Management of Generalized Anxiety Disorder in Primary Care: Identifying the Challenges and Unmet Needs

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Background: Generalized anxiety disorder (GAD) is one of the most common psychiatric disorders in primary care, although it is often underrecognized and undertreated. GAD is chronic, disabling, and associated with other health problems. Treatment response is often unsatisfactory, but the clinical evidence base for new treatments has expanded substantially in the past decade and suggests a growing range of options for reducing the burden of GAD. The objective of this article was to review current literature on GAD and its management to provide an overview of the clinical importance of GAD in primary care and available treatments.

Data Sources: Recent studies (ie, over the past decade) on the epidemiology and treatment of GAD were identified by searching Medline using the term *generalized anxiety disorder* only and in combination with the terms *epidemiology* and *treatment* and for each drug class (*benzodiazepines*, *azapirones*, *antidepressants*, *antihistamines*, *alpha-2-delta ligands*, and *antipsychotics*) and for named drugs (*buspirone*, *venlafaxine*, *duloxetine*, *fluoxetine*, *escitalopram*, *olanzapine*, *paroxetine*, *pregabalin*, *quetiapine*, and *risperidone* in addition to *psychological therapies* and *cognitive-behavioral therapy*. The literature search was conducted in August 2008 for the period 1987–2009.

Study Selection: Studies were included if judged to be relevant to a review of the epidemiology and management of GAD. Articles were excluded if they were not written in English or were published more than 10 years before the literature search was conducted. A few older studies were included for which more recent research evidence was not available. Recent national and international guidelines for the management of GAD were also reviewed.

Data Extraction/Synthesis: Most currently available interventions have similar overall efficacy, and treatment choices should reflect the situation of individual patients. Important unmet needs exist for treatments (1) that work rapidly, with (2) broad spectrum benefits, (3) that can improve rates of remission and well-being, (4) are devoid of risk for withdrawal symptoms, and (5) have few if any adverse interactions with other drugs. Additional needs include (6) safer drugs for the elderly, (7) safe and effective drugs for children with GAD, (8) further evaluation of psychotherapy, and (9) understanding the appropriate circumstances for, and optimal choices of, drug combination.

Conclusion: While the development of novel treatments evolves, current management approaches can focus on improving identification and defining optimal use of available therapies for GAD.
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Anxiety disorders are the most prevalent of all psychiatric disorders, with generalized anxiety disorder (GAD) being the most common disorder to be seen in the primary care setting.[1] Despite this, it is a diagnosis that can easily be missed, although the condition is responsive to treatment.[2] The research base for the management of this disorder has expanded rapidly over the past decade, and it is the goal of this review to draw attention to this literature.

METHOD

Search Strategy and Selection Criteria

Recent studies (ie, over the past decade) on the epidemiology and treatment of GAD were identified by searching Medline using the term *generalized anxiety disorder* only and in combination with the terms *epidemiology* and *treatment* and for each drug class (*benzodiazepines*, *azapirones*, *antidepressants*, *antihistamines*, *alpha-2-delta ligands*, and *antipsychotics*) and for named drugs (*buspirone*, *venlafaxine*, *duloxetine*, *fluoxetine*, *escitalopram*, *olanzapine*, *paroxetine*, *pregabalin*, *quetiapine*, and *risperidone* in addition to *psychological therapies* and *cognitive-behavioral therapy*. The literature search was conducted in August 2008 for the period 1987–2009. Articles were excluded if they were not written in English or were published more than 10 years before the literature search was conducted. A few older studies were included for which more recent research evidence was not available. Recent national and international guidelines for the management

Clinical Points

- Generalized anxiety disorder is common and remains chronic if not treated.
- Effective treatments include serotonergic antidepressants, benzodiazepines, other drugs, and certain forms of psychotherapy.
- If monotherapy fails to bring about remission, other approaches can be tried, eg, augmentation with a drug from another class, switch to drug with a different mechanism, or addition of psychotherapy.

of GAD were also reviewed. Relevant articles were identified by this strategy and are reviewed here.

Definition, Epidemiology, Comorbidity, and Burden of GAD

Nearly 8% of patients consulting a primary care physician have GAD according to a 6-month prevalence rate reported in a World Health Organization (WHO) study in 14 countries, including the United States.[3,4] Estimates of the lifetime prevalence for the condition vary, but studies suggest it is about 5%–6% using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria[5]; however, the European Study of the Epidemiology of Mental Disorders (ESEMeD) gives a lower estimate of 2.8%.[6] Although prevalence estimates in the ESEMeD surveys are roughly comparable with earlier studies, it has been suggested that underestimation of some prevalence rates might have occurred due to methodological features of the ESEMeD, including the way the diagnostic interviews were conducted.[7] GAD is reported around twice as often in women as in men[1,6] and is more commonly seen in middle age, with prevalence rates rising after the age of 35 years in women and 45 years in men.[3] GAD is believed to be common in the elderly, with estimates as high as 7.3% being reported.[8]

The main diagnostic criteria of GAD are excessive anxiety and worry that is difficult to control along with at least 3 from a list of 6 symptoms (restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances, and being easily fatigued) and duration of the disorder for at least 6 months. Symptoms must be distressing or impairing and not adequately explained by another related disorder.[9,10] By contrast, the diagnostic criteria in the *Tenth Edition of the International Classification of Diseases* (*ICD-10*)[10] place greater emphasis on the presence of somatic symptoms, a difference that is noted in the International Psychopharmacology Algorithm Project (IPAP) GAD Algorithm,[11,12] as it is somatic symptoms that often serve as the presenting complaint. Broadening of the definition of GAD is being considered for the next major revision of the *DSM* (*DSM-V*), expected to be published in 2012.[13] To take into account the latest genetic, epidemiologic, and other research findings, the task force is considering whether GAD and major depressive disorders are different forms of the same disorder, closely related or distantly related disorders. Furthermore, amendment of the requirement for 6 months' duration of symptoms and the primacy of persistent worry are also under consideration, as well as the number of symptoms within the definition.

