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CLINICAL PRACTICE GUIDELINES

Management of Anxiety Disorders

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COVER Partners In Psychiatry has ownership of the illustration. Arthur Sciberras is a creative art director at Partners In Medicine. Originally a traditional media graphic artist, he produces work in both traditional and digital formats. He created the branding for the Canadian Anxiety Disorder Guidelines Treatment Initiative, and the cover image is an illustrative rendition of the brand. It is intended to convey the concept of a Canadian guide in the area of anxiety, and the idea of hope for treatment. The components of the graphic where derived from the letter A, the initial for Anxiety and Anxieté and the Inukshuk, an Inuit structure used as a guide for travelers and hunters, with the sun in the background representing hope.

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CLINICAL PRACTICE GUIDELINES

Management of Anxiety Disorders

1. Introduction

Anxiety disorders are among the most prevalent of mental disorders, yet the chronic and disabling nature of these conditions is often seriously underestimated (1–3). This has led to underdiagnosis and undertreatment, resulting in considerable disability and overuse of both psychiatric and nonpsychiatric medical services (4–6).

These guidelines were developed to provide practical, evidence-based recommendations to primary care physicians and specialists in psychiatry for the diagnosis and treatment of anxiety disorders in Canada, including panic disorder (PD), with and without agoraphobia; specific phobia; social anxiety disorder (SAD) (social phobia); obsessive–compulsive disorder (OCD); generalized anxiety disorder (GAD); and posttraumatic stress disorder (PTSD). The objectives are to review assessment and diagnosis and to provide recommendations for improving assessment, diagnosis, and management of these disorders in clinical practice. They are based on an intensive review of the current literature by a panel of Canadian experts in anxiety disorders and were developed through a consensus process.

We obtained data on psychological treatment and pharmacotherapy for the treatment of anxiety disorders through MEDLINE searches of English-language citations (1980–2005) and meeting abstracts (2003–2005), using the specific treatments and specific anxiety disorders as search terms. This was supplemented by searches using PsycINFO, as well as by hand searches of the bibliographies of efficacy studies, metaanalyses, and review articles. We then rated treatment strategies on strength of evidence for the intervention and made a clinical recommendation for each intervention, based on global impression of efficacy, effectiveness, and side effects, using a modified version of the periodic health examination guidelines (Tables 1.1 and 1.2).

Table 1.1 Levels of evidence

1	Metaanalysis or replicated RCT that includes a placebo condition
2	At least one RCT with placebo or active comparison condition
3	Uncontrolled trial with at least 10 or more subjects
4	Anecdotal reports or expert opinion

Table 1.2 Treatment recommendation summary

First-line	Level 1 or Level 2 evidence plus clinical support for efficacy and safety
Second-line	Level 3 evidence or higher plus clinical support for efficacy and safety
Third-line	Level 4 evidence or higher plus clinical support for efficacy and safety
Not recommended	Level 1 or Level 2 evidence for lack of efficacy

The committee included 13 psychiatrists, 2 psychologists, and 1 family physician organized into subcommittees according to expertise in each type of anxiety disorder as well as in treating children and the elderly. At a meeting in May 2005, the group

A list of the abbreviations used in this publication appears on p 91S.

reviewed preliminary evidence and treatment recommendations; the subcommittees developed draft guidelines, which were then presented to the entire group for consensus ratification in September 2005. At the Canadian Psychiatric Association annual meeting in November 2005, the draft version of the guidelines was presented to the Canadian psychiatric community for its input prior to submission of the guidelines for publication.

These guidelines are divided into 9 sections, including this introduction. Section 2 discusses principles of diagnosis and management. This section provides an overview of the differential diagnosis of anxiety disorders in general, discusses issues that affect all anxiety disorders, including comorbidities, and presents the general advantages and disadvantages of psychological treatment and pharmacotherapy options. An overall management algorithm that outlines decision points in treating anxiety disorders is provided. Sections 3 through 8 review the specific diagnosis and management of PD, specific phobia, SAD, OCD, GAD, and PTSD. Pharmacologic and psychological treatment recommendations are provided in each section. Section 9 describes the special issues that require particular attention in diagnosing and treating anxiety disorders in children and adolescents, as well as in elderly patients. The guidelines do not address the treatment of anxiety disorders that are due to a medical condition, substance-induced anxiety disorder, or anxiety disorders not otherwise specified because literature on evidence-based treatment for these conditions is lacking.

