Benzodiazepines in Clinical Practice: Consideration of Their Long-Term Use and Alternative Agents

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Despite increasing focus on the use of antidepressants and other agents for the treatment of anxiety, benzodiazepines have remained a mainstay of anxiolytic pharmacotherapy due to their robust efficacy, rapid onset of therapeutic effect, and generally favorable side effect profile. In this article, we examine issues related to the long-term use of benzodiazepines, including concerns about the development of therapeutic tolerance, dose escalation, and adverse cognitive effects. We also consider currently available alternatives to benzodiazepines and novel mechanisms of action that may prove fruitful in the development of future generations of anxiolytics.

(J Clin Psychiatry 2005;66[suppl 2]:21–27)

The American Psychiatric Association (APA) guidelines for the treatment of panic disorder (1998)[1] essentially advocate initiating pharmacotherapy of panic disorder with a selective serotonin reuptake inhibitor (SSRI) and suggest benzodiazepine use for acute anxiety management rather than long-term treatment. However, benzodiazepines continue to be frequently prescribed for the initial treatment of panic disorder as well as other anxiety disorders. Bruce and colleagues[2] found that, although benzodiazepine monotherapy by patients with panic disorder has decreased slightly over the past 10 years and combined treatment with antidepressants has increased, overall use of benzodiazepines to treat panic disorder has remained high. In fact, benzodiazepine therapy remained the most commonly prescribed pharmacotherapy for the treatment of panic disorder from 1989 to 2001.[2] Furthermore, according to a 2001 pharmacy database, though antidepressants as a class were the most widely prescribed agents for the treatment of mood and anxiety disorders, the benzodiazepine alprazolam was the single most commonly prescribed anxiolytic agent.[3]

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This article is derived from the roundtable discussion "Utilizing Benzodiazepines in Clinical Practice: An Evidence-Based Discussion," which was held August 16, 2004, in Boston, Mass., and supported by an unrestricted educational grant from Pfizer Inc.

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While a moderate increase in SSRI use for panic disorder took place during the 1990s, more than two thirds of this increased SSRI use occurred as part of concomitant treatment with a benzodiazepine.[2] In a survey by Scott and colleagues,[4] 483 clinicians were presented with a case of a patient who remained symptomatic despite 6 weeks of SSRI therapy and were queried as to their "next-step" intervention. Their "top" choices were (1) an increase in the dose of the SSRI (26%), (2) the addition of cognitive-behavioral therapy (34%), and (3) the addition of a benzodiazepine (27%). Notably, nearly 1 in 3 of the clinicians surveyed would turn to initiation of benzodiazepine treatment as their first-line augmentation in this situation. Thus, benzodiazepines continue to be widely prescribed for the treatment of anxiety disorders, including panic disorder, despite guidelines such as those formulated by the APA recommending alternate pharmacologic treatments.

POTENTIAL ADVANTAGES OF BENZODIAZEPINES

The frequent use of benzodiazepines for the treatment of anxiety is likely a reflection of their effectiveness, rapid onset of anxiolytic effect, and tolerability. For example, data from an 8-week treatment trial by Tesar and colleagues[5] demonstrated that patients receiving either alprazolam or clonazepam reported a significant reduction in the frequency of panic attacks at the endpoint of the study when compared to subjects treated with placebo. In a randomized controlled study in patients with generalized anxiety disorder, Rickels and colleagues[6] demonstrated that patients treated with diazepam experienced a significant reduction in anxiety symptoms as early as week 1 as compared to patients treated with an antidepressant. Furthermore, the equivalent reduction in anxiety for patients tak-

ing the antidepressant did not occur until the third week of treatment, and antidepressant treatment was associated with increased rates of side effects.

Initially, researchers posited that potency was a critical determinant of antipanic efficacy, with higher-potency agents being more effective. However, studies addressing this issue have demonstrated that all benzodiazepines administered at equipotent doses are likely to be effective. A 6-week randomized trial[7] compared the effectiveness of equivalent doses of the benzodiazepines alprazolam (3 mg) and lorazepam (7 mg), demonstrating that both medications were equally effective in significantly reducing panic symptoms. Equal efficacy was also found in a double-blind, placebo-controlled, randomized trial[8] comparing equivalent doses of the benzodiazepines diazepam (40 mg) and alprazolam (4 mg). Data from another study[5] provided evidence for the equivalent efficacy of 2 high-potency benzodiazepines, alprazolam and clonazepam, in the treatment of panic disorder.