The onset of GAD is usually gradual, and the condition is generally recurrent and chronic in nature. Although GAD tends to fluctuate in severity, the chances of complete recovery are low.[14] The Primary Care Anxiety Project (PCAP), a longitudinal study of 539 primary care patients with anxiety disorders, has shown that GAD is a chronic and persistent illness.[15] In a subsample of 113 patients who met *DSM-IV* criteria for GAD, only 44 patients (39%) recovered fully during 2-year follow-up, with the remainder showing no recovery (28%) or only partial recovery (33%). Furthermore, people with GAD experience impaired social functioning and quality of life[16] and disability equivalent to that observed in major depression.[1,17]

GAD is frequently associated with other psychiatric conditions such as other mood or anxiety disorders,[18,19] somatoform/pain disorders,[20] medically unexplained symptoms,[21] and substance use disorders.[19,20,22] Another analysis of patients in the PCAP showed a high rate of psychiatric comorbidity in patients with GAD, with 61% having multiple anxiety disorders and 79% with more than 1 Axis I disorder.[23]

GAD has also been linked with medical disorders such as heart disease and gastrointestinal and chronic pain disorders.[24–27] These associations are important at a clinical level, because patients with psychiatric or medical comorbidities have an extended clinical course and poorer outcome than patients with GAD alone.[28] The PCAP has shown that the course of anxiety disorders is adversely affected by the presence of pain.[29] In the subgroup of patients with GAD, the presence of back pain was associated with a reduced chance of remission. Patients with comorbidities therefore present a greater treatment challenge and need for either novel treatments or the combination of different treatment approaches, such as polypharmacy with drugs of different classes or additional nonpharmacologic approaches.

GAD is often unrecognized or misdiagnosed as a physical condition due to the range of clinical presentations, including somatic symptoms, and the frequent occurrence of comorbid conditions. Data from the PCAP showed that almost half (47%) of patients with anxiety disorders were untreated, although results for GAD were not presented.[30] The main reasons for nontreatment of anxiety disorders with pharmacotherapies were that the doctors did not recommend treatment (39%) and that patients did not believe that medication was appropriate for emotional problems (37%). Similarly, the most common reasons for patients not receiving psychotherapies were that they did not believe that psychotherapy would be helpful for them (28%) or that the patients did not think that they had a treatable problem (24%). These data highlight the importance of ongoing education in this field for primary care practitioners and of informing patients of the nature of their condition and recommended treatments. When patients did receive treatment, the most common approach involved a combination of medication and psychotherapy (25% of the entire sample), with 21% receiving medication alone and 7% receiving psychotherapy alone.

In another primary care survey, the diagnosis of GAD was made in only 34% of actual GAD cases and only 20% were receiving treatment.[2] Once the condition had been recognized, the treatment rate increased to 44%–60%, suggesting that enhanced recognition of GAD leads to more frequent initiation of treatment. The likelihood of a diagnosis of GAD is also influenced by the way the patient presents to the primary care physician. One study, in patients with depression or anxiety, has shown that patients who "normalize" their symptoms (ie, attribute symptoms to a nonpathologic cause, for example, explaining the symptom of fatigue by inadequate levels of exercise or overexertion) are less likely to receive a diagnosis of an anxiety disorder than those who adopt a more "psychologizing" style (ie, view their symptoms in terms of their psychological state, for example, attributing fatigue to emotional exhaustion).[31]

According to information gathered by the Midlife Development in the United States survey,[32] and as separately reported elsewhere,[33] GAD was associated with noticeable per capita work impairment days.

Treatment Goals

The treatment plan for GAD should account for (1) predominant symptoms, (2) severity of the condition, (3) presence of concomitant medical illness, (4) complications such as substance abuse or the risk of suicide, (5) outcomes of any previous treatments, (6) cost issues, (7) availability of treatment in a given area, and (8) patient preferences.[34] The overall aims of treatment are 4-fold: (1) to reduce the core symptoms of GAD (both the psychic and somatic), including restoration of sleep; (2) to improve patient function and quality of life; (3) to treat comorbid disorders—present at the time of diagnosis and those that appear over the long term; and (4) to continue treatment for long enough to produce remission and, where possible, prevent relapse.

Treatment of core symptoms of GAD. Patients with GAD are generally managed in the primary care setting, and a range of pharmacologic and nonpharmacologic treatment options are available. Most patients will receive drug treatment with or without psychological therapy. The choice of drug(s) will depend on the severity of GAD; other comorbidity, including depression and insomnia; an assessment of the adverse effects; possible drug-drug interactions and other risks; and the need for an early onset of action.