2. Principles of Diagnosis and Management of Anxiety Disorders

Epidemiology

Prevalence and Impact

Anxiety disorders are among the most common mental disorders, with lifetime prevalence rates for experiencing any anxiety disorder ranging from 10.4% to 28.8% (1,2,4,7) and 12-month prevalence rates of about 18% (3). The 12-month prevalence rates for specific anxiety disorders range from about 1% for OCD to 8.7% for specific phobia (3); however, rates vary widely across different studies depending on the criteria used to determine distress or impairment. Overall, about 1 in 5 to 1 in 12 patients presenting to primary care will have symptoms of an anxiety disorder (8–10). GAD appears to be more common in primary care than in the general population, suggesting that these patients are high users of primary care resources (9,11). Conversely, patients with SAD make fewer visits to primary care physicians than those with other anxiety disorders (12).

While very common, specific phobia is less likely than other anxiety disorders to result in sufficient impairment to cause sufferers to present for diagnosis and therapy (1,3,13–15). However, these individuals often have multiple phobias and this condition may be associated with considerable distress and disability (16,17).

Anxiety disorders cause a substantial burden for patients and their families, as well as a considerable economic burden on society. Chronic anxiety is associated with profound functional impairment (18,19). There is substantial overuse of both psychiatric and nonpsychiatric medical services (4,11,20,21) and reduced work productivity among patients with anxiety disorders, compared with the general population (4,22).

Suicide Risk

Anxiety disorders are associated with an increased risk of suicidal behaviour (23–25). A review of 20 076 anxiety disorder patients participating in clinical trials found the annual risk of suicide was 193 per 100 000 patients and of suicide attempts was 1350 per 100 000 patients (24). These rates are 10 times higher than rates in the general population. The data indicate that anxiety disorder patients warrant explicit evaluation for suicide risk. The presence of 1, 2, 3, or 4 symptoms of PTSD has also been associated with an increased risk of suicidal ideation (25,26). The presence of a comorbid mood disorder, especially major depressive disorder (MDD) or bipolar disorder, significantly increases the risk of suicidal behaviour (27–32). However, a lifetime history of an anxiety disorder was a risk factor for subsequent suicide attempts, independent of depression, in a population-based longitudinal study (32).

Diagnosing Anxiety Disorders

Anxiety disorders are a group of mental disorders characterized by various combinations of key features—excessive anxiety, fear, worry, avoidance, and compulsive rituals—that are associated with impaired functioning or significant distress. Anxiety as a feeling state, expressed as physical, emotional, and behavioural responses to perceived threats, is a normal part of everyday life. Certain criteria can help identify when anxiety becomes a problem and warrants a diagnosis of a disorder (Table 2.1) (33,34). Some patients may present with complaints of anxiety and stress, drawing attention to the problem immediately. Others will present with sleeplessness, vague pains, headache, dizziness, stomach upset, or other somatic symptoms. Complaints of loss of concentration, tiredness, and reduced effectiveness in routine tasks may also be prominent symptoms.

When a patient presents with excessive or uncontrollable anxiety as described in Table 2.1, it is important to identify other potential causes of the symptoms, including a medical condition, depression, substance use disorder, symptoms secondary to medication, somatoform disorders, or psychotic disorders. However, the presence of these conditions does not preclude the diagnosis of an anxiety disorder, since patients with anxiety disorders frequently have comorbid conditions (see below) and anxiety disorders are more common in patients with certain medical and psychiatric conditions (35–37).

Table 2.1 When does anxiety become a disorder?

Anxiety becomes a problem, and a disorder should be considered when:

- It is of greater intensity and (or) duration than usually expected, given the circumstances of its onset (consider context of family, societal, and cultural behaviour and expectations)
- It leads to impairment or disability in occupational, social, or interpersonal functioning
- Daily activities are disrupted by the avoidance of certain situations or objects in an attempt to diminish the anxiety
- It includes clinically significant, unexplained physical symptoms and (or) obsessions, compulsions, and intrusive recollections or memories of trauma (unexplained physical symptoms, intrusive thoughts, and compulsion-like behaviours are very common among people who do not have an anxiety disorder)

Adapted from Singapore Ministry of Health (33) and New Zealand National Health Committee (34)

Table 2.2 Common risk factors in patients with anxiety disorders

- Family history of anxiety (or other mental disorder)
- Personal history of anxiety in childhood or adolescence, including marked shyness
- Stressful life event and (or) traumatic event, including abuse
- Being female
- Comorbid psychiatric disorder (particularly depression)

Adapted from Antony and Swinson (4)

Certain risk factors and sociodemographic variables have been associated with anxiety disorders and should increase the clinician's index of suspicion (Table 2.2). The most important factors are a family history of anxiety and a personal history of stressful or traumatic life events (4). Each of the anxiety disorders has been shown to run in families, suggesting a genetically mediated component. Anxiety disorders, with the possible exception of OCD, are more common in women than in men (4). PD may be precipitated by stressful or traumatic events, and PTSD by definition follows significant trauma (1,2,4). Most patients with anxiety disorders experience the onset of anxiety in childhood or adolescence; however, PD, GAD, PTSD, and certain specific phobias (for example, phobias regarding driving and enclosed places) can begin in early adulthood (2). Onset of anxiety in GAD may be earlier, but recognition and diagnosis are delayed. Therefore, a patient older than age 45 years who presents with anxiety for the first time and has no childhood history of significant shyness, separation fears, or anxiety disorder; no personal or family history of anxiety disorder until adulthood; and no recent experience of a significant life event should be assessed for the possibility of an underlying medical condition or medication-related problem. Consider that late-onset anxiety disorders may be related to a medical illness as a stressor.