Although benzodiazepines are apparently equivalent in efficacy, differences in their pharmacokinetics have implications for clinical practice. Agents with rapid onset of effect such as diazepam, alprazolam, or sublingual lorazepam may be useful for episodic p.r.n. "as needed" dosing. Longer-acting agents such as clonazepam and extended-release alprazolam offer potential advantages that include the need for less frequent dosing (i.e., q.d. or b.i.d. dosing compared to q.i.d. dosing) and decreased interdose rebound anxiety.[9] Compared to the more rapid onset of peak effects associated with other agents, the relatively gradual onset of effects associated with clonazepam and extended-release alprazolam are associated with less rapid onset of sedation and other adverse effects, as well as less euphoria, which may decrease abuse potential.[9] Agents with a longer excretion half-life (e.g., clonazepam and diazepam) may be associated with decreased discontinuation effects with rapid taper or abrupt discontinuation, though differences in discontinuation-related difficulties between long and shorter half-life agents may be obviated with more gradual taper.[6]

LONG-TERM USE OF BENZODIAZEPINES

Long-term use of benzodiazepines has raised concerns about the development of therapeutic tolerance, which could be manifested by either a loss of efficacy or a need to escalate the dose to maintain benefit. However, the majority of follow-up studies that have examined this issue do not suggest a significant loss of therapeutic anxiolytic effect over time, nor do they provide evidence for escalation of dose.[10–12]

For instance, a study of 2440 New Jersey Medicaid patients[10] examined the long-term use of benzodiazepines with a specific focus on dose escalation over time. Significant dose escalation in this study was operationalized as an increase to more than 40 mg/day of diazepam or its equivalent or to 20 mg/day of diazepam in the elderly over a 2-year period of observation. This study did not control for the various reasons that patients were being treated with benzodiazepines; therefore, the population was composed of a mixture of patients in treatment for anxiety and other psychiatric disorders, as well as sleep disturbance. The investigators observed that the average dose stayed constant at about 10 mg of diazepam or its equivalent over a 2-year period. Only 1.6% of patients increased above the prespecified threshold level of concern. For the majority of patients, doses tended to remain stable over time, although 2 subgroups in this sample had an increased liability to dose escalation: those treated concomitantly with antidepressants, suggesting perhaps more severe or comorbid illness, and those filling duplicate prescriptions for benzodiazepines at different pharmacies, indicating evidence of either cognitive impairment or potential illicit behavior. Contrary to the predictions of the investigators, elderly and disabled patients demonstrated a lower risk of dose escalation when compared to the younger population.[10]

The authors of this study concluded that the data collected from Medicaid recipients did not provide evidence that long-term use of benzodiazepines resulted in notable dose escalation for the vast majority of treated patients.[10] Although this study did not examine therapeutic outcomes, the lack of dose escalation was inconsistent with development of tolerance or abuse across a large naturalistic sample of patients. The results of more systematic assessments of the treatment of anxiety patients over time are consistent with data from this broader population. For instance, Nagy and colleagues[11] followed up patients with panic disorder who had received a 4-month combination of behavior therapy and alprazolam. After 2.5 years, most patients had improved and 43% were in remission. Although a small proportion (5%) of patients who remained on alprazolam therapy increased their dose during the 2.5-year period, approximately 60% of the patients who continued treatment with the benzodiazepine decreased their dose over time. On average, doses dropped from 3.1 mg/day to 1.8 mg/day, providing no evidence for significant dose escalation over time across the patient population.[11]

Pollack and colleagues[12] examined patients in a double-blind, placebo-controlled trial of alprazolam and clonazepam for panic disorder. At follow-up assessment a year and a half after initiation of treatment, the majority of patients remained well and approximately 57% were panic-free. Most patients remained on medication. Similarly to the Nagy et al. study,[11] there were a few patients who increased their dosages, but on average, doses tended to decrease over time in both the alprazolam and clonazepam groups.[12]

