7. Generalized Anxiety Disorder

Epidemiology

The 1-year prevalence of GAD in the general population is about 1% to 3%, and the lifetime prevalence is about 6% (2, 3,469). GAD is diagnosed more frequently in women than in men (about 2 to 1) (1). It is associated with high rates of comorbidity; 68% of individuals report a current prevalence of at least one other psychiatric illness (usually depression, another anxiety disorder, or substance abuse) (470). GAD is associated with disability, suicidality, and high use of health care resources (471).

Diagnosis

GAD is a chronic anxiety disorder characterized by persistent, excessive, and difficult-to-control worry, which may be accompanied by several psychic and somatic symptoms (Table 7.1). In fact, in a primary care study, only 13% of patients with GAD presented with anxiety as the primary complaint; presentations more often include somatic illness, pain, fatigue, depression, and (or) sleep disturbances (471). Patients with GAD experience a multitude of disabilities affecting work, education, and social interactions (18,472). Table 7.2 lists interview questions that may help to screen for GAD in patients presenting with multiple unexplained somatic symptoms, intense illness worries, depressed mood, and (or) sleep difficulties. Diagnosis for these patients can easily be confused with hypochondriasis or major depression if one fails to ask about worries other than those about health. Also, it is helpful to establish a history of excessive, difficult-to-control worry, which often predates the core symptoms of depression (depressed mood and anhedonia) by months or years.

Assessing Response to Therapy

In GAD, illness severity and response to therapy may be assessed with a standard tool appropriate for anxiety, such as the clinician-rated HARS. Self-rated tools appropriate for anxiety include the Depression Anxiety Stress Scale, a 42-item scale to assess symptoms of depression, anxiety, and stress (a brief 21-item version is also available), as well as the Penn State Worry Questionnaire and the Generalized Anxiety Disorder Questionnaire–IV (for reviews, see Antony and others, 115; and Campbell and Brown, 473).

In clinical trials of pharmacotherapy, response is often defined as a CGI Improvement score of ≤ 2 (very much or much improved) or a 50% reduction in the HARS score. Remission is usually defined as an HARS score ≤ 7 (no or minimal anxiety). It has been suggested that full recovery in GAD should be defined as no longer meeting the diagnostic criteria for the disorder (symptomatic resolution) as well as a return to premorbid functioning in all aspects of life (117,474).

Psychological Treatment

Approach to Psychological Management

Metaanalyses clearly demonstrate that CBT reduces anxiety symptoms and is more effective than no treatment and nonspecific psychological treatment methods for GAD (Level 1) (475–479). The magnitude of benefits is comparable to those reported in studies of antidepressant drugs (480–482). CBT appears to be beneficial in both individual and group settings (483). The benefits of therapy tend to be maintained over 6 months to 2 years of follow-up (479–481,483,484).

Initially, CBT approaches to GAD focused on relaxation, with later approaches adding cognitive interventions (485). Although these approaches produce significant improvement, patients are often left with continued anxiety and other problems. Several common problems have been identified among individuals with GAD, including intolerance of uncertainty, poor problem-solving approaches, and beliefs that worry is a helpful way to deal with problems (486). A CBT intervention targeting these aspects was effective in clinical trials (483,487). In addition, individuals with higher levels of interpersonal problems improved less with therapy (481), and this aspect of GAD may also need to be addressed (488). Adding components focused on increasing the sense of psychological well-being was associated with improved outcome (484). Typical elements included in CBT for GAD are shown in Table 7.3 (485), although treatment for any single patient would often consist of only a subset of these strategies.

Table 7.1 DSM-IV-TR diagnosis of GAD

- Excessive anxiety and worry (apprehensive expectation) occurring for at least 6 months about several events or activities
- Person finds it difficult to control the worry
- The anxiety and worry are associated with 3 (or more) of the following:
  - Restlessness or feeling on edge, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance
- Anxiety and worry are not due to substance abuse or another medical or mental disorder
- The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Adapted from DSM-IV-TR (1)

Table 7.2 Interview questions to screen for GAD

- What kinds of things do you worry about?
- Do you worry excessively about everyday things such as your family, health, work, or finances?
- Do friends or loved ones tell you that you worry too much?
- Do you have difficulty controlling your worry, such that the worry keeps you from sleeping or makes you feel physically ill with headaches, stomach troubles or fatigue?

Since CBT protocols involve several different components, there have been efforts to evaluate which components most effectively reduce anxiety. A recent metaanalysis suggests that treatments involving more than one component produce larger effects (479,483). Conversely, direct comparisons of treatment conditions involving different components of common CBT approaches have tended to show modest or no differences between treatment conditions (479,481,489). In clinical practice, as opposed to clinical trials, experienced therapists develop interventions focused on the case formulation and individualize the approach to the problems experienced by the patient (485,490).

