Strategies for Treatment of Generalized Anxiety in the Primary Care Setting

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Generalized Anxiety Disorder (GAD) is a highly prevalent condition whose course of illness is often chronic in nature and fluctuating in severity. Pharmacotherapy options include the benzodiazepines, the azapirones, of which only buspirone is marketed at the present time, and the antidepressant imipramine. Buspirone is probably the treatment of choice when prolonged therapy is indicated because it does not produce physical dependence, dose not interact with alcohol, and does not cause psychomotor impairment. Dosing instructions for buspirone and guidelines for switching patients from benzodiazepines to buspirone are offered. Non-drug therapies such as interpersonal and cognitive therapies are often also found helpful in treating patients with GAD.

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SCOPE OF THE PROBLEM

Generalized anxiety disorder (GAD) is a highly prevalent condition that frequently presents in primary care settings as fluctuating levels of worry associated with insomnia and symptoms of muscle tension, fatigue, feeling irritable or on edge, and poor concentration. In the general population, GAD is reported to have a 1-year prevalence of at least 3% and a lifetime prevalence of 4% to 6%.[1] These rates are higher in medical settings, where GAD is reported to occur at a rate that is more than double what is observed in the community. Unrecognized and untreated generalized anxiety is associated with an unusually high rate of both psychiatric (especially depression and panic disorder) and medical comorbidity, as well as medical utilization. Katon and colleagues[2] found GAD to occur at a rate of 22% in high utilizers of medical health care.

To meet DSM-IV GAD criteria, patients suffering from generalized anxiety must have been ill on more days than not for a minimum of 6 months. Those who suffer from briefer episodes of generalized anxiety are placed in the residual diagnostic category of anxiety disorder NOS (not otherwise specified). The prevalence of anxiety disorder NOS is uncertain, although the Epidemiologic Catchment Area (ECA) survey suggests that subsyndromal levels of generalized anxiety are very common.

PATTERNS AND COURSE OF ILLNESS

Despite their high prevalence, both GAD and anxiety disorder NOS have been relatively neglected in terms of research on their various clinical presentations and typical courses of illness. This is particularly true for anxiety disorder NOS, for which almost no published research is available.

Patterns of illness that have been described lately for affective illness include brief intermittent depression and double depression, as well as long-established diagnoses such as dysthymic disorder. Parallel diagnostic concepts might be usefully applied to the clinical reality of generalized anxiety as it is commonly observed, especially in primary care settings, where most anxiety disorders are managed. We would propose applying the concept of "brief intermittent anxiety" to a patient who reports brief, recurrent flare-ups of anxiety symptomatology either against a nonanxious baseline or against a background of neurotic "trait" anxiety. We have observed this transient/situational anxiety to be very common in our primary care based Private Practice Research Group. In ambulatory settings there are many anxious patients who do not fulfill strict DSM-IV GAD criteria, but who have a dispositional tendency to develop intermittent bouts of anxiety in response to high stress, be it the death of a loved one, the sudden loss of a job, or the realization of a serious illness.

In addition to brief intermittent anxiety, we have observed another generalized anxiety course pattern that parallels one in the affective field: "double anxiety." We have

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suggested[3] the concept of double anxiety to reflect the fact that many anxious patients report chronic, low-grade trait anxiety or neuroticism (analogous to dysthymic disorder) and then may have a superimposed level of more severe generalized anxiety.

SITUATIONAL AND BRIEF INTERMITTENT ANXIETY

Treatment research conducted on generalized anxiety patients consists, almost exclusively, of efficacy research sponsored by pharmaceutical companies on relatively homogeneous populations of patients with low comorbidity, high chronicity "pure" GAD. As useful as these studies are to establish anxiolytic efficacy for a new compound, they may have only modest generalizability to the management of the various clinical presentations of generalized anxiety in primary care settings.

Virtually no clinical research addresses the management of brief or subsyndromal episodes of anxiety, whether these episodes occur once, in response to a situational stressor, or intermittently. One of the authors conducted a study of the treatment of anxiety neurosis in waitlisted patients,[4] which tested the effect of a brief course of medication coupled with positive versus neutral physician statements about expected drug effect. Positive physician interpretation of medication effect was a strong predictor of a favorable anxiolytic response.

