

Selecting Pharmacotherapy for Generalized Anxiety Disorder

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Selection of appropriate treatment for generalized anxiety disorder (GAD) is influenced by several considerations, including psychiatric comorbidity. Emerging data suggest that GAD has a chronic course and a high comorbidity with depression. Successful treatment can be facilitated by first establishing treatment goals, which include managing acute anxiety and following through to remission. Prevention of GAD recurrence should be the ultimate objective. Many treatments exist to aid in the realization of treatment goals, including benzodiazepines, hydroxyzine, buspirone, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Some SSRIs and an SNRI have been demonstrated effective in both acute and long-term trials, establishing them as first-line therapies. Benzodiazepines are helpful because of their rapid onset of action and efficacy in somatic and autonomic symptoms of GAD. Other medications in the pipeline include γ -aminobutyric acid (GABA) modulators, which may have lower abuse potential than currently available agents that act at the GABA receptor; corticotropin-releasing hormone (CRH) antagonists; and pregabalin. The recent realization of the chronic nature of GAD and the recognition of its frequent comorbidity with depression, coupled with data from randomized clinical trials of newer generation agents, should help physicians better diagnose GAD and achieve the goal of bringing patients to full remission.

(J Clin Psychiatry 2004;65[suppl 13]:8–13)

Treatment of generalized anxiety disorder (GAD) is a continuing challenge for several reasons. First, the diagnosis was changed in the early 1990s, leaving doubt as to its relationship with other mood disorders and hampering historical comparisons.^{1,2} Second, the arsenal of pharmacologic treatments for mood disorders has been rapidly expanding, and current information on treatment possibilities (pharmacotherapies, psychotherapies, and alternative therapies) is of daunting proportions.³ Third, the incidence of comorbidity with other psychiatric disorders is very high (90%), introducing the possibility of misdiagnosis and concomitant medication issues.^{4,5} Finally, increasing evidence indicates that GAD is a chronic disorder, with a high relapse rate in a large percentage of GAD patients.⁶

Treatment of GAD may be challenging, but successful remission brings wide-ranging relief to both the patient and the primary care physician.⁵ Recent advances in

the same areas that pose the greatest challenges in treating this disorder have led to increasingly successful management. These advances include (1) a distinct diagnostic definition of GAD; (2) the recognition of high GAD comorbidity with depression; (3) a major expansion in treatment, including anxiolytic agents and cognitive-behavioral therapy; and (4) evidence of effectiveness, safety, and tolerability of several pharmacotherapies in long-term treatment of GAD.^{5,7}

TREATMENT GOALS

The first step to successful treatment is to properly outline the important treatment targets and to continue progressive treatment until these targets are met. These treatment targets are as follows: first, the rapid management of acute anxiety, if warranted,⁴ such as somatic and autonomic symptoms or panic attacks⁸; second, a clinically meaningful improvement in symptoms (response; e.g., $\geq 50\%$ decrease in baseline Hamilton Rating Scale for Anxiety [HAM-A] score)²; and third, a progression to a full resolution of symptoms and functional recovery (remission; e.g., score of ≤ 7 on the HAM-A, $\geq 70\%$ decrease in baseline HAM-A score, or Sheehan Disability Scale score ≤ 1).^{2,5,9} Along with these improvements, there should be a significant increase in the quality of life from the patient's perspective and a significant decrease in utilization of primary care resources.^{4,5,9} Finally, the prevention of relapse is a priority; 63% to 81% of

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This article is derived from the teleconference "New Perspectives for Treating GAD," which was held May 5, 2003, and supported by an unrestricted educational grant from Forest Laboratories, Inc.

