Consensus Statement on Generalized Anxiety Disorder From the International Consensus Group on Depression and Anxiety

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Objective: To provide primary care clinicians with a better understanding of management issues in generalized anxiety disorder (GAD) and guide clinical practice with recommendations on the appropriate treatment strategy. ***Participants:*** The 4 members of the International Consensus Group on Depression and Anxiety were James C. Ballenger (chair), Jonathan R.T. Davidson, Yves Lecrubier, and David J. Nutt. Four additional faculty members invited by the chair were Karl Rickels, Hans-Ulrich Wittchen, Dan J. Stein, and Thomas D. Borkovec. ***Evidence:*** The consensus statement is based on the 6 review articles that are published in this supplement and the scientific literature relevant to the issues reviewed in these articles. ***Consensus process:*** Group meetings were held over a 2-day period. On day 1, the group discussed the review articles and the chair identified key issues for further debate. On day 2, the group discussed these issues to arrive at a consensus view. After the group meetings, the consensus statement was drafted by the chair and approved by all attendees. ***Conclusions:*** GAD is the most common anxiety disorder in primary care and is highly debilitating. Furthermore, it is frequently comorbid with depression and other anxiety disorders, which exacerbates functional impairment. Antidepressants (serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and nonsedating tricyclic antidepressants) are generally the most appropriate first-line pharmacotherapy for GAD, since they are also effective against comorbid psychiatric disorders and are suitable for long-term use. Cognitive-behavioral therapy is the preferred form of psychotherapy for GAD, although when GAD is comorbid with depression, pharmacotherapy is increasingly indicated.

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Generalized anxiety disorder (GAD) is a chronic, prevalent, and disabling anxiety disorder, but it is responsive to treatment. It is a pure disorder in some 25% to 33% of cases.[1–3] However, recent data suggest that comorbidity is no more frequent for GAD than for other anxiety disorders, although the spectrum of comorbidity is wider.[4]

For decades, there was skepticism about the diagnosis of GAD, probably more among psychiatrists than among primary care physicians, with a clinical view that it was a residual disorder, only to be diagnosed in the absence of other mental disorders. Studies of the life course of GAD have proved useful in defining the specificity and reality of the disorder. GAD is now accepted as a specific anxiety disorder, defined by chronic worrying or free-floating anxiety about the future, and as an impairing disorder in itself, not simply impairing as a result of comorbid conditions. GAD causes psychosocial disability at least comparable to that of chronic somatic diseases[3,5] and depression.[6,7]

GAD was the subject of the sixth meeting of the International Consensus Group on Depression and Anxiety. Our objective, as in earlier meetings, was to provide clinicians with a better understanding of the condition by identifying what is known in the field and what requires further research. This article represents our views and clinical recommendations on the management of GAD, based on our assessment of the current clinical evidence.

CLINICAL PRESENTATION

GAD is the most common anxiety disorder in primary care,[8] and physicians will often identify it among the prob-

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lem population of high health care utilizers and high complainers in their clinical practice.

Chronic worrying and the effects of chronic tension (reports of restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance) are the specific features that define GAD, although patients may only emphasize or report either the worrying or the tension. Yet, fewer than 20% of GAD patients present in primary care with psychological complaints. The majority have a somatic presentation, with muscle pain or headache (as a result of chronic tension), irritability, insomnia, fatigue, and restlessness as the most significant presenting symptoms.[9] Some GAD sufferers may complain about feeling under stress, and the physician should react to the mention of stress-related problems by probing for chronic worry. Around 90% of those diagnosed with GAD will say "yes" to the question "During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?" compared with very few of those without the condition.[10,11]

Around two thirds of GAD patients will be found to have other conditions at the time of presentation or later in their course, including physical illness and depressive symptoms or even full-blown depressive episodes. We recommend careful probing for a constellation of both psychic and somatic symptoms to elicit the true clinical picture. The physician needs to probe for both chronic tension and chronic worrying, since different patients will emphasize either one or the other of these.

