Optimizing Pharmacotherapy of Generalized Anxiety Disorder to Achieve Remission

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More than half of patients with generalized anxiety disorder (GAD) have chronic and persistent symptomatology that may warrant ongoing pharmacotherapy. Many of these patients also have significant comorbid mood and anxiety disorders. There is growing consensus among clinicians that the treatment goal for anxiety disorders should be remission, including the minimization of anxiety and depression and resolution of functional impairment. Clinical management strategies for optimizing pharmacotherapy aimed at achieving remission in GAD include attention to drug selection, dosing levels, and duration of treatment. To optimize treatment for GAD with the goal of achieving remission, it is reasonable to select an agent with demonstrated effectiveness for GAD and associated comorbidities as well as a favorable side effect profile. Dosing and duration of treatment should be adequate, and consideration of adjunctive strategies for refractory patients may be warranted. This article discusses the optimization of pharmacotherapy with the goal of promoting remission in patients with GAD. *(J Clin Psychiatry 2001;62[suppl 19]:20–25)*

Generalized anxiety disorder (GAD) is a chronic condition.[1,2] However, in contrast to major depression, for which the value of maintenance therapy is well established, the benefits of long-term therapy for GAD are still unclear.[3] Although long-term studies evaluating the pharmacologic treatment of GAD have been performed,[4] the results are inconclusive because the patient selection criteria were based on the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III),[5] which classified GAD as a "residual" category. The more recent DSM-III-R[6] and DSM-IV[7] criteria classify GAD as a distinct anxiety disorder.[4]

Patients with acute or time-limited anxiety may exhibit a spontaneous resolution of anxiety symptoms with time or can be managed with short-term (i.e., 1 to 4 weeks) or intermittent anxiolytic pharmacotherapy. Generally, however, it appears that patients diagnosed with GAD based on DSM-IV criteria will need long-term management.[3] The medical[8,9] and psychiatric[10–12] comorbidities present in many patients tend to increase the risk of chronicity and severity of GAD.[13] This article reviews current guidelines establishing treatment goals for GAD and discusses recommendations for optimizing the pharmacologic treatment of this distressing and often disabling condition.

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ESTABLISHING REMISSION AS A TREATMENT GOAL

Clinical trials in depression and anxiety disorders have classically equated treatment efficacy with treatment response, defined as at least a 50% improvement from baseline levels of symptomatology. However, it is possible for a patient to demonstrate a treatment response by this criterion yet still have significant distress linked to substantial impairment. As in depression,[14,15] the persistence of subsyndromal symptoms of anxiety prolongs the illness and deters treatment-related resumption of premorbid functioning.

Most patients with GAD have comorbid mood disorders, most commonly major depression.[12,16,17] The shared diathesis between GAD and depression,[18,19] with the onset typically in that order,[11] suggests that an aggressive approach to the treatment of GAD can prevent the progression of the disorder to a more severe state. Pharmacotherapeutic agents with a broad spectrum of efficacy[20,21] have been shown to be effective in eradicating the symptoms of GAD[22,23] and enhancing social adjustment,[24,25] therefore facilitating remission.

Because suboptimal patient outcomes can be manifested despite a treatment response, there is growing consensus among clinicians that, as with depression,[26–28] the treatment goal for anxiety disorders should be remission.[29] Remission is a more rigorous treatment goal that requires a Hamilton Rating Scale for Anxiety score ≤ 7 or a reduc-

Table 1. Guidelines for the Remission of GAD[a]

Subjective Goals	Objective Goals	Time Course
Minimize anxiety	HAM-A score ≤ 7–10 or 70% improvement on patient-rated scale	8–12 wk
Eliminate depression	HAM-D score ≤ 7 or 70% improvement on patient-rated scale	3–6 mo
Prevent recurrence of depression	HAM-D score ≤ 7 or 70% improvement on patient-rated scale	3–12 mo
Resolve functional impairments	Sheehan score ≤ 1 (mildly disabled)	3–12 mo

[a]Adapted, with permission, from Ballenger.[29] Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Score for Anxiety, HAM-D = Hamilton Rating Scale for Depression, Sheehan = Sheehan Disability Scale.

tion of at least 70% in baseline levels of symptoms, resulting in a virtually asymptomatic state associated with significant social and functional improvement. Table 1[29] summarizes the current guidelines for the remission of GAD.