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GAD patients relapse after discontinuing benzodiazepine therapy.⁹ While there is a subset of GAD patients who may not require long-term therapy, others may^{2,10} and should be allowed to remain on pharmacotherapy as long as is needed, even benzodiazepines, provided there is no evidence of misuse or abuse.¹¹ If pharmacotherapy is going to be tapered, it may be helpful to continue psychotherapy during that time.¹¹

BASELINE ASSESSMENT

When assessing the treatment of GAD, it is important to establish a baseline evaluation of the patient's condition.¹¹ There is no ideal scale, but the HAM-A measurement is often used. This, plus the use of several other measures, such as the Clinical Global Impressions-Severity of Illness scale, Hospital Anxiety and Depression Scale, and Covi Anxiety Scale, should give a relatively complete baseline measurement, which is very important because it allows the tracking of the therapeutic value of the treatments given.¹¹ There are an increasing number of choices of pharmacotherapies for mood disorders. In regard to antidepressants, it appears that some agents work better than others in individual patients, thus the baseline measurement and periodic (every 2–4 weeks) assessment are essential.^{3,11,12}

PHARMACEUTICAL CLASSES

There are several general classes of antianxiety pharmacologic treatment options (Table 1).¹³ The oldest agents still in regular use are the benzodiazepines, which activate the γ -aminobutyric acid (GABA) system via GABA_A receptors, but these have now been relegated to at least second-line therapy,⁵ due to side effects, lack of long-term efficacy, and addiction issues.^{9,11} An even older therapy that may be enjoying a reintroduction is the antihistamine hydroxyzine, an H₁ antagonist, which may be particularly suited for long-term or successive intermittent treatment of GAD.¹⁴ The azapirone buspirone possesses anxiolytic properties, possibly by reducing serotonin release as a partial agonist at 5-HT_{1A} receptors.^{5,6,9} Buspirone does not have the sedating effects observed with benzodiazepines and antihistamines, but has a delayed onset of therapeutic effect and requires administration 3 times daily.^{11,15} This leaves antidepressants that also exhibit anxiolytic properties as the foundation for anti-anxiety pharmacotherapy, which includes primarily selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).¹¹ Trazodone, tricyclic antidepressants, and the monoamine oxidase inhibitor phenelzine also have anxiolytic properties, but these agents are generally reserved as later treatment options.¹¹ There is increasing evidence that the noradrenergic and specific serotonergic antidepressant nefazo-

Table 1. Pharmacologic Interventions for Generalized Anxiety Disorder (GAD)^a

Medication	Initial Dose (mg/d)	Dose Range (mg/d)
FDA-approved for treatment of GAD		
Paroxetine (SSRI)	10	10–50
Escitalopram (SSRI)	10	10–20
Venlafaxine XR (SNRI)	37.5	75–300
Alprazolam (benzodiazepine)	1	2–10
Lorazepam (benzodiazepine)	0.75	3–10
Diazepam (benzodiazepine)	4	4–40
Buspirone (azapirone)	15	15–60
Off-label use for treatment of GAD ^b		
SSRIs		
Fluoxetine	5–10	10–80
Sertraline	25	25–200
Citalopram	10	20–60
Fluvoxamine	25	25–300
TCAs		
Clomipramine	25	25–250
Desipramine	10	150–300
Nortriptyline	10	75–150
Imipramine	75	50–200
Benzodiazepines		
Clonazepam	0.25	1–5
Atypical antidepressants		
Nefazodone	50	300–500
Mirtazapine	15	30–45

^aModified with permission from Van Meter et al.¹³

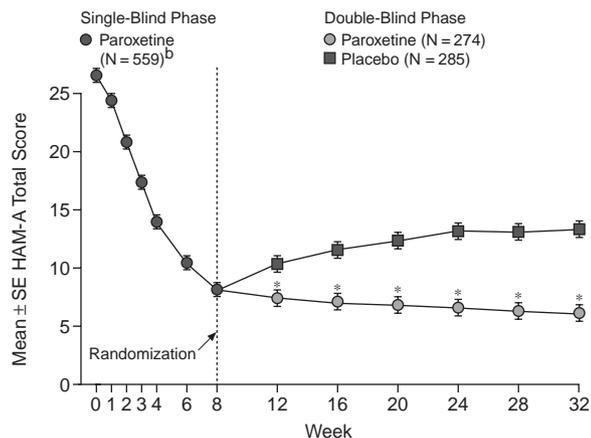
^bClinician must make a risk/benefit determination on a case-by-case basis.