GAD can often precede, and is a risk factor of, the development of depression.[3] There are suggestions that pharmacotherapy for GAD can result in lower rates of depression among susceptible people.[3,35] Timing of an intervention may be important in that delayed treatment of GAD may result in poorer clinical outcomes compared with patients treated within a year of the onset of symptoms.[36]

Improvement of patient function and quality of life. Recovery implies not only the relief of symptoms but also restoration of patients to their previous high level of functioning, including resumption of family, social, and work-related roles; however, in some lifelong cases of GAD, recovery sometimes produces a level of well-being that had never been previously experienced and that is far better than the premorbid baseline. Patients with GAD are likely to need help with managing insomnia, which can have a substantial impact on quality of life and function at work. While rapid symptom relief is desirable, the more important issue is to inform patients that persistence with therapy is necessary to achieve maximum benefit and to ensure a sustained improvement in their condition. Remission may not occur until 4–6 months into treatment.[37]

Treatments for GAD

The main treatment approaches for GAD comprise pharmacotherapy or psychotherapy or a combination of both. The often chronic and disabling nature of GAD means that some individuals may fail to respond fully to first-line treatment.[34,38] Patients may therefore require a sequential trial of treatments or possibly the use of combination therapy.

In addition to published trials in this area, which will be reviewed below, clinical practice can be informed by the guidelines of various consensus groups, in particular those of the following:

- International Psychopharmacology Algorithm Project (IPAP)[11,12]
- Canadian Clinical Practice Guidelines for the Management of Anxiety Disorders[39]
- British Association for Psychopharmacology (BAP)[38]
- World Federation of Societies of Biologic Psychiatry (WFSBP)[34]
- International Consensus Group on Depression and Anxiety[40]
- National Institute for Clinical Excellence (NICE) in the UK[41]

While all the above guidelines are evidence based, they vary with respect to purpose and clinical utility. Some are government driven for cost-containment purposes, have little practitioner input, and offer limited clinical advice (eg, NICE), whereas others (eg, BAP, Canadian guidelines, and WFSBP) are driven mainly by a clinical practice perspective. The IPAP guidelines are unique in offering a web-based algorithm specifically for clinical situations and questions.

Pharmacologic Therapies: Short-Term Efficacy

Short-term (ie, 4–12 weeks) placebo-controlled trials have consistently shown that the following drug groups are efficacious in GAD: benzodiazepines, azapirones (buspirone), antihistamines (hydroxyzine), and 4 different types of antidepressant. However, there have been few direct comparisons between different drug classes. Therefore, the relative merits of various agents are generally established by means of (1) comparative studies, to the extent that they have been conducted; (2) extrapolation from the various 2-arm placebo-controlled trials of each drug; (3) extrapolation of knowledge obtained from other disorders (eg, side effect profiles in depression); and (4) textbooks and recommendations of consensus groups (Table 1).

Benzodiazepines. Historically, benzodiazepines have been widely used in the management of anxiety disorders.[42] Their presumed mechanism of action rests in their ability to modulate the γ-amino-butyric acid (GABA) receptor and indirectly promote GABA activity. They have a rapid onset of action and are effective in GAD. While benzodiazepines improve the core symptoms of GAD, they are not recommended as monotherapy for depression, dysthymia, obsessive-compulsive disorder, and posttraumatic stress disorder, which commonly occur with GAD.[40,43] However, benzodiazepines can be effective for panic[44] and social anxiety disorders,[45] as well as for insomnia,[42,46] a symptom that is commonly associated with GAD. According to the Canadian guidelines, benzodiazepines also have a role in the management of severe GAD, or GAD with comorbid panic disorder, wherein the rapid onset of action can be useful. In these cases, benzodiazepines are often recommended as adjunctive therapy to help patients in acute crisis or while waiting for a selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI) to take effect.[39]

However, benzodiazepine use can be problematic, particularly in older people, due to side effects such as falls, memory impairment, incoordination, drowsiness, and confusion.[47] Benzodiazepines can disrupt sleep architecture, and rebound insomnia may occur after stopping treatment.[48] Benzodiazepine withdrawal is also associated with distressing symptoms, which although commonly observed in patients treated with benzodiazepines for 6 months or longer, can appear earlier in the course of treatment.[49] Even if benzodiazepine therapy is tapered gradually, patients can experience prolonged (for several months) anxiety, insomnia, and depression.[48] Furthermore, at least 1 author claims that around a third of long-term users of these drugs experience withdrawal effects, even after tapered withdrawal of the drug.[50] It is important to note that no benzodiazepine has GAD listed in its prescribing information as an indication for therapeutic use. There has been some controversy about possible cognitive impairment from long-term use of benzodiazepines in GAD. Benzodiazepines cannot be entirely exonerated in this regard, but, in general, the risk is low (possibly lower than the risk of inadequately treated GAD) and is influenced by dose and age (ie, somewhat more likely at high doses and in older people).[51]

Benzodiazepines also have modest abuse potential[52] and should not generally be administered to patients with a history of misuse of these drugs.[34] There are some circumstances for which benzodiazepine use is justified in this population, but the use of another drug with less abuse potential should be considered first as an alternative. In this type of clinical situation, the primary care physician may decide to refer the patient to a psychiatrist or addiction specialist.