It is, however, worth noting that, in both the Nagy et al.[11] and the Pollack et al.[12] studies, the changes in dose of medication did not seem directly responsive to therapeutic outcome. Rather, doses tended to decrease in the face of

persistent symptomatology for many of these patients.[11,12] In an analysis of a longitudinal study of panic disorder,[13] doses of clonazepam (either alone or in combination with an antidepressant) remained stable in the 1- to 2-mg range over a 24-month time period with one half to two thirds of patients achieving remission; 50% of patients decreased their dose over the period of observation, while 33% increased their dose.[13]

POTENTIAL DRAWBACKS OF BENZODIAZEPINES

Although the rapid onset of effect, efficacy for acute situational anxiety, generally favorable side effect profile, and maintenance of benefit over time represent advantages for the administration of benzodiazepines, their use may be associated with potential drawbacks as well. Benzodiazepines can cause sedation, ataxia, or other psychomotor impairment, as well as cognitive deficits (see next section).[14,15] In addition, benzodiazepine administration may be associated with disinhibition in vulnerable populations including the young[16] and those with histories of substance abuse, primitive character pathology, or organic brain syndromes.[17]

Thirty percent of patients in one study experienced withdrawal after 8 weeks of benzodiazepine treatment, suggesting that, for many patients, benzodiazepines cannot be abruptly stopped without risk of significant discontinuation-related difficulties, even after relatively acute regular dosing.[18] Furthermore, individuals who are predisposed to abuse substances have an increased liability to abuse benzodiazepines.[19,20] Benzodiazepines may also interact negatively with alcohol, which may lead to a risk of respiratory depression and death.[21] Additionally, benzodiazepines generally lack antidepressant efficacy and can potentially induce or amplify comorbid depressive symptoms in some patients.[14,15] This last concern is particularly salient given the high rates of comorbid depression in anxiety patients.[22] Additional drawbacks of benzodiazepines with an increased excretion half-life include the possibility of accumulation with increasing side effect burden, particularly in elderly patients, in whom longer half-life agents may be associated with more falls and fractures.[23]

Furthermore, there is a small amount of data suggesting that administration of benzodiazepines soon after trauma may have an adverse effect on recovery, predisposing patients to an increased risk of developing posttraumatic stress disorder (PTSD). In a study by Gelpin and colleagues,[24] patients received a benzodiazepine (alprazolam or clonazepam) or no treatment at least 1 month after an acute trauma and were followed up 6 months later. Sixty-nine percent of the patients who received treatment with benzodiazepines had developed PTSD by the 6-month follow-up visit, whereas only 15% of the control population had developed PTSD. It is unclear whether benzodiazepine administration was dictated by the acuity of the early distress, which may confound interpretation of the results. However, contrary to expectations, early administration of benzodiazepines to patients with high levels of initial distress did not have a positive effect on the course of their illness.[24] Rather, benzodiazepine administration seemed to be associated with increased rates of development of PTSD, despite the fact that the agents acutely reduced sleep disturbance, anxiety, and agitation.

Mellman and colleagues[25] reported a similar outcome in a study of patients who were admitted to a medical trauma center and showed early acute stress symptomatology and sleep disturbance. These patients were randomly assigned to receive either the benzodiazepine temazepam or placebo for 7 nights. Acuity of symptoms was not a determinant of treatment received. At the 6-week follow-up, 50% of the patients who were treated acutely with the benzodiazepine had developed PTSD, whereas only 27% of the placebo group met PTSD criteria. Here too, the benzodiazepine improved sleep, but that effect did not persist after discontinuation of the medication. Both the Mellman et al.[25] and the Gelpin et al.[24] studies suggest a potential negative effect of persistent benzodiazepine administration soon after trauma exposure.

EFFECTS OF BENZODIAZEPINES ON COGNITION AND PSYCHOMOTOR FUNCTION

Concerns have also been raised about the cognitive effects of long-term benzodiazepine use. The results of a meta-analysis done by Barker and colleagues[26] suggest that long-term benzodiazepine use could lead to cognitive impairment. However, the authors recognized a number of limitations to this meta-analysis. Only 13 studies met criteria for inclusion in the meta-analysis, and most were based on a relatively small number of patients. The studies varied widely in their definitions of duration of use and in the measures used to test cognitive impairment. Patient diagnoses were characterized by marked heterogeneity, and some of the included studies did not specify whether patients were being treated for generalized anxiety disorder, panic disorder, sleep disturbance, or other syndromes. Furthermore, these studies did not always attend to substance abuse confounds. In addition, self-selection issues relevant to the patients included in a number of the studies confound their interpretation. Some participants enrolled in the studies specifically because they wanted to cease benzodiazepine treatment, which may or may not reflect the more general population of people treated with benzodiazepines over time.