Abbreviations: FDA = U.S. Food and Drug Administration, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

done may also have anxiolytic properties.^{5,11,15} There are also several agents currently in development, including a novel GABAergic agent,¹⁶ a corticotropin-releasing hormone receptor antagonist,¹⁷ and a calcium channel blocker.¹⁸

FIRST-LINE THERAPY

The comorbidity of anxiety with other psychiatric disorders (90%) may at first appear problematic, but the major component is comorbid major depression (> 40%–62%) and/or dysthymia (40%).^{4,11} This simplifies the first-line therapeutic approach, since some antidepressant pharmacotherapies also carry antianxiety therapeutic indications. The 1998 treatment guideline from the American Pharmacists Association suggests that pharmacotherapy may not be required in nondepressed GAD patients.¹¹ There is increasing evidence, however, that the presence of GAD may be a predictor of secondary major depressive disorder,² the combination of which produces the highest levels of impairment.⁴ GAD may actually be a precursor or risk factor for major depressive disorder,¹⁹ so an aggressive treatment approach, including a pharmacotherapeutic approach, even in GAD patients who do not yet exhibit depressive symptoms, may prevent the development of major depression.²

Figure 1. Efficacy of Long-Term Treatment With an SSRI^a

^aReprinted with permission from Stocchi et al.⁷

^bFive hundred fifty-nine patients in the single-blind treatment phase continued to the double-blind treatment phase. One patient in the intent-to-treat efficacy population had no postrandomization HAM-A assessment and is not included in this analysis.

* $p < .001$.

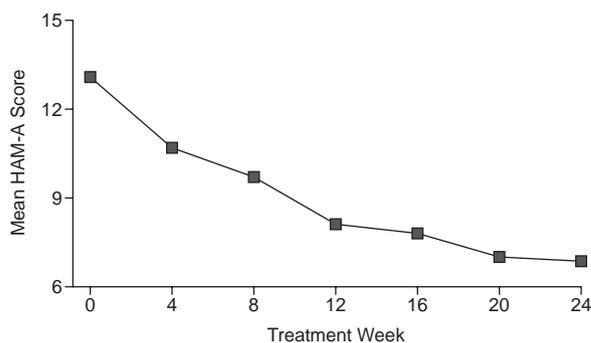
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety,

SE = standard error of mean, SSRI = selective serotonin reuptake inhibitor.

SSRIs

Among the antidepressants, the SSRIs are considered first-line therapy. Paroxetine (starting dose; 20 mg/day)¹¹ and escitalopram (starting dose; 10 mg/day) are SSRIs that are approved for the treatment of GAD as well as depression by the U.S. Food and Drug Administration (FDA).^{5,20} There are several other SSRIs for which there is evidence of anxiolytic effects in anxious patients, but these agents do not currently carry an indication for GAD. Sertraline (50 mg/day), fluoxetine (20 mg/day), and fluvoxamine (50 mg/day titrating to 100–200 mg/day) have been used as starting doses.¹¹ Because agitation can be a side effect of fluoxetine and sertraline, half doses or another SSRI should be used initially in GAD patients, especially in those with panic symptoms.¹¹

As seen with the treatment of depression, there is typically a 2- to 4-week delay in onset of therapeutic effect with the use of SSRIs as anxiolytics, but the therapeutic effect that is then observed can be dramatic.⁶ Moreover, it appears that individual aspects of GAD may improve earlier. For example, a significant reduction in the specific measure of “anxious mood” was observed with paroxetine by 1 week as compared with placebo.²¹ Furthermore, paroxetine remains significantly effective compared with placebo during long-term (32 weeks) treatment (Figure 1), with the rate of remission in paroxetine responders reaching 73% and only 11% relapsing while continuing to take the medication.⁷ Escitalopram has demonstrated efficacy in the treatment of GAD, based on the results of three 8-week, multicenter, flexible-dose, placebo-controlled stud-

Figure 2. Hamilton Rating Scale for Anxiety (HAM-A) Scores by Visit for Observed Cases in Patients Treated With Escitalopram^a

^aReprinted with permission from Davidson et al.²²

ies, which demonstrated that escitalopram produced significantly greater mean improvement on the HAM-A compared with placebo.²⁰ Additionally, in a 24-week, open-label, flexible-dose trial of escitalopram 10 to 20 mg/day,²² long-term escitalopram treatment led to continuing improvement of anxiety symptoms; mean HAM-A score at week 24 for all study completers was 6.9 (Figure 2), with 92% of completers achieving a Clinical Global Impressions-Improvement scale score of 1 or 2 (mild to moderate).