Gath and Catalan[5] conducted a study of 150 anxious patients seeking treatment in a family practice setting. Patients were randomly assigned to either a brief, one-time supportive and psychoeducational intervention by the primary care physician or a brief trial of a benzodiazepine. The one-time supportive intervention was comparable to medication in its anxiolytic effect.

The lesson from this and the previous study is that the management of the less severe forms of generalized anxiety in primary care settings often involves a mixture of brief benzodiazepine therapy, supportive techniques, problem solving, psychoeducational interventions, and the healing effects of time. The attitude of the physician toward the medication probably should be that it is being prescribed to "help patients to help themselves" and not as a promised "panacea" that will solve all problems. The reflexive use of benzodiazepines for every stressful situation is very likely to promote drugs as a primary means of coping. In this regard, Gath and Catalan[5] found that the best predictor of nonresponse to the one-time counseling approach was an established tendency in the patient to self-medicate problems with over-the-counter (OTC) medication. Similarly, Davidson and Lucki[6] have demonstrated an interesting effect in rodents in an electric-shock stressor model. They found that helping the animals to "cope" with the electric shock stress by means of diazepam treatment made them less able to cope during future stressor situations. The clinical implications of this preclinical research must be interpreted cautiously, but they suggest that overreliance on drugs for coping with everyday stressors may be counterproductive in the long run.

There are, of course, numerous clinical presentations of subsyndromic anxiety that persist for variable amounts of time that are best managed by targeted, short-term (3–6 weeks), pharmacologic intervention. For many patients, one course of therapy may suffice; for others intermittent management of their symptoms may be appropriate. The benzodiazepines are probably the treatment of choice for this type of short, time-limited form of generalized anxiety because of their rapid onset of action and notable efficacy in reducing the insomnia and somatic/adrenergic symptoms that cause such acute situational distress. Sometimes, a benzodiazepine hypnotic may be all that is needed, while at other times a benzodiazepine anxiolytic may be prescribed for a few days to a few weeks.

Frequently, the prescription of anxiolytic medications is combined with some kind of supportive psychotherapy offered by the physician and often taking no more than 3 to 5 minutes of a given office visit. Nevertheless, those physicians who combine medication therapy with some kind of support or cognitive interpretations frequently obtain better results than those physicians who rely solely on the medication as a panacea to resolve all the patient's problems. A preferable physician approach would be to say: "I understand that you are going through a difficult time period, that this has been going off and on for some time, and that these are difficult problems to take care of. However, I have something here that might make you feel a little bit better and thus will allow you to cope with your problems more efficiently." Putting the medication in the proper context in terms of patient expectations can go a long way toward enhancing its efficacy, as well as limiting unrealistic and magical beliefs that will later come back to haunt the physician.

GAD: ITS SHORT- AND LONG-TERM MANAGEMENT

Choice of Drug

For patients with severe or chronic forms of GAD, an aggressive course of pharmacotherapy may be indicated. Currently there are three distinct options for the treatment of GAD: the benzodiazepines, the azapirones (of which only buspirone is marketed in the United States), and the antidepressants, particularly imipramine.

Buspirone should probably be favored over benzodiazepines in the following clinical situations: (1) where there is a concern about impairment in psychomotor function, attention, vigilance, or cognition and memory, for example in the elderly or in patients who have to drive a motor vehicle for a living; (2) where there is a concern about potentiation of alcohol or sedative effects of other medications; (3) where aggressivity and/or irritability are prominent, since there is some evidence that buspirone may

ameliorate these symptoms, while high potency benzodiazepines, in some instances, may actually disinhibit aggressivity; (4) where there is a concern about abuse potential, based on either personal or strong family history, for example of alcoholism; and (5) where there is a concern about physical dependence and withdrawal. Finally, there is some evidence[7] that buspirone may have relatively greater efficacy in treating the psychic symptoms of anxiety, such as worry, tension, and perhaps even obsessionality, than the somatic symptoms.

In contrast, use of a benzodiazepine is probably favored when there is evidence of episodes of panic or when GAD presents with prominent adrenergic symptoms, even if panic attacks are not present.