Combined Psychological and Pharmacologic Treatment

There is strong evidence for the effectiveness of either CBT or pharmacotherapy alone for GAD. Unfortunately, few studies compare these approaches in the same trial, and even fewer evaluate combined treatment. A recent metaanalytic review identified 2 studies that compared groups receiving diazepam with CBT and CBT alone (479). There is no current evidence to support the routine combination of CBT and pharmacotherapy. However, as in other anxiety disorders, when patients do not benefit from CBT or have a limited response, a trial of pharmacotherapy is advisable. Similarly, patients who show limited benefit from pharmacotherapy may benefit from CBT. Studies are required to evaluate whether CBT reduces the rate of relapse when pharmacologic treatment is discontinued. Issues related to the combination of these 2 effective treatments warrant further research.

Pharmacologic Treatment

Approach to Pharmacologic Management

The management of patients with GAD should follow the principles discussed in Section 2 and mapped in Figure 2.1. Pharmacotherapeutic interventions that have demonstrated efficacy in treating GAD include SSRIs, SNRIs, TCAs, anticonvulsants, benzodiazepines, buspirone, and other therapies. These treatments have been evaluated according to the criteria for strength of evidence (Tables 1.1 and 1.2) for their use (summarized in Tables 7.4 and 7.5).

If pharmacotherapy is prescribed, treatment should be initiated with a first-line agent such as escitalopram, paroxetine, sertraline, or venlafaxine XR (Table 7.5). Antidepressants have the additional benefit of being effective against depressive symptoms and treat ruminative worry (the core feature of GAD) much more effectively than do benzodiazepines. If response to therapy with one of the first-line agents is inadequate, dosing should be optimized and compliance assessed before switching or augmentation is considered. In patients who have an inadequate response to optimal dosages of a first-line agent (for 8 to 12 weeks) or who are not able to tolerate the medication, another first-line agent should be substituted before considering a second-line medication. If an SSRI was chosen initially and was ineffective after optimization, a switch to a second SSRI or an agent with a different mechanism of action (an SNRI) would be a reasonable choice. Second-line choices include benzodiazepines

Table 7.3 Common components of CBT for GAD

Education	• Educates about GAD, including common worries and bodily symptoms • Explains the CBT procedures used to treat GAD • Recommends relevant self-help reading materials (for example, Hazlett-Stevens H. *Women who worry too much: how to stop worry & anxiety from ruining relationships, work, & fun*. Oakland (CA): New Harbinger Publications; 2005)
Cognitive interventions	• Reappraise unrealistic beliefs concerning the value of worry (for example, that worry motivates problem solving, helps prepare for misfortune, or shows caring about others) • Work on realistic estimation of likelihood of negative outcome occurring and evaluation of the harm caused by these events • Deal with problems related to intolerance of uncertainty and perfectionism
Exposure	• Offers imaginal exposure to worry-related imagery and feared catastrophes (for example, illness or death of a family member, financial disaster, or failure at work or school) • Practises elimination of unrealistic safety behaviour (for example, insisting that a family member phone to say he or she has arrived safely, excessive reassurance seeking about worries) • Involves learning to tolerate, rather than avoid, anxiety-related experiences
Emotion-regulation approaches	• Teach relaxation strategies • Work on acceptance of anxiety, mindfulness-based meditation
Problem solving	• Individuals with GAD may respond to a wide range of challenges by worrying, with little effort focused on problem solving; develops stronger problem-solving skills that may provide a more appropriate response to these challenges • Deals with problems with sleep routine, time management, procrastination, avoidance of problems and emotions • Deals with interpersonal problems and difficult relationships • Focuses on goals and direction in life, planning enjoyable activities, activities to increase sense of psychological well-being
Relapse prevention	• Prepares for periods of increased anxiety when exposed to threatening experiences that relate to the theme of the worries (for example, family member with serious illness, financial threat)

(that is, alprazolam, bromazepam, lorazepam, and diazepam), bupropion extended release (XL), buspirone, imipramine, and pregabalin. Although benzodiazepines are a second-line treatment, they may be used at any time if agitation or anxiety is severe. However, they should ideally be used short-term according to the principles described in Section 2.