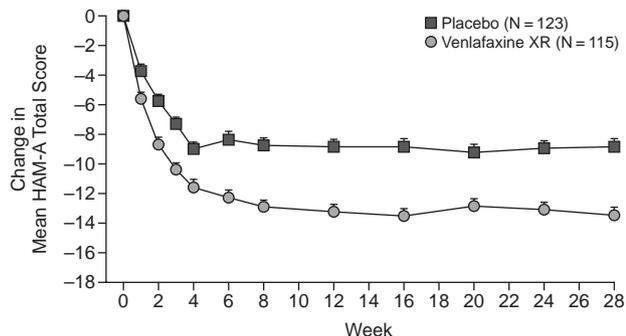
As a group, SSRIs are safe, nonaddictive, and generally very well tolerated, and the side effects associated with SSRIs tend to be mild.⁵ For example, the most common adverse side effects of paroxetine include nausea, headache, insomnia, and abnormal ejaculation in men, with a slight increase in nausea and decreased libido with other SSRIs.^{7,19} For escitalopram, the most common adverse side effects include nausea, abnormal ejaculation, insomnia, fatigue, and decreased libido.²⁰

SNRIs

The SNRI antidepressant venlafaxine (75–225 mg/day)⁹ has also been shown to be an effective anxiolytic, and carries the first FDA-approved specific indication for GAD.⁵ It has been shown to be effective in depressive patients with associated anxiety symptoms, patients with comorbid GAD and depression, and in “pure” GAD patients,^{9,10,14} reaching a response rate of 66% and remission rate of 43%.⁵ Two studies show that this efficacy is maintained over long treatment periods of 24 weeks⁵ and 6 months (Figure 3).²³

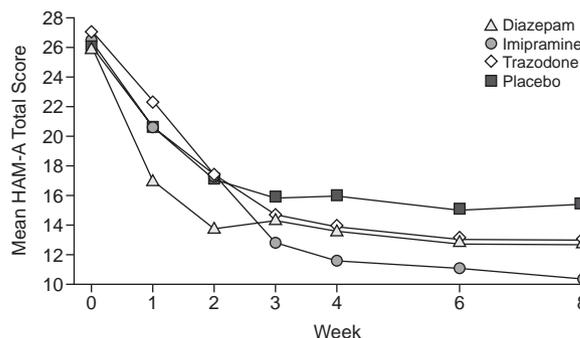
Like SSRIs, the side effects associated with the SNRI venlafaxine are usually mild to moderate and commonly subside with continued use.¹⁴ These include nausea, dizziness, asthenia, somnolence, sexual dysfunction, and dry mouth.^{5,14,23} There is also a small, but statistically significant, risk of hypertension with acute and continuation

Figure 3. Long-Term Treatment With Venlafaxine Maintains Significantly Low Hamilton Rating Scale for Anxiety (HAM-A) Total Score^a



^aReprinted with permission from Gelenberg et al.²³ $p < .001$ for venlafaxine versus placebo for all study weeks except week 1 ($p = .003$), week 4 ($p = .002$), and week 20 ($p = .007$). Error bars indicate standard deviation.