Much less is known that helps guide the clinician as to when to opt for using an antidepressant such as imipramine to treat generalized anxiety. We recently published the results of a study[8] comparing imipramine and trazodone to diazepam and placebo in patients diagnosed with GAD. As expected, the benzodiazepine therapy yielded the most rapid response—within 1 week. However, after 6 weeks of therapy, the antidepressants had achieved comparable efficacy. In fact, imipramine treatment yielded the best results by 8 weeks. Though any form of depression was reason for exclusion, even mild, subsyndromal depressive symptoms predicted an unfavorable response to diazepam and a much more favorable anxiolytic response to the antidepressants. This study needs to be replicated, and extended to maintenance treatment, before specific treatment recommendations can be made about the use of antidepressants in the management of GAD.

The management of the more severe and chronic forms of GAD may, at times, require considering use of long-term antianxiety drug therapy. This decision should be made in collaboration with the patients and after the benefits and risks of maintenance drug therapy are reviewed with them. As part of this review of treatment options, the physician should discuss the use of such nondrug interventions as interpersonal or cognitive psychotherapy.

The drawbacks of maintenance benzodiazepine therapy primarily relate to the risk of physical dependence and the withdrawal reaction that occurs upon drug discontinuation. Early rebound anxiety has been observed to occur in some patients after as little as 4 to 6 weeks of treatment, notably for the benzodiazepines with a short half-life.[9] Table 1 lists some of the risk factors that appear to predict greater withdrawal difficulty.

In general, the clinical and medicolegal issues surrounding the long-term use of benzodiazepines have discouraged many clinicians, especially in primary care settings, from using this class of drugs, except in unusual cases. Since antidepressants such as imipramine are associated with significant side effects and are less established in their anxiolytic efficacy, it appears that presently buspirone may be the drug of choice for the chronic management of many anxious patients. We, therefore, would like to discuss in greater detail the use of buspirone by the family physician.

Table 1. Risk Factors Associated With Greater Benzodiazepine Withdrawal Difficulty

Higher residual levels of anxiety and depression pre-taper
Higher dose of benzodiazepine
Use of a benzodiazepine with a short half-life (unless taper is gradual)
Current tobacco use
History of recreational drug use
Higher level of Axis II personality psychopathology
Panic disorder diagnosis
Rapid rate of benzodiazepine taper

Dosing Instructions for Buspirone Therapy

The current dosing recommendation suggests initiating treatment with 5 mg given t.i.d. with meals and then increasing in incremental steps of 5 mg every few days. Though buspirone is well tolerated in general, too aggressive initial dosing, which frequently leads to such adverse events as dizziness, headaches, and nausea, is a common reason for premature drug discontinuation. For this reason, it is better to err on the side of gradual titration, since tolerance readily develops to these initial adverse effects.

Clinical experience suggests that identical results can be obtained by prescribing buspirone on a b.i.d. basis, with an initial dose of 7.5 mg b.i.d., and incremental increases of 7.5 mg every few days. Buspirone is now available in a "dividose" form, which allows physicians to divide a 15-mg tablet into either two 7.5-mg halves or into three parts of 5 mg each. The average therapeutic dose is usually in the range of 20 to 30 mg per day; patients who are experiencing concurrent symptoms of depression frequently benefit from a somewhat higher daily dose in the range of 40 to 60 mg.[10]

The advantage of a b.i.d. regimen is the improved compliance that is associated with less frequent dosing. Besides clinical experience suggesting the utility and efficacy of b.i.d. dosing, one double-blind study, yet unpublished, (Bristol-Myers Squibb Company, data on file) has been conducted that demonstrated comparable efficacy to the traditional t.i.d. regimen. However, until these results are confirmed by additional research, it is recommended that t.i.d. dosing be attempted before discontinuing buspirone for ineffectiveness during b.i.d. dosing.

An important part of achieving a successful outcome with buspirone treatment is to properly prepare the patient for what to expect from treatment. It is widely known by the lay public that the drug therapy of depression, as effective as it is, frequently takes 3 to 5 weeks to achieve its antidepressant effect. In contrast, the expectation by the lay public, conditioned perhaps by years of benzodiazepine use, is that response in anxiety should be rapid. This expectation of an extremely short latency of response is understandable given the nature of anxiety. Nonetheless, it is

crucial that the patients understand the more gradual nature of buspirone's anxiolytic effect and that they do not expect rapid sedative and muscle relaxant effects. This is not to say that subtle improvements may not occur after only 1 week of therapy. The reduction in tension and irritability often seen with buspirone, however, frequently is first pointed out to a patient by a spouse or other family member who has noticed the difference before the patient became aware of the change.