Benzodiazepines may interact adversely with other drugs, including hypnotics, sedating antidepressants, opiate analgesics, anticonvulsants, antihistamines, and alcohol.[48,52] Interactions with drugs that either inhibit or induce certain cytochrome P450 isoenzymes can also pose problems.

Benzodiazepines are generally recommended only for short-term use[39] and are not recommended for first-line long-term treatment of GAD,[39] although they have a role in the management of acute anxiety[34,40] and may have a role in some cases in which somatic symptoms are more prominent than psychic symptoms.[12] Despite these recommendations, benzodiazepine use remains widespread, perhaps reflecting the complexity and tenacity of GAD, as well as intolerance in some patients to SSRIs/SNRIs.

Table 1. Advantages and Disadvantages of Currently Available Treatment Options for Generalized Anxiety Disorder (GAD)

Type of Treatment	Advantages	Disadvantages
Benzodiazepines	Have been widely used in GAD	Problematic side effects, including drowsiness and confusion
	Can reduce psychic and somatic symptoms	Risk of dependence and discontinuation symptoms
	Rapid onset of action	Abuse potential
	Role in acute management	Ineffective against depression
Azapirones	Some efficacy in GAD	Limited efficacy
	Not associated with risk of dependency	Slow onset of action
		Variable tolerability, including risk of sedation and nausea
		Perceived as ineffective against comorbid conditions
Tricyclic/atypical antidepressants	Possible role as second-line therapy in GAD	Slow onset of action
	Sedating tricyclics can be useful in presence of insomnia	Poor tolerance
	Not associated with risk of dependency	
SSRIs/SNRIs	Recommended first-line treatments in GAD	Slow onset of action
	Effective against comorbid depression	Sexual dysfunction and other side effects limit compliance
		Tolerability/withdrawal issues
Antihistamines	Have been widely used in GAD	Slow onset of action
	Not associated with risk of dependency	Lack of demonstrated efficacy against comorbid disorders
		Sedation and anticholinergic effects
$\alpha_2\delta$ ligands	Effective for psychic and somatic symptoms of GAD	Not indicated for depression
	Rapid onset of action	Somnolence, dizziness
	Low potential for withdrawal effects	Weight gain
	Low incidence of drug-drug interactions	Low abuse potential
Antipsychotics	Effective for symptoms of GAD	Data currently unpublished
		Metabolic side effects
Psychological therapies	Some psychological approaches demonstrated to be effective, such as cognitive-behavioral therapy	Not all psychological therapies have demonstrated efficacy in clinical trials
	Can avoid need for pharmacotherapy	Some patients reluctant to undergo psychological therapy
		Limited availability of trained therapists can restrict service provision

Abbreviations: CBT = cognitive-behavioral therapy, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

In some conditions, because GAD waxes and wanes, benzodiazepines may be useful on an intermittent basis to supplement other more long-term treatments.

Other GABAergic drugs. The selective GABA reuptake inhibitor tiagabine has been studied in 3 large placebo-controlled trials, which enrolled 1,830 patients with GAD and showed no significant difference from placebo.[53] Moreover, side effects were troublesome and the drop-out rate for patients taking the drug was as high as 47%. On the basis of this evidence, it seems hard to justify the use of tiagabine for GAD.

Antidepressants. The following antidepressants have demonstrated efficacy in GAD relative to placebo: SSRIs, SNRIs, tricyclic antidepressants (TCAs, particularly imipramine), and, in a single controlled trial, trazodone. Several analyses have shown similar efficacy among antidepressant agents in the management of GAD.[38,54] Of these, SSRIs and SNRIs are generally preferred as first-line therapy, as the evidence supporting their efficacy is more robust, and they are usually better tolerated than the other classes of antidepressants.[38,41]

Paroxetine has been shown to be efficacious in GAD; however, the US Food and Drug Administration (FDA) labeling for its use in pregnancy was reclassified to category D (ie, positive evidence of risk) due to reports[55] that it was associated with an increased risk of congenital malformations, especially septal defects, when used during the first trimester of pregnancy. A more recent prospective report failed to confirm this association, so the extent of actual risk is still not completely understood.[56] More recently, sertraline has been shown to be efficacious in GAD,[57–59] and citalopram has demonstrated efficacy in older patients (≥ 60 years of age) with GAD.[60]

Although the SSRIs are well tolerated, these agents are nonetheless associated with a range of adverse effects, including gastrointestinal symptoms, somnolence, disrupted sleep, and agitation.[61,62] Weight gain and sexual side effects can also occur and can persist during the treatment period.[63,64] The prevalence of sexual dysfunction has been estimated to be as high as 40% during treatment with SSRIs and SNRIs.[65] Clayton et al[66] have shown a high rate of limited sexual dysfunction in a specific phase (eg, desire, arousal, or orgasm) even when global function (ie, all phases together) was not measurably impaired from SSRI antidepressants, so the clinician may need to obtain a more detailed history addressing the various aspects of sexual function before ruling out the occurrence of the drug-induced sexual dysfunction.