Figure 4. Efficacy of a Benzodiazepine or a Tricyclic Antidepressant (TCA) in Treating Anxiety^{a,b}



^aReprinted with permission from Rickels et al.²⁵
^bThe benzodiazepine diazepam acts rapidly (within 1 week), but by week 4 the TCA imipramine is more effective. Diazepam worked better than imipramine hydrochloride and trazodone hydrochloride at weeks 1 and 2 ($p < .05$). HAM-A total score, completers only ($N = 145$); repeat-measures analysis. Time effect: $F = 280.0$, $df = 1$, $p < .001$; drug-by-time effect (linear): $F = 3.90$, $df = 3$, $p < .01$. Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

treatment. An increase in blood pressure becomes clinically significant at doses above 300 mg/day. For these patients, careful serial monitoring of blood pressure is clearly indicated.²⁴ In addition, there are no serious drug interaction concerns.¹⁴

OTHER PHARMACOTHERAPIES

Benzodiazepines

Benzodiazepines have a proven track record in the rapid onset of action and efficacy in somatic and autonomic symptoms of GAD, specifically in severe or acute situations in which more immediate anxiolytic effects are required.^{5,9} One study²⁵ comparing imipramine, diazepam, trazodone, and placebo demonstrated the more rapid effect of diazepam (within 1 week), whereas imipramine became significantly different from placebo at 3 weeks. By 4 weeks, however, imipramine had a greater effect than diazepam or trazodone, an effect that was maintained over the long term (Figure 4).²⁵ This finding and the results of similar studies have led to the recommendation that while benzodiazepines may be useful in some patients for the beginning phases of treatment,⁹ they may not necessarily be appropriate for longer-term treatment.^{2,5}

In at least one study, it has been suggested that while benzodiazepines may relieve the behavioral manifestations of anxiety, the primary cognitive symptom, uncontrollable worry, is not relieved.⁵ Moreover, it has been shown that many GAD patients (> 33% to > 50%) do not reach remission with benzodiazepine treatment, and there is a significantly higher rate of recurrence with benzodiazepines versus other classes of anxiolytics.^{5,9} Furthermore, benzodiazepines have no antidepressant properties and in some instances may increase depressive symptoms.^{4,5} This is of considerable concern, in light of the co-

morbidity rates and predictive nature of GAD and depression discussed earlier.

The problematic side effects of benzodiazepines typically include sedation, hypnotic effects, cognitive impairment (including anterograde amnesia), and motor impairment.^{5,11} Addiction issues are another troublesome point with benzodiazepine use.^{5,11} It may be possible to reduce the likelihood of misuse or abuse⁵ by providing careful dosing instruction and by avoiding recommending “as needed” dosing; however, benzodiazepines should not be prescribed to patients with a past or present history of substance or alcohol abuse.¹¹ If a rapid alleviation of the somatic symptoms of GAD is urgent,⁹ particularly in patients experiencing panic or insomnia,¹¹ it may be advantageous to prescribe benzodiazepines only in the first few weeks of therapy⁵ concomitant with an SSRI, as evidenced from comparative studies,^{4,9,11} to provide rapid relief until the SSRI begins to take effect. It is important to carefully consider any combination of SSRI and benzodiazepine used, because benzodiazepines can have drug interactions with some antidepressants.¹⁴ When discontinuing treatment with benzodiazepines for any reason, it is important to taper the dose slowly, even over the course of several months.¹¹

Buspiron

The azapirone bupirone (20–60 mg/day)⁹ is more effective than benzodiazepines in relieving the cognitive aspects of GAD, with a smaller risk of developing dependence.^{5,9,11} The onset of therapeutic effect, however, is similar to the SSRIs, having a delay of 2 to 4 weeks or more.^{5,9,11} Accumulating evidence suggests, however, that like benzodiazepines, bupirone has a relatively low effi-

cacy in the long-term treatment of anxiety, is not effective for the behavioral manifestations of anxiety, and is not an effective antidepressant.^{4,5,9} The side effects associated with buspirone are generally mild, including dizziness, light-headedness, headache, nausea, and nervousness, but buspirone requires 2 or 3 times per day dosing, which may be problematic in terms of compliance.^{2,5,11}