Treatment Nonresponse

Treatment-resistant individuals should be assessed for comorbid medical and psychiatric conditions (for example, hypothyroidism, hyperthyroidism, covert substance abuse, or bipolar disorder) that may be affecting response to therapy. Third-line agents may be useful when patients fail to respond to an optimal treatment trial of adequate dosage and duration with first- and second-line therapies used alone and in combination. Adjunctive olanzapine and risperidone, hydroxyzine, mirtazapine, and trazodone are third-line options for the treatment of GAD.

First-Line Agents

SSRIs. Evidence from randomized, placebo-controlled trials supports the use of SSRIs, including paroxetine (Level 1) (491–494), escitalopram (Level 1) (455,456,496,524), and sertraline (494,497) (Level 2) for the first-line treatment of GAD.

Paroxetine has demonstrated good efficacy for the treatment of GAD, with response rates (CGI ≤ 2) of 62% to 68% and remission rates (HARS ≤ 7) of 30% to 36%, compared with 46% to 47% and 20% to 22%, respectively, for placebo (492,493). Significant improvements in quality of life (492) and symptom-related functional disabilities (492,493) have also been reported. In a comparative trial, no significant differences were found between paroxetine and sertraline therapy (494). Response rates of 58% have been reported with escitalopram, compared with 38% for placebo (455). In one trial, remission rates were greater for escitalopram (43% to 48%) compared with paroxetine (33%) (496), but these treatments were equally effective in another

Table 7.4 Strength of evidence of pharmacotherapy for GAD

Agent	Level of evidence
Antidepressants	
SSRIs	
Paroxetine (491–495)	1
Escitalopram (455,456,495,496)	1
Sertraline (494,497)	2
Citalopram (498)	4
TCAs	
Imipramine (491,499–501)	1
Other antidepressants	
Venlafaxine XR (491,502–506)	1
Bupropion XL (507)	2
Mirtazapine (508)	3
Other therapies	
Anxiolytics	
Benzodiazepines	
Alprazolam (502,509–511)	1
Bromazepam (502,512)	1
Lorazepam (502,513–515)	1
Diazepam (502,516,517)	1
Azapirones	
Buspirone (502,503,514,518,519)	1
Anticonvulsants	
Pregabalin (511,513,520)	1
Atypical antipsychotics	
Adjunctive olanzapine (521)	2
Adjunctive risperidone (522)	2
Other agents	
Hydroxyzine (512,519)	1
Trazodone (500)	2
Propranolol (523)	–2

study (495). One trial reported significantly higher response rates for sertraline (63%), compared with placebo (37%) (497).

SNRIs. There is strong evidence from RCTs to support the efficacy of venlafaxine XR in patients with GAD (Level 1) (491, 502–506), with response rates generally around 67%, compared with 44% for placebo. In one study, remission rates with venlafaxine XR were 63%, compared with 9% for placebo (504). In addition to its marked anxiolytic effects, venlafaxine XR appears to be of particular benefit for the psychic symptoms (ruminative worry) associated with GAD (525).

Second-Line Agents

Benzodiazepines. Alprazolam (502,509–511), bromazepam (502,512), lorazepam (502,513–515), and diazepam (502, 516,517) have demonstrated efficacy for the treatment of GAD (Level 1). The magnitude of effect appears to be similar to that for cognitive therapy (478). Despite rapid initial relief of anxiety symptoms, evidence suggests that the effects of benzodiazepines may not be significantly different from those of placebo after 4 to 6 weeks of treatment (209,525–527). In addition, benzodiazepines primarily relieve the somatic symptoms rather than the key psychic features (ruminative worry) that define GAD (499,501,525,526,528). Although RCTs evaluating clonazepam are not available, it is likely that the benefits seen with other benzodiazepines would be similar with this agent, which has a long half-life and low potential for rebound anxiety (82). Clonazepam is used extensively in clinical practice for the treatment of anxiety disorders.

Because of side effects (sedation and potential for cognitive impairment and ataxia, particularly in the elderly) and dependence and withdrawal issues, benzodiazepines are generally recommended only for short-term use. To stay well, however, some patients will require long-term adjunctive treatment with benzodiazepines.

Bupropion XL. Bupropion XL was more effective than escitalopram in an RCT, with remission rates of 63% and 39%, respectively (Level 2) (507). Patients treated with bupropion XL also showed greater improvement in their ability to cope, compared with patients treated with escitalopram.

Buspirone. Buspirone was more effective than placebo and as effective as benzodiazepines in several RCTs (Level 1) (502, 503,514,518,519). It appears to be less effective than venlafaxine XR (503) or hydroxyzine (519). Some evidence suggests that buspirone may have less efficacy in patients who have previously used benzodiazepines (529). Limited effectiveness in clinical practice relegates buspirone to use as a second-line agent.