During long-term therapy, one should employ drug holidays or holiday weeks to assess further need for medication. These holidays are much easier to conduct with a drug that lacks withdrawal symptoms than with the benzodiazepines.

Switch from benzodiazepine to buspirone

Switching a patient from a benzodiazepine (frequently one that has been prescribed for many months or years) is a common clinical situation facing primary care physicians. In fact, more than 50% of patients prescribed buspirone have had some prior exposure to benzodiazepine treatment. As is usual with practical issues of clinical management, little research has been conducted to help guide clinical practice. What is known can be summarized as follows: for patients who have developed physical dependence after long-term (≥ 6 months) benzodiazepine therapy, treatment with buspirone does not appear to reduce either the severity or likelihood of experiencing a withdrawal reaction.[11,12] One small placebo-controlled study[13] found 2 weeks of pretreatment with buspirone to reduce withdrawal severity significantly ($p < .05$) in patients taking alprazolam for at least 3 months, but taper success rate did not differ (buspirone 58%, placebo 47%, N.S.).

Confirming this finding are the results of a recent study conducted by Chiaie and colleagues.[14] Patients who had been treated with various benzodiazepines for 3 to 9 weeks were treated double-blind with buspirone versus placebo after a 5-week stabilization on 3 to 5 mg of lorazepam. Under cover of buspirone (or placebo) treatment, lorazepam was then tapered. At the end of 3 additional weeks of buspirone therapy, it, too, was discontinued. The severity of anxiety and withdrawal symptomatology was reduced in the buspirone-treated group; however, taper success rates were similar for both groups. Yet 3 weeks after successful taper, patients responded significantly better to buspirone than to placebo.

In summary, while buspirone may not be effective at managing withdrawal in chronically benzodiazepine-dependent patients, it may be helpful in controlling anxiety symptomatology in patients taking benzodiazepines for less than 6 months. To achieve maximal benefit while switching medications, the most effective strategy is to pretreat patients with 20 to 40 mg of buspirone for 2 to 4 weeks prior to undertaking a gradual taper off the benzodiazepine at a reduction rate of approximately 25% or less per week. For those patients able to discontinue benzodiazepine intake, buspirone treatment can be expected to produce at least similar beneficial results than did the benzodiazepine taken prior to taper.

Buspirone does not exhibit cross tolerance to benzodiazepines and thus does not block benzodiazepine withdrawal symptoms,[11] even if it may slightly decrease withdrawal symptoms compared with placebo.[13,14] For this reason, patients should never be abruptly switched from a benzodiazepine to buspirone, and patients should be warned that benzodiazepine discontinuation symptoms will still be present but that they are *not* caused by buspirone. In fact, all these symptoms may be milder than what they would be without buspirone, but they are clearly there. These symptoms will, however, disappear within a few weeks and buspirone will, at that time, be at least as effective as the former benzodiazepine with none of the dependence and sedative liabilities.

SUMMARY

Management of anxiety is frequently performed in the offices of family physicians. The best results can be obtained if the use of medication is combined with supportive management and practical advice and, most importantly, by placing the use of the drug in the proper context—by explaining that it will usually work not as a panacea, but by reducing anxiety sufficiently to allow patients to cope more effectively on their own with their problems. In other words, drugs are not given to solve problems but to help patients improve their coping skills and deal with problems efficiently and, hopefully, eventually even without medication. Clearly, nondrug therapies, such as interpersonal therapy, cognitive therapy, and other psychotherapies, are also often helpful. For the short-term treatment, the passage of time or the short-term use of benzodiazepines is the treatment of choice. For more chronic anxiety, however, when benzodiazepines given for a prolonged period of time may produce withdrawal symptoms, other drugs such as buspirone or the tricyclic imipramine may be preferred.

Drug names: alprazolam (Xanax), buspirone (BuSpar), diazepam (Valium and others), imipramine (Tofranil and others), lorazepam (Ativan and others), trazodone (Desyrel and others).

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