As noted, GAD often occurs in the elderly, therefore, it is important to keep in mind the possibility of less common but potentially serious or even life-threatening side effects of SSRIs in this age group. Possible concerns exist over the increased risk of bleeding with SSRIs,[67] reduced femoral bone density in women, and increased risk of falls.[68] Inappropriate antidiuretic hormone excretion in the elderly may be as high as 12%–39% in patients receiving SSRI or SNRI treatment.[69] The resultant hyponatremia can lead to misdiagnosis or misattribution (eg, fatigue, confusion) and serious consequences.

Side effects of SSRIs and SNRIs (eg, insomnia, agitation, tremor, and anxiety with SSRIs or SNRIs)[61,62] add to the symptom burden of patients with GAD and are a common reason for treatment discontinuation in depression, and it is likely that a similar situation exists for GAD.[70] Withdrawal symptoms from SSRIs/SNRIs are not uncommon (except for fluoxetine, which has a prolonged elimination half-life).[38,71]

In 2005, the FDA issued a black box label warning stating that short-term studies of major depressive disorder and other psychiatric indications have shown that antidepressant drugs can increase the risk of suicidal thinking and behavior in children and adolescents. While noting that depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide, the warning was extended in 2007 to young adults aged 18–24 years with clarification that there is no change in risk for adults aged 25–64 years and a reduction in risk for elderly adults (aged 65 years and over).[72–76] This labeling was controversial,[77] particularly because of the concern that reduced prescribing of antidepressants for mental disorders might lead to increases in suicide due to undertreatment, as may in fact have happened.[78,79] Although the majority of the trials in the FDA analysis involved patients with depression, the FDA warning was applied to the antidepressant drugs, not to a specific indication.

The SNRIs venlafaxine and duloxetine are also effective in the treatment of GAD.[80–84] The adverse effects include those associated with the SSRIs, as well as orthostatic hypotension, increased blood pressure, sweating, and urinary hesitancy. Patients taking venlafaxine or duloxetine should be monitored for increases in blood pressure.[85] Both venlafaxine[86] and duloxetine[87] are associated with discontinuation symptoms and serious toxicity in overdose,[88,89] although these problems are by no means unique to the SNRI class and should be kept in mind for all antidepressants.

The tricyclic drug imipramine is effective in GAD but is associated with the usual range of tricyclic antidepressant side effects, which limits its use for those who have not responded to an SSRI or SNRI.[38,40] Another possible second-line antidepressant[12] includes trazodone.[90]

Buspirone. Buspirone, an azapirone that acts as a partial agonist at the 5HT1a receptor, is effective for the treatment of GAD[91] though may be less effective than the benzodiazepines.[92–94] A recent review of 36 short-term studies[95] that included 5,908 patients concluded that azapirones, including buspirone, were useful in GAD, although the drugs were less effective than the benzodiazepines. Common side effects of buspirone included drowsiness, dizziness, and nausea. Furthermore, buspirone has a slow onset of action, variable tolerability, and overall lack of benefit against most comorbid conditions. For these reasons, buspirone is not recommended as first-line treatment for GAD.[12,34,40] Other azapirones (ipsapirone, gepirone, tandospirone) have been studied as GAD treatments, but none have been approved for GAD in the United States.

Antihistamines. Hydroxyzine is an H1 antagonist that has been reported to be effective in the treatment of GAD in well-controlled studies.[96–98] Hydroxyzine has been widely used in the United States and elsewhere[41] for the management of GAD, although some guidelines recommend that this drug should not be used as first-line therapy due to associated side effects (in particular, sedation and anticholinergic effects), slow onset of action, and lack of efficacy for cormorbid disorders.[12,34]

$\alpha_2\delta$ ligands. The new generation $\alpha_2\delta$ ligand pregabalin has consistently shown efficacy in GAD, in addition to its nonpsychiatric uses.[99–101] Although the name suggests a GABA-ergic effect, the drug in fact works by modulating presynaptic voltage-sensitive calcium channels, thereby reducing release of glutamate and other neurotransmitters.[102–104] Pregabalin is approved in Europe for the treatment of GAD[105] and is marketed in the United States for other indications. The drug improves both psychic and somatic symptoms in adults with GAD, including the elderly.[105,106] Data also suggest that the efficacy of this agent compares favorably with other anxiolytics: in an effect-size analysis of current treatments for GAD versus placebo, pregabalin was found to have a higher effect size than all of the other pharmacologic modalities in the study (antihistamines, SSRIs, SNRIs, benzodiazepines, azapirones, and herbal or homeopathic medicines).[92]

The most common side effects associated with pregabalin are somnolence and dizziness.[99–101] Weight gain, which is related to dose and duration of exposure, can occur with pregabalin, even after short-term administration.[99] Pregabalin is a schedule V controlled substance in the United States, although it is not controlled in Europe, indicating that it has some abuse potential, albeit less than with the benzodiazepines (which are generally schedule IV). Medication discontinuation symptoms have occurred in some patients following abrupt or rapid

discontinuation of treatment, indicating that pregabalin should be discontinued by gradual tapering.