Pregabalin. In patients with GAD, the anticonvulsant pregabalin was more effective than placebo in 3 RCTs (511,513,520) and as effective as benzodiazepines (511,513) (Level 1). Patients receiving pregabalin showed improvements in both psychic and somatic symptoms, and its effects were significant as early as Week 1 (511,513,520). However, pregabalin is presently a second-line choice because there is little clinical experience with its use in Canada.

Imipramine. Imipramine was superior to placebo and as effective as benzodiazepines in RCTs in patients with GAD (Level 1) (491,499–501). Imipramine was particularly effective for psychic symptoms (499,501). However, side effects and risk of death in overdose relegate TCAs to use as a second-line option for the treatment of GAD.

Table 7.5 Recommendations for pharmacotherapy for GAD

First-line	Paroxetine, escitalopram, sertraline, venlafaxine XR
Second-line	Alprazolam, bromazepam, lorazepam, diazepam, buspirone, imipramine, pregabalin, bupropion XL
Third-line	Mirtazapine, citalopram, trazodone, hydroxyzine Adjunctive olanzapine, risperidone
Not recommended	Beta blocker (propranolol)

Third-Line Agents

Atypical Antipsychotics. Early, small RCTs have suggested that olanzapine (Level 2) (521) and risperidone (Level 2) (522) may be effective adjunctive agents for patients who are refractory to other therapies. However, because of the potential for weight gain and metabolic side effects, their use should be reserved for treatment-refractory cases.

Other Therapies. In an open-label study, mirtazapine was effective in 80% of patients with GAD (Level 3) (508). Citalopram was effective in 85% of patients with GAD in a small, retrospective case series (Level 4) (498). The efficacy of hydroxyzine was superior to that of placebo and similar to that of buspirone in RCTs (Level 1) (512,519); however, clinical experience in treating GAD with this agent is limited. Trazodone has demonstrated efficacy comparable to that of diazepam but has undesirable antihistamine effects (drowsiness) if taken at the required dosages (Level 2) (500).

Not Recommended

The beta blocker propranolol is not recommended for the treatment of GAD. Propranolol did not have significant efficacy over placebo after 3 weeks of treatment in an RCT (523).

Dosing and Duration

It is important that patients receive adequate dosages (see Table 2.10) for an adequate duration before a therapeutic trial is deemed ineffective. While some benefit may be seen as early as 1 week with most antidepressant options, significant improvements may not been seen for 6 to 12 weeks and may continue to accrue for 6 to 12 months (530). Pharmacotherapy should be continued for as long as necessary. Even adjunctive benzodiazepines may be used long-term if there is no evidence of detrimental side effects, misuse, or abuse, which is uncommon in patients without comorbid substance abuse disorders (531). It has been recommended that GAD be treated for at least 1 year after a good response is achieved (532). If pharmacotherapy is discontinued, it should be tapered gradually (10% to 20% of maintenance dosage weekly); psychological treatment may be useful during that time (531).

Long-Term Treatment

Patients with GAD may require a long treatment duration to obtain full benefits, particularly those who have had severe chronic anxiety for many years (530). Paroxetine (495,533), venlafaxine XR (534,535), and escitalopram (495,536,537) have demonstrated long-term efficacy with response rates continuing to increase over 6 months of treatment.

Evidence shows that, after discontinuation of pharmacotherapy, about 20% to 40% of patients with GAD will relapse within 6 to 12 months (533,538), suggesting that long-term treatment is often needed. Open follow-up data of psychological treatments suggest that benefits can be maintained for 1 to 2 years after treatment (480,483,484,489,539). Two double-blind discontinuation trials have demonstrated significantly lower relapse rates with paroxetine, compared with placebo (11% and 40%, respectively) (533), and escitalopram, compared with placebo (19% and 56%, respectively) (536) over 6 to 18 months.

Summary

Clinical experience and epidemiologic data indicate that GAD is a chronic waxing and waning disorder. Comprehensive psychopharmacologic management of GAD should incorporate education about the disorder and the medication. CBT is the first-line choice for psychological treatment and has good evidence for maintenance of gains after treatment is completed. On the basis of current evidence, the antidepressants paroxetine, escitalopram, sertraline, and venlafaxine XR are recommended as first-line pharmacotherapy for GAD. Venlafaxine XR, paroxetine, and escitalopram have also shown efficacy in long-term treatment. Pregabalin is a promising agent in GAD, but it is presently recommended as a second-line treatment because of limited clinical experience with it. Therapy should be continued for at least 12 months, with many patients requiring long-term therapy to prevent relapse.