RECOGNIZING GAD

Duration of symptoms is an important focus in recognizing GAD. One distinguishing factor from other anxiety disorders is that the symptoms of anxiety and worry have been present for months, and this long duration may increase the likelihood of association with other conditions. Although a diagnosis of GAD using DSM-IV requires a 6-month duration of symptoms, most patients have a much longer duration of evolution of the disorder. Typically, the GAD patient suffers from symptoms for 5 to 10 years before diagnosis and treatment.

We accept that DSM-IV criteria represent a significant advance in the diagnosis of GAD. These criteria, which emphasize the symptom of worry, are relatively easy to apply and also make descriptors much more specific than "free-floating anxiety," and so make it easier to correctly recognize GAD.

GAD is commonly associated with chronic physical conditions, but the existence of a physical diagnosis significantly reduces the likelihood that GAD will be correctly recognized. When physicians make a diagnosis of diabetes, for example, they may consider the presence of anxiety as normal and explicable (and justified) by the physical illness. In this way, they may miss the psychiatric diagnosis. If GAD coexists with a chronic physical condition, it will worsen the patient's prognosis, and it should be detected, diagnosed, and treated.[12] A similar phenomenon exists in the tendency to discount the possibility of major depression when it is comorbid with cancer[13] or other serious illnesses.

We are in agreement that primary care physicians should consider the presence of GAD in patients with unexplained symptoms such as insomnia, headaches, or sleeping disorders. As a first step, they should screen their population of problem patients with frustrating unexplained symptoms. GAD will not explain all the psychological problems seen, since this population also includes a high percentage of subjects with panic disorder and depression. It should be remembered that subjects who fulfill diagnostic criteria for GAD might still have subthreshold depressive symptoms of some significance or other syndromes that might flare up as a main problem.

We endorse the concept of asking 2 screening questions, for example, "During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?" and "Are you frequently tense, irritable, and having trouble sleeping?" If the patient answers "yes" to either question, then the physician can explore further symptoms. There are many good and extremely sensitive screening instruments, including screening questionnaires that focus on 1 or 2 questions and can be completed in the physicians' waiting room. Examples of self-report measures include the Penn State Worry Questionnaire[14,15] and a validated diagnostic instrument for GAD using DSM criteria.[16]

Although GAD is typically a disorder of adulthood, the physician should not rule out the possibility of its occurring in younger patients. Another group in which GAD is commonly overlooked is women aged 40 to 50 years. Given the high rate of coexistence of GAD and depressive disorders, the physician should not exclude probing for GAD in the patient with depression.

ONSET AND COURSE OF GAD

The pattern of onset of GAD is different from those of the other anxiety disorders in that although some cases occur before the age of 25 years, there is a strong increase in the incidence of GAD later in life, at around 35 to 45 years. GAD is also the most prevalent of the pervasive anxiety disorders diagnosed in later life.[17] GAD has a life course that is waxing and waning, with intervening symptoms or syndromes of other disorders, such as depression or medical conditions. Patients with GAD can be described as having periods of worsening disease alternating with periods of remission. The spontaneous remission rate is around 20% to 25%.

In contrast to other anxiety disorders, which typically occur a long time before secondary conditions develop, GAD is frequently associated with a wide range of other

conditions, some of which are primary and some secondary. In around 50% of GAD cases, simple phobia, social phobia, panic disorder, or agoraphobia precede GAD. In 50% or more of cases, major depression, dysthymia, and alcohol abuse are secondary to GAD.[18]

Although GAD is not a risk factor for the first onset of depression, a history of GAD increases the subsequent number and duration of depressive episodes, so it is a risk factor for longer episodes and less likely remission of depression.

Research Needs:

1. Further studies are needed on the relationship between GAD and physical illness and whether GAD increases morbidity, and even mortality, associated with physical illness and thus has a negative impact on prognosis.
2. Detailed examination is needed of the diagnoses preceding or following GAD.

