side Effect Profiles of Drug Classes With Efficacy in GAD

Agent	Gastro-intestinal	Agitation	Insomnia	Sedation	Sexual	Discontinuation Syndrome	Weight Gain
SNRIs[a]	+	+	+	–	+	+	–
SSRIs[b]	+	+	+	+/–	+	+	+/–
TCAs[c]	+	+	–	+	+	+	+
Benzodiazepines[d]	–	–	–	+	+/–	+	–
Buspirone[e]	+	+/–	–	–	–	–	–
Pregabalin	–	–	–	+	+/–	+/–	+
Antihistamines	–	–	–	+	–	–	+
Atypical antipsychotics	+	–	–	+	+/–	–	+

[a]The SNRIs may produce increased sweating and blood pressure.
[b]Not all SSRIs cause withdrawal symptoms.
[c]The TCAs may have cardiovascular side effects.
[d]Benzodiazepines may cause psychomotor impairment and slowed reaction time.
[e]Buspirone can produce agitation in some patients.
Abbreviations: GAD = generalized anxiety disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
Symbols: + effect, – no effect, +/– variable effect.

Pharmacologic Treatments to Prevent Relapse

Because GAD is a chronic illness, long-term treatment is necessary and stopping treatment can lead to relapse.[38] Stopping treatment with an anxiolytic after about 4 to 6 weeks of acute treatment led to relapse within a year in 60% to 80% of patients.[38] Abruptly stopping pharmacologic treatment for GAD after 6 months of treatment led to relapse within a month in about 25% of patients treated with buspirone.[39]

Several medications have been shown to prevent relapse in patients with GAD over the long term. For example, 375 patients who responded to 12 weeks of open-label treatment with escitalopram were randomly assigned to double-blind treatment with escitalopram or placebo for up to 76 weeks. Among patients who stayed on the drug, 19% relapsed, but, among patients taking placebo, 56% relapsed.[40]

Similarly, duloxetine was found to help prevent relapse of GAD in patients who received 26 weeks of open-label treatment followed by random assignment to the drug or placebo for a 26-week double-blind phase.[41] Relapse rates were 13.7% for those who stayed on duloxetine and 41.8% for those who received placebo.

In a study[42] of paroxetine, 566 patients with GAD who responded to 8 weeks of treatment with paroxetine were randomly assigned to a further 24 weeks of treatment with paroxetine or placebo. Of the paroxetine-treated patients, 10.9% relapsed, versus 39.9% of the placebo-treated patients.

A time-to-event, double-blind, relapse prevention study[16] examined quetiapine XR in 433 patients with GAD. Subjects received 4 to 8 weeks open-label treatment, were stabilized for 12 to 18 weeks with open-label drug therapy, and then were randomly assigned to quetiapine XR or placebo. Over a maximum period of 52 weeks, 10.2% of patients treated with quetiapine experienced relapse compared with 38.9% of patients who received placebo.

Side Effects

Overall side effect profiles for several categories of drugs used in the treatment of GAD are summarized in Table 2. Some side effects may have benefits; for example, someone who has trouble sleeping may benefit from a more sedating than activating agent. If an adverse event is particularly bothersome to an individual patient, a switch to a different class may help. While switching is sometimes the best option, adjusting the dose, following the adage of "start low, go slow," has much merit and can enhance the benefit obtained from monotherapy. Considerable support and physician availability are required to get the best out of a drug.

Psychotherapy

When used in GAD, cognitive-behavioral therapy (CBT) involves helping patients detect cues that provoke anxiety and learn new coping skills that target the psychic and somatic symptoms of GAD.[43] Patients learn to self-monitor anxiety triggers and symptoms, use imagery rehearsal techniques to practice coping skills, and develop relaxation skills. In cognitive therapy sessions, patients can practice identifying and challenging maladaptive thoughts or assumptions, and then they can apply these skills in everyday life.

Few recent studies of the efficacy of CBT in GAD are available, but Borkovec and Ruscio[43] reviewed controlled clinical trials of CBT several years ago. Control groups included placebo/alternate therapy, behavioral or cognitive therapy alone, or wait list/no treatment. The effect size after treatment with CBT versus placebo or alternate therapy was 0.71 but dropped to 0.30 at follow-up.

Another review[44] examined results of 6 randomized controlled outcome studies in patients with GAD. At 6 months, the recovery rates were 51% for individual CBT, 33% for group CBT, and 60% for applied relaxation. The treatments that were least effective at producing recovery

were individual behavioral therapy (11%) and traditional analytical psychotherapy (4%).

Many questions about CBT for GAD remain unanswered. No useful research is available to clarify whether CBT is comparable to pharmacotherapy for GAD and whether CBT and medication together are more potent than either treatment alone. It would be useful to know whether CBT in combination with medication is effective for patients with refractory symptoms, persistent dysfunctional cognitive factors and behavioral patterns, and high anxiety sensitivity. There is some evidence that well-being therapy, which emphasizes the constructs of positive psychology and building of resilience, is superior to regular CBT in patients with anxiety, including GAD, who have shown only a partial response to first-line treatment.[45] Such approaches offer considerable promise as a form of therapy that goes beyond the reduction of symptoms or faulty cognitive patterns. This form of therapy may also serve those who relapse while on antidepressant drugs for depression.[46] In 1 randomized controlled trial, well-being therapy with CBT was superior to CBT alone in GAD when followed over a long period.[47]

CONCLUSION

The low rate of adequate treatment for GAD is unacceptable, especially because several drug classes and nonpharmacologic therapies have proven efficacy. Drug classes that have approved agents for treating GAD include SSRIs, SNRIs, benzodiazepines, azapirones, and antihistamines. Antidepressants are generally preferred over nonantidepressants because patients with GAD frequently have Axis I comorbidity. Emerging treatment options with evidence of efficacy include atypical antipsychotics and $\alpha_2\delta$ Ca++ channel modulators. More data are needed for other options. Drug choice and dosage need to be individualized for each patient. Psychological treatments are underutilized despite evidence that cognitive distortions are core features of GAD and that psychosocial factors may be associated with chronicity. Well-being therapy and other resilience-enhancing techniques may turn out to be of benefit in GAD. Remission is attainable in over 50% of patients with GAD but may take some time, and long-term treatment is desirable for most patients with GAD.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), diazepam (Valium and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), hydroxyzine (Vistaril and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), pregabalin (Lyrica), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, chromium picolinate, citalopram, fluoxetine, imipramine, mirtazapine, nefazodone, olanzapine, pregabalin, quetiapine, Rhodiola rosea, risperidone, sertraline, trazodone, and venlafaxine are not approved by the US Food and Drug Administration for the treatment of generalized anxiety disorder.

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