Most studies in the Barker et al. meta-analysis[26] did not assess patients prior to initiation of benzodiazepines, thus making it difficult to determine the contribution of the medication to the detected abnormalities. Additionally, most of the studies compared patients treated with ben-

zodiazepines to normal control patients, as opposed to untreated anxiety patients who might represent a more appropriate comparison with which to disentangle the potential contributions of the medication and the disorder. Moreover, none of the studies compared anxiety patients taking benzodiazepines to those who received other treatments, and thus these studies were unable to assess whether the impact of treatment was specific to benzodiazepines. In addition, there was relatively little examination in these studies of the clinical impact of the cognitive deficits that were noted on testing. For instance, these studies did not assess whether the effects of benzodiazepines interfered with the acquisition of safety cognitions, which appear to be a critical component of the successful cognitive-behavioral therapy of anxiety disorders. In a review of the cognitive effects of long-term benzodiazepine use, Deckersbach[27] pointed out that most studies that examined chronic benzodiazepine effects did not exclude patients with significant psychiatric conditions, including anxiety disorders. The cognitive deficits that were observed after chronic benzodiazepine use in those studies may reflect effects of the anxiety disorders themselves. Because patients were not studied prior to benzodiazepine administration, it is possible that many of these deficits may have existed prior to initiation of treatment.

Two studies have examined psychomotor performance and memory function in patients with anxiety disorders who have been chronically medicated with benzodiazepines.[28,29] These studies compared patients with anxiety disorders who either were treated with benzodiazepines or received no treatment. Neither study provided evidence for the benzodiazepine-related episodic memory and psychomotor impairments that have been reported in past studies, in which data from patients with anxiety disorders were combined with data from patients with other mental disorders.[28,29] Studies focusing exclusively on patients with anxiety disorders did not provide evidence for a substantial adverse effect of benzodiazepines on most memory paradigms when compared to anxiety disorders, particularly panic disorder, alone,[30] although some abnormalities were apparent. For instance, reports of deficits in verbal episodic memory for patients on chronic benzodiazepine treatment are inconsistent with the deficits that are seen in panic disorder alone and do suggest an impact of benzodiazepine administration.[27]

In sum, contradictory data from meta-analyses and a range of other studies may reflect a variety of confounds. However, the data do suggest some specific memory effects associated with chronic benzodiazepine use that cannot be explained by the presence of an anxiety disorder alone. The clinical implications for these effects remain unclear, but may be relevant when considering the impact of benzodiazepine administration for patients with PTSD, patients undergoing cognitive behavioral therapy, or patients who may wish to come off medication.

ALTERNATIVES TO BENZODIAZEPINES: CURRENT AND FUTURE INTERVENTIONS

Standard Agents

A variety of treatment interventions beyond benzodiazepines are used to treat anxiety disorders. Standard pharmacologic alternatives include antidepressants and azapirones. The antidepressants, including SSRIs and serotonin-norepinephrine reuptake inhibitors, as well as older agents such as the tricyclics and monoamine oxidase inhibitors appear generally effective but have a number of limitations including a variety of adverse effects and delayed onset of therapeutic effect.[31] The azapirone buspirone, though generally well tolerated, has demonstrated inconsistent efficacy in practice.[32,33] Psychosocial therapies, and behavioral therapies in particular, are clearly effective for anxiety disorders[34]; however, their use is limited by a lack of available clinicians able to provide these empirically based treatments as well as the degree of work necessary on the part of patients to benefit from these interventions. In addition, the presence of multiple comorbidities may require tailoring of specific interventions beyond the standard manuals targeting particular disorders.

Novel Uses of Available Agents

Currently, alternative pharmacologic therapies to improve treatment outcome for anxiety disorders are being examined. Many of these alternatives represent new uses for drugs presently available rather than the development of novel classes of agents.