SELECTING THE APPROPRIATE PHARMACOTHERAPEUTIC AGENT

Setting the goal of treatment toward remission raises the threshold for defining treatment efficacy. Accomplishing this goal necessitates a comprehensive treatment strategy that includes reducing social and functional impairment. Hence, the management of GAD involves a thorough and integrated treatment approach. The patient's medical and psychiatric history should be evaluated so that the pharmacotherapeutic choice will be compatible with the patient's clinical profile. The selection of an appropriate drug for a specific patient is an important initial step in the treatment process. (See the article by Ballenger[30] in this supplement for pharmacotherapeutic treatment options in GAD.) To summarize, 3 drug groups have been shown to be effective in GAD: benzodiazepines, azapirones, and antidepressants. Benzodiazepines have been used extensively for the treatment of short-term anxiety,[3] and some are specifically indicated for GAD.[31] The clinical advantages of benzodiazepines include their relatively rapid onset of action, wide margin of safety when used for short courses of therapy, and ease of use.[3] While all benzodiazepines are effective anxiolytics, the choice of the specific benzodiazepine to use should be made by matching the pharmacokinetic properties of the agent with the patient's clinical profile.[32] Slowly metabolized benzodiazepines such as diazepam and chlordiazepoxide have multiple active metabolites amenable to a more rapid tapering schedule. Missing a dose of these slowly metabolized benzodiazepines has less adverse consequences and has been associated with fewer intradose symptom breakthroughs. On the other hand, the more rapidly metabolized benzodiazepines such as oxazepam and lorazepam are more appropriate for brief, intermittent anxiolysis; these types of benzodiazepines are also suitable for slow metabolizers (e.g., the elderly, patients with hepatic disease).[31] It is noteworthy, however, that significant drug-drug pharmacodynamic interactions resulting from additive effects of multiple medications may occur when benzodiazepines are taken with other central nervous system depressants (e.g., alcohol, barbiturates, antihistamines).[32,33] Moreover, the prolonged use of benzodiazepines can be problematic because of concerns about associated physiologic dependence and abuse liability in predisposed individuals; in addition, the lack of efficacy of benzodiazepines in the treatment of depression limits their utility among patients with GAD who have comorbid depression (indicative of a greater degree of illness severity).[34] Despite the fact that benzodiazepines have been a mainstay in the treatment of GAD, some studies indicate that they, and related agents, are ineffective for the long-term management of GAD and are associated with relatively low rates of remission in treated individuals.[35,36]

Buspirone, an azapirone, has a preferential effect for the psychic symptoms of anxiety, irritability, and aggression.[37] A meta-analysis of 8 controlled studies using buspirone found that patients with both GAD and moderate symptoms of depression responded well to treatment with this azapirone.[38] However, in a study involving attempts to taper benzodiazepine use among long-term utilizers, the administration of buspirone during the tapering period failed to demonstrate significantly different efficacy in comparison to placebo.[39] Buspirone is generally well tolerated, and any adverse reactions that occur are usually mild. It lacks the anticonvulsant, muscle-relaxant, and hypnotic effects as well as the motor impairment and dependence associated with benzodiazepines,[40] although the anxiolytic effects of buspirone may not be apparent until after a 2- to 3-week period. Hence, it is appropriate for use in anxious patients for whom benzodiazepine treatment is contraindicated or poses a special hazard.[3] Abrupt discontinuation of this agent has not been associated with a withdrawal syndrome.[41] The most common side effects of buspirone are dizziness and light-headedness, which typically occur within 30 minutes after taking the drug,[37] a potentially important consideration for the elderly patient.

Tricyclic antidepressants (TCAs) such as imipramine are effective for GAD,[39] but long-term treatment with TCAs is complicated by an aversive side effect profile that reduces treatment compliance.[42] As a result, they have been largely supplanted by newer classes of antidepressants with a broader spectrum of efficacy and more benign side effect profiles. Hence, TCAs are no longer justified as first-line antidepressant therapy in most settings.[43]