Burden of GAD

The pattern of excessive use of medical services that has been well documented for patients with panic disorder[19] also exists for patients with GAD. GAD itself is associated with a high rate of health care utilization.[20,21] Around one third of GAD patients seek medical help for their symptoms,[21] most commonly from family doctors. Those most likely to seek help are women and those aged less than 45 years. GAD ranks third among anxiety disorders (after posttraumatic stress disorder and panic disorder) in the rate of use of primary care physicians' time.[20]

The burden of GAD is increased by comorbidity.[22] Comorbidity is reported to increase the rate of help seeking associated with GAD by more than 50%.[21] Hospitalization is more prevalent in patients with comorbidity, with particular emphasis on the emergency room and internal medicine.[22]

The medical specialists consulted most frequently by GAD patients are gastroenterologists.[23] In this respect, it is important to remember that more than 50% of patients with irritable bowel syndrome also suffer from GAD. Physicians, particularly gastroenterologists, need to be aware that both conditions may coexist and require effective treatment.

Remarkably, GAD is the leading cause of workplace disability (in the United States).[4] Also, the costs associated with work days lost to illness are reported to be significantly higher in GAD patients with comorbid conditions than in those with the noncomplicated form of the disorder.[22]

Comorbidity

As in other anxiety disorders, comorbidity is a common and characteristic feature of the nature and course of GAD. An estimated 80% of subjects with lifetime GAD will have a comorbid mood disorder during their lifetime.[7,24] Depression is one of the most common and important conditions comorbid with GAD. As many as 80% of patients with GAD have symptoms of depression,[6] and when depression and GAD occur together, patients experience significantly increased disability and dysfunction and a worse prognosis. If a patient with depressive disorder also has GAD, he or she is likely to experience longer episodes of depression and is less likely to remit. In 50% or more of cases of GAD and comorbid depression, GAD precedes the first episode of major depression.[25]

As is the case for social anxiety disorder and panic disorder, when GAD is comorbid with other conditions, the rate of attempted suicide increases.[26]

MANAGEMENT OF GAD

Over the last decade, there has been a trend to a decrease in the prescription of benzodiazepines and an increase in the prescription of antidepressants for GAD. Some very important treatment findings are emerging, with the potential to do more for GAD than we ever considered possible. The recent demonstration of the effectiveness of antidepressants in GAD, particularly the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), and the advent of specific psychotherapies are changing clinical thinking and are starting to change clinical practice.

In general health care, physicians tend to overdiagnose patients as anxious rather than as depressed. However, they would use the term *depression* in 26% of depressed and 15% of GAD patients, the term *anxious disorder* in 22% of depressed and 12% of GAD patients, and the term *anxious depressed* in 5% of both groups.[27,28] This is consistent with the fact that diagnosis is often related to the global symptomatic severity rather than to a specific symptom pattern.[29] As a consequence of a relatively low recognition rate and the absence of specificity, only about 15% of patients with GAD are treated with antidepressants and 15% with anxiolytics. In addition, hypnotics are prescribed in almost 10% of patients.

A nonspecific supportive relationship with the physician is an important aspect of overall clinical management in the primary care setting. We identify the need to develop support materials—validated packages and self-help manuals—for physicians to give to GAD sufferers (see Psychotherapy section).

Psychotherapy

The low profile of GAD has meant that less attention has been paid to the study of psychotherapy for this disorder than for any other anxiety disorder. Cognitive-behavioral therapy (CBT) has now reached a stage of development that demonstrates it is the only consistent and empirically validated form of psychotherapy for GAD.

One of the practical problems facing physicians is a lack of information about good cognitive-behavioral

therapists to whom they can refer their patients. Good therapists who have been certified in behavioral, cognitive, and cognitive-behavioral therapies by rigorous competency examinations can be identified through The American Board of Professional Psychology Web site (www.abpp.org) and through The Academy of Cognitive Therapy Web site (www.academyofct.org). Even if such a contacted clinician is unable to provide therapy for a given patient, he or she would be able to recommend other quality psychotherapists. We believe physicians should have educational packages and self-help manuals to hand out to their patients. We feel that educational material for patients is helpful, although the degree of helpfulness will vary with the individual patient. As yet, however, there are no research data supporting the use of educational materials, and it would be valuable to assess the approach of using self-help manuals in a large clinical practice.