Physicians have been using antipsychotics such as thioridazine or chlorpromazine for the treatment of anxiety for decades. However, apprehension about induction of extrapyramidal effects and the potential for tardive dyskinesia raised concerns and limited the widespread use of these agents for nonpsychotic individuals. The availability of the atypical antipsychotics, which have a more favorable side effect and safety profile, has rekindled interest in using these agents for a variety of indications beyond the psychotic disorders, including anxiety. Data from studies of refractory depression, obsessive-compulsive disorder, PTSD, and generalized anxiety disorder have suggested the potential efficacy of a number of the atypicals, usually as augmentation to treatment with antidepressants.[22,35] For instance, in a study of patients with persistent PTSD,[36] about 90% of whom were taking concurrent SSRIs, individuals were randomly assigned to treatment with low-dose risperidone or placebo. Patients receiving the atypical experienced a significant reduction in PTSD symptoms and general measures of psychopathology as compared to those receiving placebo.

β-Blockers may also have a role to play in the reduction of anxiety symptoms, including the performance anxiety subtype of social anxiety and the residual autonomic

symptoms of arousal associated with anxiety. In addition, intriguing work suggests that early administration of a β-blocker (i.e., propranolol) may reduce the likelihood of PTSD development. In a pilot study by Pitman and colleagues,[37] patients requiring emergency room care were administered a 10-day course of 160 mg/day of propranolol or placebo within hours after the experience of a traumatic event. At 3-month follow-up, patients who had acutely received the β-blocker were less likely to experience increased physiologic and subjective arousal when listening to an evocation of their trauma. These pilot data are consistent with the hypothesis that early β-blocker administration after a trauma may reduce the overconsolidation of memories associated with the trauma and thereby, the subsequent development of PTSD.

Another small controlled trial[38] tested the potential efficacy of prazosin, an α_1-adrenergic antagonist, as an augmentation agent for diminishing symptoms associated with PTSD. The drug was superior to placebo in reducing recurrent, distressing dreams, aiding patients to fall and stay asleep, reducing overall PTSD severity, and improving functional status.

There has been increasing interest in the use of anticonvulsants for the treatment of anxiety. Controlled trials have provided evidence that gabapentin may be effective in treating social anxiety disorder[39] and panic disorder.[40]

Lamotrigine acts via effects on voltage-gated sodium channels, with consequent inhibition of glutamate and aspartate release. In a small but randomized trial[41] (one of the few controlled tests thus far of a potential role for agents with glutaminergic effects in the treatment of anxiety), lamotrigine was demonstrated to be effective in the treatment of PTSD. Lamotrigine appeared to improve PTSD symptomatology including reexperiencing and avoidance/numbing, which often prove difficult to treat in practice. Topiramate is another novel anticonvulsant that blocks sodium channels and alters GABAergic and glutaminergic activity, as well as the sensitivity of glucocorticoid receptors.[42] It appeared effective as monotherapy or adjunctive treatment for PTSD in a retrospective case series of 35 civilians with chronic PTSD.[43]

Tiagabine is a selective GABA reuptake inhibitor that increases GABA levels. In a large randomized controlled trial for generalized anxiety disorder,[44] tiagabine showed evidence of significant efficacy during the first week of treatment and again at week 8. In a post hoc mixed-model analysis, tiagabine demonstrated an overall positive benefit compared to placebo at an average dose of about 10 mg/day. Levetiracetam, another novel anticonvulsant, led to significant reduction of phobic symptoms in patients with social anxiety disorder in a small open trial of 20 patients.[45]

Potential Agents of the Future

Pregabalin, an anticonvulsant with efficacy for neuropathic pain, has a novel mechanism of action, acting, as does gabapentin, as an α_2 delta calcium channel antagonist. Data from controlled trials demonstrate the efficacy of pregabalin for the treatment of generalized anxiety disorder[46] and social anxiety disorder.[47] Pregabalin was generally well tolerated in trials and, of particular interest, demonstrated a similar speed of onset of anxiolytic effect to a benzodiazepine comparator.[48]

Attempts have been made to develop agents with partial agonist effects on the benzodiazepine receptor as potential anxiolytics, including drugs such as pagoclone, abecarnil, and alpidem. The hope is that partial agonists will have anxiolytic effects but will cause less physiologic dependence and abuse liability than full agonists such as benzodiazepines. However, thus far, these drugs have not proven to be reliably or robustly effective.[49] In addition, in a study of abecarnil for generalized anxiety withdrawal,[49] withdrawal effects were observed during discontinuation, particularly from higher doses, suggesting that, at therapeutic doses, it may act more like a full agonist at the benzodiazepine receptor.