Atypical antipsychotics. Some first-generation ("typical") antipsychotics were approved for a condition similar to GAD, and recent studies have suggested that atypical antipsychotics may also have a role in GAD as defined by current criteria.[107,108] Several preliminary reports of monotherapy trials of quetiapine versus placebo have described efficacy at doses in the range of 50–150 mg/d,[107,108] but quetiapine cannot yet be recommended as a routine GAD treatment until a full description of efficacy and safety from these studies has been published. However, the use of quetiapine could be considered after other classes of drugs have proved ineffective or when certain types of symptoms are present. While some might advocate olanzapine or risperidone on the basis of published data, these results have been obtained in partial responders to antidepressants rather than as monotherapy in all patients.[109,110]

Augmentation treatment strategies. In patients who do not respond adequately to initial pharmacologic treatment for GAD, the addition of an atypical antipsychotic agent may provide additional benefit. To date, 3 small, randomized, placebo-controlled augmentation studies have been reported. Low doses of risperidone have been shown to produce improvements in anxiety symptoms when added to existing treatment in patients who had not responded to first-line anxiolytic drugs.[58] A study of quetiapine augmentation of paroxetine controlled release, however, did not provide evidence to support the use of quetiapine as an augmenting agent in GAD and found that tolerance of the combination was sometimes problematic, perhaps because both drugs are somewhat sedating or possibly because of CYP 450 isoenzyme interactions.[111]

Olanzapine has shown augmentation effects in GAD patients who had responded insufficiently to 6 weeks of open-label treatment with fluoxetine. Olanzapine has shown similar augmentation effects when added to fluoxetine in patients with refractory GAD, although this efficacy was achieved at the expense of substantial weight gain.[109] Metabolic side effects remain important concerns when atypical antipsychotics are used for GAD; therefore, it is recommended that they be reserved for second-line augmentation treatment. Patients will benefit greatly from more effective and tolerable augmentation agents.

Other augmentation strategies might include addition of a benzodiazepine or other GABAergic drug to an antidepressant. Although we are unaware of any controlled trials in which a benzodiazepine was added to pre-existing antidepressant therapy in GAD,[11] it is recommended as a possible strategy. While not an augmentation study in partial responders, there is a single positive study in patients with GAD and marked insomnia in which the nonbenzodiazepine GABA agonist eszopiclone produced a faster and greater response when added to the SSRI antidepressant escitalopram compared with the addition of placebo.[112] Augmentation of medication with cognitive-behavioral therapy (CBT) has not been studied meaningfully in GAD, and its benefit still awaits adequate evaluation[11]; for other anxiety disorders, the evidence of greater gain, relative to single treatment, is mixed, but most studies of this modality have been undertaken in non–treatment-resistant cases.

Pharmacologic Therapies: Long-Term Efficacy

An increasing number of studies show benefit for long-term pharmacotherapy of GAD. Efficacy of venlafaxine extended release (ER) has been demonstrated in two 6-month, placebo-controlled, parallel-group studies of GAD.[80,113] The importance of long-term treatment has been demonstrated in a trial with venlafaxine extended release (XR), with increased remission rates at 6 months among patients who had not remitted by week 8.[114] In a 24-week, non–placebo-controlled, randomized study comparing the tolerability of escitalopram with paroxetine, the drugs were equally effective, but escitalopram was better tolerated with fewer subjects experiencing adverse events and fewer subjects dropping out early due to adverse events.[115]

Relapse prevention studies. Two studies have evaluated the role of SNRIs in the prevention of relapse in patients with GAD. The only venlafaxine relapse-prevention study failed to show benefit of maintenance with the drug versus substitution with placebo.[116] Duloxetine has been shown to have long-term efficacy among patients with GAD who responded to 26 weeks of open-label treatment; administration of duloxetine for a further 26 weeks reduced the risk of relapse compared with placebo.[82]

The SSRIs escitalopram (10–20 mg/d) and paroxetine immediate release (20–50 mg/d) have also been shown to be effective in the long-term treatment of GAD.[115] Relapse prevention studies have been reported for both drugs.[117,118] Escitalopram reduced the risk of relapse compared with placebo during 24 to 72 weeks of randomized treatment following 12 weeks of open-label treatment. Similar results were found with paroxetine versus placebo in a shorter study.

The long-term efficacy of pregabalin has also been demonstrated in patients with GAD. Pregabalin reduced the risk of relapse compared with placebo, during 24 weeks of randomized treatment following 8 weeks of open-label treatment.[119] However, differences in study design do not allow for a meaningful comparison of relapse rates between studies.

Psychological therapies. Psychological therapies are an important first-line option in the management of GAD. "Psychoeducation," including provision of information to patients about the causes and treatment of their condition, has been recommended for all patients.[34] This approach also includes paying attention

to alcohol, caffeine, and tobacco consumption; regulating sleep; and the control of external stimuli for improving sleep. Simple coping techniques can be taught in the primary care setting for the control of worry, such as setting aside time to rationalize concerns, organizing these into minor and major worries, and identifying priorities and next steps toward addressing them.[120] Although data are limited, a review of current research showed that exercise can have a role as an alternative or adjunctive treatment in the management of psychiatric conditions, including anxiety disorders.[121]