An extensive database including both acute and long-term studies using DSM-IV[7] criteria demonstrates high rates of remission of GAD in patients taking venlafaxine extended release (XR), a serotonin-norepinephrine reup-

take inhibitor (SNRI).[23] (See the article by Sheehan[44] in this supplement.) Because venlafaxine XR is the only agent indicated for both the short- and long-term treatment of GAD and depression, it is useful for patients with GAD who have comorbid depression; this finding has been confirmed in recent studies.[45,46] Consistent with this clinical advantage is a pharmacoeconomic finding that concomitant use of anxiolytics was less among patients prescribed venlafaxine for depression in comparison to those prescribed TCAs or selective serotonin reuptake inhibitors (SSRIs).[47] On the other hand, placebo-controlled studies on the use of SSRIs specifically for GAD are limited, with a number of recent studies indicating that the SSRI paroxetine is efficacious for the treatment of this condition.[48,49]

There are 3 main issues to address in selecting the appropriate pharmacotherapeutic agent. First, it is reasonable to initiate treatment with an agent that has demonstrated efficacy for the treatment of GAD. Second, the drug's tolerability and safety should be considered. This is particularly important because long-term treatment of GAD is anticipated. In addition, tolerability is also an issue when treating patient populations such as the elderly, who are sensitive to adverse side effects. Unacceptable side effects are a potent impetus for patient noncompliance. Treatment should be initiated with an agent with a favorable side effect profile.[50] Third, comorbidity issues should be considered in treatment selection. The presence of a comorbid medical condition (e.g., neuropathic pain) that may be responsive to particular pharmacotherapeutic interventions may also guide treatment selection for patients with GAD. The newer-generation antidepressants have been shown to be effective in pain associated with psychogenic or somatoform disorders.[51,52] In particular, agents that influence serotonergic and noradrenergic mechanisms appear to have a consistent antinociceptive effect.[53–57] Potential drug interactions for patients such as the medically ill receiving polypharmacy should be identified and considered as well.

Besides comorbid medical illnesses, the coexistence of psychiatric illnesses with GAD is common.[10–12] In particular, antidepressants that are efficacious for GAD and depression should be considered when these 2 psychiatric disorders coexist. For example, numerous studies have provided evidence for the efficacy of venlafaxine in depression[58–60] and GAD.[22,23,61,62] Preliminary clinical trial data on paroxetine (an SSRI with proven efficacy in depression)[63–65] indicate that it is also efficacious in the treatment of GAD.[48,49] Pertinent for patients with treatment-resistant depression is a comparative study evaluating venlafaxine and paroxetine in refractory depression, including many patients who had failed prior SSRI trials; in this study, significantly more patients taking venlafaxine than taking paroxetine achieved remission.[66,67] Venlafaxine XR is the first antidepressant indicated for both depression and the short- and long-term treatment of GAD. Its efficacy in comorbid depression and GAD has been demonstrated[46] and has been supported by pharmacoeconomic findings demonstrating a reduction in expenditures for anxiolytic agents in patients treated with venlafaxine for depression.[47] Moreover, consistent with the goal of reducing social impairment as part of achieving remission, venlafaxine XR has been shown to substantially enhance social adjustment in patients with GAD.[68]

ADEQUATE DOSING AND DURATION OF TREATMENT

Anxiolytic treatment, like antidepressant treatment, should be initiated at low dosages and gradually escalated to effective levels depending on treatment-emergent side effects and therapeutic response. In general, newer agents such as SSRIs, nefazodone, mirtazapine, and venlafaxine XR are better tolerated than TCAs and monoamine oxidase inhibitors (MAOIs).[69] Targeting therapeutic dose levels is also a critical step in achieving remission.[70] Pertinent to dose escalation is the dose-response relationship of the different agents. Although there are significant differences among individual patients in treatment response, some studies of depressed patients treated with SSRIs suggest a relatively flat dose-response curve—i.e., higher dosages fail to elicit greater treatment responses or remission rates.[71,72] For example, varying dosages of sertraline[73,74] and fluoxetine[75,76] have been shown to result in equivalent improvement in depressive symptoms. On the other hand, TCAs and the SNRI venlafaxine tend to demonstrate a positive dose-response relationship.[77] In a randomized controlled trial of venlafaxine (75–375 mg/day) in patients with major depression,[78] the higher doses tended to be more effective and were also associated with early onset of action (as early as week 1). Similar findings have been shown in a study of venlafaxine XR in patients with GAD.[79] Although TCAs are not known to appreciably affect the pharmacokinetics of other drugs, their narrow therapeutic index is a predisposing factor for the development of toxicity.[80] Venlafaxine, on the other hand, has a more favorable adverse effect profile than TCAs[81,82] and has clinically negligible pharmacokinetic effects with most other drugs.[83,84] As with other agents, however, the overall occurrence of adverse effects with venlafaxine tends to increase with increasing dosages.[78]