Drugs that target subunits of the GABA-A receptor may also prove to be effective anxiolytics,[50] with agents selective for the α_2 subunit potentially causing significant anxiolysis without associated sedation or amnestic effects. The observations that mice lacking 5-HT_{1A} receptors exhibit pronounced anxious and fearful behaviors and do not respond to SSRIs[51] have led to studies of specific postsynaptic 5-HT_{1A} receptor agonists as possible treatments for anxiety disorders.[50] Other agents with novel mechanisms of action include triple reuptake inhibitors of norepinephrine, serotonin, and dopamine. Whether this class of agents will offer advantages over currently available compounds remains an uncertain but intriguing possibility. Preclinical data suggest that corticotropin-releasing factor (CRF) is important in the genesis of anxiety.[52] These data have led to the hypothesis that a CRF antagonist will prove to be an effective anxiolytic, perhaps with a more favorable side effect profile than that associated with currently available drugs. However, to date no agent of this class has successfully demonstrated the necessary safety and efficacy profile required for introduction into clinical practice.

Several substance P NK_1 receptor antagonists have also been tested but do not at this point appear to have been robustly effective. Nevertheless, given the potential role of substance P in the modulation of anxiety, a role for agents affecting this system remains a possibility.[53]

A potentially exciting avenue of investigation in the development of novel compounds is the modulation of the excitatory glutamatergic system, with agents that either act as direct receptor antagonists or block release of glutamate. Metabotropic glutamate receptor (mGluR) modulators, which block the release of glutamate, have demonstrated efficacy in reducing anxiety in some studies,[54] but thus far no agents of this class have been consistently safe

or effective. Nevertheless, this remains an active area of inquiry.

Another potential area of drug development is in the examination of neurotrophic factors with evidence that antidepressant and presumably anxiolytic effects are associated with increases in brain-derived neurotrophic factor (BDNF).[50] At this point, no studies have directly used BDNF or neurotrophic factors as anxiolytics or antidepressants, but this is another area of inquiry that may prove fruitful for drug development in the future.

CONCLUSIONS

Benzodiazepines have remained a mainstay of anxiolytic pharmacotherapy because of their robust efficacy, rapid onset of therapeutic effect, and generally favorable side effect profile. With the exception of patients with a substance abuse diathesis, the available data are generally reassuring regarding the lack of development of therapeutic tolerance or dose escalation associated with long-term use of benzodiazepines. Although some available studies suggest potential cognitive effects associated with long-term benzodiazepine use, the clinical relevance of these findings remains uncertain, and data from definitive studies that address the existing methodological confounds are needed. Anxiolytic alternatives to benzodiazepines exist but have their own risk/benefit considerations that need to be taken into account when selecting among current interventions; novel interventions in development may represent important advances for the future treatment of patients with anxiety disorders.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), chlorpromazine (Thorazine, Sonazine, and others), clonazepam (Klonopin and others), diazepam (Valium and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), levetiracetam (Keppra), lorazepam (Ativan and others), prazosin (Minipress and others), propranolol (Innopran, Inderal, and others), risperidone (Risperdal), temazepam (Restoril and others), tiagabine (Gabitril), topiramate (Topamax).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, alprazolam and clonazepam are not approved by the U.S. Food and Drug Administration for the treatment of social anxiety disorder and posttraumatic stress disorder (PTSD); clonazepam and alprazolam-XR are not approved for the treatment of generalized anxiety disorder (GAD); lorazepam is not approved for the treatment of panic disorder, social anxiety disorder, or PTSD; and chlorpromazine, gabapentin, lamotrigine, levetiracetam, prazosin, propranolol, risperidone, temazepam, tiagabine, and topiramate are not approved for the treatment of anxiety disorders, including panic disorder, social anxiety disorder, PTSD, and GAD.

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