Data strongly support the efficacy of psychosocial treatments for GAD, in particular cognitive therapies and applied relaxation.[122,123] A Cochrane collaboration review concluded that current evidence demonstrates that CBT is effective for the short-term management of GAD relative to wait-list control or usual treatment (ie, psychological therapy or pharmacotherapy) but not active supportive therapy or supportive treatment (ie, active supportive therapies underpinned by humanistic principals).[124] Either way, the typical controls used in studies of CBT do not approximate to the active treatment as closely as does a placebo tablet to an active drug. However, although CBT is the most effective of the psychological treatments available for GAD, available data indicate that a clinical response occurs in less than 50% of people receiving this form of therapy (46% versus 14% for control), so unmet needs still remain.[124]

One promising form of psychotherapy emphasizes the promotion of positive emotional states and active coping behaviors, rather than focusing on how to reduce symptoms. This resilience-building treatment is referred to as "well-being therapy" and appears to be superior to CBT on some measures in treatment-resistant GAD and other forms of anxiety.[125]

Treatment Challenges

Enhancing recognition of GAD. Screening for GAD can potentially be helpful in improving detection rates in primary care, which in turn, can lead to more appropriate treatment and improved patient outcomes. Until recently, there was no validated clinical tool for identifying probable cases of GAD. In view of this unmet need, a 7-item anxiety scale, GAD-7, was developed to facilitate the diagnosis of GAD.[126] The GAD-7 scale has been shown to be an efficient tool that can screen for likely cases of GAD and can assess symptom severity and could form an important component of the clinical treatment assessment of GAD.[126] Furthermore, another recent study from university-affiliated primary care clinics[127] has shown that a 5-question screening questionnaire, the Anxiety and Depression Detector, was a useful screening tool for several anxiety and depressive disorders. Further work needs to be done to determine its usefulness in the primary care setting.

Screening for GAD can be a practical aid to detection and can provide a useful first step within a collaborative or stepwise approach to management. Generally, a positive screen would call for a thorough clinical evaluation on which to base a diagnosis, but it can identify "high-likelihood" cases.[127] For such screenings to be useful, it is necessary to have adequate resources for diagnosis and treatment.

Mathias et al[128] found that simply reporting the results of positive tests to physicians (who were educated about anxiety and informed of their patients' condition but did not receive treatment recommendations) and having them monitor progress did not improve physician-reported anxiety symptoms and functional outcome versus patients seen by physicians who did not receive the patient reports.[128] Interestingly, patients seen by physicians who received the intervention reported greater improvements in anxiety symptoms and functional status than those who did not.

Recent research indicates that, when patients with GAD did receive psychopharmacologic treatment (ie, SSRIs, SNRIs, TCAs, trazodone) in primary care, it was similar to the type of treatment and doses provided by psychiatrists.[30] Overall, these observations support the idea that improved detection of GAD in primary care can help to improve the management of GAD when adequate resources for diagnosis and treatment are available.[30]

Collaborative care. One innovative form of collaborative care for GAD in the primary care sector is the Coordinated Anxiety Learning and Management (CALM) intervention that has been developed in the United States.[129] CALM is currently being evaluated in a prospective, longitudinal, randomized, controlled trial. The intervention has been designed for easy implementation in a variety of primary care settings, and the clinical specialist is involved in the initial patient assessment and patient education.[129] The clinical specialist also assists the prescribing physician with medication management and delivering computer-assisted CBT to patients with GAD, as well as panic disorder, posttraumatic stress disorder, social anxiety disorder, and associated comorbidities. Treatment is provided on a stepped-care basis, with additional treatment modalities being added or substituted as necessary. Anxiety symptoms, patient functioning, and satisfaction with care and health care utilization will be assessed at 6-month intervals for 18 months, and the results of this treatment approach are awaited with interest.[129]

Patient Subgroups

GAD can affect all age groups, including children and the elderly, although few data are available for treatment in these groups.

Elderly. Management of GAD presents challenges in the elderly, owing to the possibility of drug interactions,

the high rate of physical comorbidity, and the need for dose adjustment of pharmacotherapy in response to metabolic changes and increased sensitivity to adverse effects.[11,130,131] For elderly patients, citalopram has been shown to be effective in the management of late-life anxiety disorders, most of which were GAD, in the first randomized controlled study to evaluate an SSRI for the treatment of GAD in this age group.[60] In this study, the most common and troublesome side effect was sedation.

In a post hoc pooled analysis of 4 randomized studies,[132] duloxetine was shown to be effective in a subset of elderly patients with GAD but was associated with a high rate of treatment discontinuations due to adverse events. A pooled analysis of 5 randomized, placebo-controlled trials of venlafaxine ER in the treatment of GAD showed that increasing age did not adversely affect response to treatment, with venlafaxine ER demonstrating similar efficacy and tolerability in older subjects (≥ 60 years) compared with younger adults.[133]

One trial compared CBT, sertraline, and wait-list control in patients with late-life anxiety disorders, of whom only a minority had GAD.[134] Patients who received sertraline or CBT experienced significantly greater improvement in anxiety, worry, and depressive symptoms compared with the control group. However, attrition rates were high for both types of intervention, randomization failed, and the intent-to-treat analysis did not match the completer analysis.