Hydroxyzine

The antihistamine hydroxyzine (50 mg/day) has been shown to have some therapeutic value as an anxiolytic; however, the mechanism underlying the anxiolytic effects of hydroxyzine are unknown. It has been suggested that its therapeutic effects are simply a by-product of its sedative effects, though this is unclear. A recent study of the long-term efficacy of hydroxyzine demonstrated its efficacy in treating GAD in comparison to placebo.¹⁴ The delay in onset of therapeutic effect was longer than that observed with antidepressants. A significant difference from placebo on the mean HAM-A psychic anxiety subscore was not observed until week 6, but like the antidepressants, the efficacy of hydroxyzine appears to be stable in long-term treatment.¹³

FUTURE DIRECTIONS

Currently, there is interest in several avenues of development of novel anxiolytic agents. Following the lead of research showing the benzodiazepines as successful anxiolytics, compounds that act on the GABAergic system have been investigated.¹⁶ Commonly prescribed benzodiazepines, such as diazepam, are full benzodiazepine agonists, and while they are effective short-term anxiolytics, they are not effective with long-term treatment, and there is potential for abuse with long-term use.¹⁶ This raises the possibility that compounds that affect GABA receptors in slightly different ways may exhibit anxiolytic properties without the abuse potential. The partial benzodiazepine agonist abecarnil may be one such agent. It has been shown to be an effective anxiolytic after 2 weeks of treatment, with fewer symptoms of withdrawal than the full benzodiazepine agonist alprazolam, utilizing a rapid, 1-week taper schedule after 4 weeks of treatment.¹⁶

There has also been some interest in developing corticotropin-releasing hormone (CRH) receptor antagonists as anxiolytics.¹⁷ It has been suggested that there is excessive activation of CRH₁ receptors in anxious and depressed people and that lowering this activity has antidepressant and anxiolytic effects.¹⁷ This possibility led to the identification of the CRH₁ antagonist R121919, which, on a small scale, has been shown to have significant antidepressant and anxiolytic effects starting at 10 days of treatment and remaining through 30 days of treatment.¹⁷ These developments may lead to a distinct avenue of treatment options for anxiety with comorbid depression.

Another emerging class of anxiolytics is agents that act via voltage-gated Ca²⁺ channels in the central nervous system to inhibit neuronal activity.¹⁸ Pregabalin binds to the $\alpha_2\delta$ subunit of these channels with no direct activity at benzodiazepine and GABA receptors.¹⁸ Pregabalin appears to be efficacious and well tolerated, but requires at least b.i.d. dosing.^{18,26} Given the high rates of depressive comorbidity in GAD, the role of pregabalin and similar agents may be confined to cases in which depression is not a problem, or they may be used in conjunction with proven antidepressants.

CONCLUSIONS

Recent advances in several areas regarding GAD treatment (distinct diagnostic definition of GAD, recognition of GAD's high comorbidity with depression [90%], increased armamentarium of treatment options, and long-term treatment options) make increasingly successful management of GAD possible. There is only limited evidence of long-term efficacy of benzodiazepines and buspirone, and the multiple daily dosing needed limits their usefulness for the long-term treatment of GAD. When managing the patient with GAD, one must ascertain the patient's medical history, paying specific attention to drug abuse history (concern for benzodiazepines), comorbid medical conditions, and the patient's nature of compliance. Antidepressants, especially paroxetine, escitalopram, and venlafaxine, which are indicated for the treatment of both depression and GAD, are considered first-line therapy. As a group, SSRIs and an SNRI are safe, nonaddictive, and well tolerated. There is typically a 2- to 4-week delay in onset of action; however, the long-term efficacy and safety profile of these agents make them desirable for the chronic nature of GAD. Novel anxiolytic agents, such as partial benzodiazepine agonists, CRH receptor antagonists, and neuronal channel blockers, offer the possibility of faster onset of action, within 1 to 2 weeks, though their efficacy is as yet limited and the role they may play (e.g., stand-alone treatments vs. adjunctive) remains to be determined. With the development of the second generation of antidepressants (SSRIs/SNRIs) and several novel anxiolytics, treatment options for GAD have been greatly expanded.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), diazepam (Diasat, Valium, and others), escitalopram (Lexapro), fluoxetine (Prozac and others), hydroxyzine (Vistaril, Atarax, and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), nefazodone (Serzone and others), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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