Exposure techniques are not ordinarily useful in GAD, as they are in other anxiety disorders, although if there is a feared situation associated with GAD, exposure through imagery or in real life may become part of the treatment procedure. Exposure can also be used as a way of rehearsing both the relaxation strategy, which is an important element in most CBT techniques in GAD, and the cognitive perspective changes that grow out of cognitive therapy. In imagery exposure, patients practice either a situation in which they are frequently anxious or an internal situation. They are instructed to close their eyes and start worrying and then to consider the situation from another point of view, letting go of the tension and the anxiety. Imagery is not used as an extinction technique; it helps patients to remember that when they notice any incipient anxiety cues or begin to enter a stress situation, they have various cognitive and relaxation responses they can choose to make rather than their habitual response.

Although the CBT package has not been found to be superior to conditions containing only its behavioral or cognitive therapy elements in the majority of such comparison studies, CBT has generated the greatest overall improvement averaged across studies, especially at 1-year follow-up.

CBT techniques appear to hold considerable promise in GAD, and we recommend them as the preferred form of psychotherapy for the disorder. However, when GAD is comorbid with depression, as it commonly is, medication is increasingly indicated. As yet, there is a lack of trials assessing the effect of combining psychotherapy with medication.

Pharmacotherapy

There are 4 classes of therapy with randomized controlled data in GAD: benzodiazepines, buspirone, hydroxyzine, and antidepressants. There are few controlled data to support the effectiveness of neuroleptics in GAD,[30] and where they have been studied, it is in mixed populations rather than in GAD. We recognize that neuroleptics are prescribed in GAD, often to avoid benzodiazepines, but there is no clinical evidence to support their use, and they can be associated with tardive dyskinesia even in low doses.

Benzodiazepines tend to be given preference in treating anxiety, but they are not appropriate for first-line treatment of GAD, which is a chronic condition needing appropriate long-term treatment. GAD is also frequently comorbid with depressive disorders, for which benzodiazepine therapy is not generally desirable, or the other anxiety disorders, including panic disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD), for which benzodiazepine therapy is not usually favored as a first choice. Benzodiazepines can be a problem in the long term (because of the problem of withdrawal reactions) or in patients with previous drug abuse or alcoholism.

The only indication for the first-line use of benzodiazepines is an acute anxiety reaction, as distinct from GAD, in which their speed of onset is appropriate to the desired aim of producing rapid symptomatic relief. Benzodiazepines are appropriate for intermittent or episodic use and may have a role as adjunctive therapy in acute exacerbation of GAD or in sleep disturbance during the initiation of antidepressant therapy. When benzodiazepines are administered concomitantly during initiation of treatment with antidepressants, the GAD patient should be stabilized on antidepressant therapy for at least 4 weeks before benzodiazepines are slowly tapered over 4 to 8 weeks.

Physicians should appreciate, however, that sedative drugs are not always needed to deal with the sleep disturbance symptom of hyperarousal. Although they acutely dampen the abnormal circuitry causing hyperarousal, they may not be effective in the longer term, whereas an SSRI should reduce and control this problem. For example, there are research data showing that the SSRI paroxetine treats chronic insomnia with some success.[31]

General physicians may fail to distinguish between an acute anxiety state and the ongoing anxiety disorder of GAD and overprescribe benzodiazepines. Acute use can become long-term use because patients experience a rapid return of well-being when they start taking benzodiazepines, like the effect, and want to continue treatment. We certainly would not argue against the acute use of benzodiazepines, but we do argue against their inappropriate first-line use in GAD, which may impede the prescription of appropriate antidepressant therapy. In our experience, physicians sometimes prescribe 2 or 3 benzodiazepines for GAD, which raises the question of the quality of current treatment.