A recent 8-week, multicenter, randomized, placebo-controlled trial found that flexibly dosed pregabalin (150–600 mg/d) was effective in improving the symptoms of GAD in this patient population.[106]

Children and adolescents. For children and adolescents, there are 5 published studies of the treatment of GAD, 3 evaluating the SSRIs sertraline, fluoxetine, and fluvoxamine[135–137] and the other 2 evaluating venlafaxine ER.[138] These data suggest that these agents may be effective in treating the symptoms of GAD in children and adolescents. The SSRIs are generally well tolerated in this population. Venlafaxine ER, though generally well tolerated over 8 weeks of treatment, was associated with increases in blood pressure and heart rate and a decrease in weight, as well as a lesser increase in height relative to placebo.[137] These effects of venlafaxine ER could become clinically significant safety concerns during long-term treatment.

Guidelines from the British Association for Psychopharmacology recommend that, in children, pharmacologic treatments should be reserved for individuals who have not responded to psychological therapies. However, it seems reasonable to consider using drugs for which there is good evidence of benefit in children with GAD, even though they may not carry an official indication, after carefully weighing the benefits and risks in individual cases. Careful consideration of dosage is also necessary when prescribing for children, along with monitoring for adverse effects, bearing in mind that young people might have difficulty describing these effects.[38] In addition, the risk of possible suicidal thoughts or behaviors should be considered and these potential adverse effects monitored when any antidepressants are administered in this age group.[73]

Treatment resistance. Patients with treatment-resistant GAD present a particular challenge. When initial treatments fail, switching to another evidence-based treatment is recommended.[38] For patients who prove to be refractory to treatment, referral to specialist mental health services is recommended.[38,41]

Adherence and Patient Education

Achieving a satisfactory treatment response and reducing the risk of relapse depends, in part, on adherence to therapy. While data to our knowledge have not been reported separately for GAD, nonadherence to antidepressant medication at 6 months in patients with anxiety disorders has been reported to be 53%–70% in 2 separate studies of managed care populations.[138,139] These rates are similar to 6-month nonadherence rates in major depressive disorder.[140,141] Possible reasons include lack of efficacy, delay in treatment effect, side effects, and improvement of symptoms (so patients feel they no longer need treatment). One study of patients with GAD or panic disorder found that personality traits involving novelty seeking predicted early discontinuation from clinical trials.[142]

Ambivalence about treatment and perceived stigma associated with receiving treatment for a psychiatric condition are also important factors that can reduce adherence to therapy.[141] For example, in major depressive disorder, compliance with antidepressant therapy has been shown to be influenced by the views of individual patients, with perceived stigma having an important negative influence on treatment adherence.[143] Research on antidepressant use in major depression has found that adherence can be improved by increasing clinician awareness about the extent of nonadherence, better understanding about stigma and other patient concerns, patient education, and strengthening the therapeutic alliance.[141] We believe these same approaches could profitably be used for GAD.

GAD is usually chronic with a waxing and waning course, and continued support and education is often required. Patients should be given clear information on how long treatment will take to become effective and how to cope with their symptoms in the meantime. Psychological and antidepressant therapies do not generally produce as rapid a response compared to benzodiazepines, antipsychotics, and $\alpha_2\delta$ ligands. Patients should be advised that speed (and type) of initial response varies according to drug but that marked

improvement may require several weeks of treatment[12] and remission even longer.[113] Patients also need to know how long to expect to remain on treatment and how to deal with any side effects that might arise. Given the chronic nature of GAD, long-term treatment of at least 12 months is usually recommended.[12,38]

CONCLUSIONS

GAD is the most frequent anxiety disorder seen in primary care. In view of its chronic and disabling nature, additional efforts are needed to recognize and diagnose the disorder and to use evidence-based effective treatments. Effective management of GAD has the potential to improve quality of life for patients and their families, as well as improve patient productivity and reduce the impact of the condition on health care resources. We believe that the use of appropriate screening tools and providing information to patients with GAD on their condition and its treatment are an important starting point toward increasing recognition and appropriate treatment of GAD.

The evidence base for GAD has grown in recent years, although many questions remain unanswered regarding the optimization of treatment for the individual patient. Most interventions have similar overall benefit, and much of the evidence to support their therapeutic value comes from studies of single treatments rather than the combinations, which are often needed for more complex cases. Here, the data are lacking. More research is needed into the treatment of comorbid and treatment-resistant forms of GAD, the impact of particular symptoms on choice of treatment, and the efficacy of treatments in patient subgroups such as children and the elderly. An additional question concerns the advisability of commencing at low doses with a progressive build-up versus beginning at a moderate dose. To some extent, this might be determined by the clinical history (eg, sensitivity to side effects of drugs), attitude toward drugs (eg, ambivalence and reluctance to tolerate untoward experiences), salient symptoms (eg, panic type and autonomic instability), and general anxiety sensitivity; to date, there is an absence of good empirical data in GAD.

At present, a need exists for the development of novel approaches for treating GAD. These include the development and dissemination of more easily adopted forms of psychotherapy, eg, self-directed therapy and briefer forms of treatment. With respect to drug therapies, the optimal properties would be a drug that is well tolerated, fast acting, beneficial on sleep, effective across a range of related disorders, and devoid of withdrawal symptoms and adverse interactions with other medications.

Drug names: buspirone (BuSpar and others), citalopram (Celexa, Lexapro, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac, Sarafem, and others), fluvoxamine (Luvox and others), hydroxyzine (Vistaril and others), imipramine (Tofranil and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), tiagabine (Gabitril), venlafaxine (Effexor and others).

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