Lack of efficacy, which can engender patient and clinician frustration and discouragement, may contribute to premature termination of treatment. For this reason, patients should be informed at the beginning of treatment about the lag in onset of efficacy often associated with antidepressant therapy (i.e., approximately 3 to 4 weeks). Management of treatment-emergent adverse effects can be a critical factor in ensuring that patients tolerate adequate doses of medication. Although the SNRIs and SSRIs are much better tolerated than older classes of agents such as the TCAs and MAOIs, treatment-emergent adverse effects

including sexual dysfunction may occur and limit compliance. A variety of adjunctive and other management strategies may be useful in reducing the morbidity associated with antidepressant administration and ensuring treatment continuity.[85] For persistently symptomatic patients, titrating to an optimal dose is usually a preferred strategy over switching to another agent.

Both the physician and patient need to be aware that the goal of achieving remission includes significant social and functional improvement as well as resolution of symptoms. This comprehensive improvement often takes time to attain, underscoring the need for long-term treatment for many affected individuals.

There is a paucity of information examining next-step strategies to improve outcome for patients remaining symptomatic despite initial pharmacotherapy for GAD. Anecdotal and case series reports suggest the potential efficacy of combination therapy with antidepressants and benzodiazepines, as well as a variety of augmentation strategies including use of atypical neuroleptics, buspirone, or anticonvulsants. The role of psychosocial interventions in GAD has not been studied as extensively as in other anxiety disorders such as panic disorder.[86–88] However, there are reports that psychotherapies significantly reduce the symptoms of GAD,[89,90] especially when integrated with pharmacotherapy.[91]

Achieving the significant degree of social and functional improvement attendant to the clinical state of remission may require time beyond that necessary for the resolution of symptoms, underscoring the potential importance of long-term treatment for GAD. Support for this assertion comes from a naturalistic study of 164 patients with GAD participating in the Harvard/Brown Anxiety Research Program.[35] After 2 years of treatment, only 25% of patients achieved full remission, a proportion that increased to 38% after 5 years of treatment.[35] The findings of this study underscore the chronicity of GAD and the improvement of symptoms over time with continued treatment. However, it is worth noting that most patients followed in that study were treated prior to the widespread use of the newer generation antidepressants; a substantial number of them received benzodiazepines. It is possible that greater use of the newer antidepressants in these clinical patients, many of whom had a variety of comorbidities, may have improved outcome, a hypothesis requiring further empirical study. Prolonged treatment not only enhances clinical improvement but, in practice, prevents relapse and recurrence. Risk of relapse increases with time following treatment discontinuation. The probability of relapse in GAD after a treatment response was found in 1 study to be 6% after 6 months, 20% after 2 years, and 28% after 5 years.[92] Although the precise relationship between duration of treatment of GAD and the prevention of relapse and recurrence has not been empirically assessed, current recommendations for treating GAD to remission are to treat patients for approximately 1 year after achieving response and before attempting discontinuation.[29]

CONCLUSIONS

Patients with GAD are likely to need long-term treatment. Comorbid medical and psychiatric illnesses have been associated with greater severity and chronicity of GAD. Treatment should be initiated with the goal of inducing remission in affected individuals. Pharmacotherapeutic agents with a favorable tolerability and safety profile and demonstrated efficacy in alleviating relevant comorbid conditions including depression and medical conditions should be considered as first-line therapy. Management of treatment-emergent adverse effects will improve compliance and increase the likelihood that patients will receive optimal doses of medication for an adequate period. Consideration of adjunctive pharmacologic and psychotherapeutic interventions may also improve outcome. The availability of newer antidepressants with a greater spectrum of efficacy and favorable tolerability and safety profile compared with older pharmacotherapies increases the likelihood that patients with GAD will achieve full remission, including symptomatic improvement and enhanced quality of life and overall functioning.

Drug names: chlordiazepoxide (Librium and others), diazepam (Valium and others), fluoxetine (Prozac), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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