Buspirone is effective in most (but not all) studies of GAD, but its lack of efficacy against comorbid conditions is the main reason for our not recommending it as a first-line treatment for GAD. More studies are needed to compare buspirone with antidepressants in GAD.

Hydroxyzine lacks a broad profile in that it has no demonstrated efficacy in depression, panic disorder, social phobia, or OCD. The use of hydroxyzine is similar to that of benzodiazepines, although while hydroxyzine does not cause dependence, it may have a sedating effect at the start of treatment. It is indicated for acute anxiety states, in which it is targeting the symptoms rather than treating the condition.

There is increasing evidence that antidepressants are effective in GAD, with particular effects on psychic symptoms. An important advantage of the SSRIs is their proven efficacy in treating depression and anxiety disorders frequently comorbid with GAD, such as panic disorder, social anxiety disorder, or OCD, although some antidepressants such as the tricyclic antidepressants (TCAs), e.g., imipramine and clomipramine, have also shown efficacy in some disorders (panic disorder and OCD) but not all conditions. As yet, there are no studies of efficacy of even the SSRIs in comorbid GAD, and this research is needed.

On the basis of current evidence, we recommend an SSRI, SNRI (e.g., venlafaxine), or nonsedating TCA as the first-line treatment for GAD. For a patient with a long-term condition or who presents with several comorbid conditions and in whom there may be an increased suicide risk, an SSRI or SNRI is indicated. With the increasing clinical recognition of GAD as a chronic condition, regulatory authorities are beginning to require evidence of long-term efficacy and safety. We feel that antidepressants are the appropriate long-term treatment for GAD because of their safety, tolerability, and effectiveness, particularly given the high rate of comorbidity.

In summary, when the patient is suffering from an acute anxiety reaction, with an expected duration of 2 to 6 weeks, the use of benzodiazepines is appropriate. However, when the patient has chronic GAD, particularly with comorbid conditions, antidepressants should be the first-line treatment. Other therapeutic options are buspirone and hydroxyzine. Neuroleptics are an inappropriate choice of therapy for GAD, with almost no clinical evidence for their effectiveness and risk of serious side effects.

Research Needs:

1. There is a paucity of good longitudinal data on GAD. This is a chronic disorder with a waxing and waning course during which other disorders occur. Given its high prevalence and associated high disability, there should be a worldwide focus on GAD, with cross-cultural studies on recognition, presentation, disease course, subtypes, and treatment outcome. The important question is whether early treatment intervention can prevent either a recurrence of the disorder or the development of depression or other comorbid conditions. Research is also needed on the effectiveness of combination treatment with CBT and pharmacotherapy.
2. How long should treatment be continued? There is a research need for large studies in which GAD patients are treated for different periods of time (6, 12, or 18 months) and then switched to placebo to assess the percentage who will remain illness-free and the duration of remission. Appropriate definition of the study population is a critical issue.
3. In the GAD population, there are some people who respond well in the short term and may not need further treatment until their next crisis. There is a research need to identify this subgroup, which may be the appropriate target for a short treatment (6 weeks) with benzodiazepines. Research is also needed to determine whether the short-term use of sedative treatment options such as benzodiazepines or hydroxyzine to control acute phases of anxiety or longer-term treatment with antidepressants will better prevent disease progression over the longer term.
4. Since patients with concurrent disorders have been routinely eliminated from clinical trials of GAD, there is a need for studies that reflect clinical practice, in which GAD is frequently comorbid with major depression, anxiety disorders such as panic disorder, or alcohol abuse. More information is needed on the outcome of comorbid physical conditions when GAD is or is not treated.

Drug names: buspirone (BuSpar), clomipramine (Anafranil and others), hydroxyzine (Vistaril and others), paroxetine (Paxil), venlafaxine (Effexor).

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