Anxiety disorders frequently co-occur with other psychiatric disorders (see below); anxiety disorders should be considered in patients being treated for other psychiatric disorders, particularly depression and substance use disorders. Comorbid anxiety disorders can negatively affect the treatment outcome of the other target disorders.

Key Features of Specific Anxiety Disorders

This section provides a brief summary of the diagnostic features (Table 2.3) that may help initiate the process of diagnosing an anxiety disorder. If the patient complains of anxiety, stress, or "nerves," or if you suspect that anxiety may be an issue, start your assessment with a broad question. For example, "How have things been going for you recently?" or "Have you been having any problems with excessive stress, worry, or anxiety?" (Appendix A). If the patient endorses anxiety symptoms, these can be explored for more details, including when the anxiety started (many patients delay seeking help for anxiety disorders for years), associations with life events or trauma, the nature of the anxiety (for example, worry, avoidance, or obsession), and the impact it has had on functioning. The Sheehan Disability Scale can be used to inquire about work or school, social life, family life, and home responsibilities (38). The Appendix A interview questions and DSM-IV criteria in the sections devoted to each anxiety disorder can then be used to probe specific anxiety disorders in more detail. An accurate diagnosis is important before instituting treatment.

Table 2.3 Key features of specific anxiety disorders

Disorder	Key features
PD with or without agoraphobia	• Recurrent unexpected panic attacks without any obvious situational trigger • Patient may actively avoid situations in which panic attacks are predicted to occur • Intolerance of physical symptoms of anxiety
SAD and (or) social phobia	• Excessive or unrealistic fear of social or performance situations • Intolerance of embarrassment or scrutiny by others
Specific phobia	• Excessive or unreasonable fear of a circumscribed object or situation, usually associated with avoidance of the feared object (for example, an animal, blood, injections, heights, storms, driving, flying, or enclosed places)
OCD	• Presence of obsessions; recurrent, unwanted, and intrusive thoughts, images, or urges that cause marked anxiety (for example, thoughts about contamination, doubts about actions, distressing religious, aggressive, or sexual thoughts) • Compulsions; repetitive behaviours or mental acts that are performed to reduce the anxiety generated by the obsessions (for example, checking, washing, counting, or repeating)
GAD	• Uncontrollable and excessive worry occurring more days than not, about a number of everyday, ordinary experiences or activities. Often accompanied by physical symptoms (for example, headaches or upset stomach) • Intolerance of uncertainty
PTSD	• Occurs after a traumatic event to which patient responds with intense fear, helplessness, or horror; patients relive the event in memory, avoid reminders of the event, and experience emotional numbing and symptoms of increased arousal • Intolerance of reexperiencing trauma

Adapted from DSM-IV-TR (1)

Comorbid Medical and Psychiatric Disorders

Anxiety disorders may present as the only current disorder, but more often they present together with other psychiatric or physical conditions (4,33). Alternatively, physical and psychiatric disorders may present with anxiety as a prominent feature without an anxiety disorder being present. Most individuals do not present with a single disorder; up to 75% of those who are diagnosed with an anxiety disorder have at least one other comorbid psychiatric condition (39). Common comorbid conditions include another anxiety disorder, depressive mood disorder (for example, major depression or dysthymic disorder), alcohol and substance abuse, personality disorders, and bipolar disorder (4,40).

The strong possibility of comorbidity must be considered when diagnosing anxiety disorders, since there are important implications for management. Patients with comorbidities typically have a greater degree of everyday impairment and rely more on health care services. Symptoms are often more severe, are present earlier in life, and are frequently prolonged, which makes their management more complex (41). Comorbidity may also be associated with a poorer treatment outcome in terms of both the initial anxiety disorder and the comorbid illness (42,43) and may be associated with an increased risk of relapse (44). Treatment costs are significantly higher when a patient with a medical or psychiatric illness is also diagnosed with an anxiety disorder (45).

The main physical conditions associated with PD are respiratory disease such as asthma, vestibular dysfunction, hypothyroidism and hyperthyroidism, and cardiovascular disease (37). In specific settings (for example, primary care facilities or emergency departments), the overlap between anxiety, especially panic, and physical disorders is very high (35,36).

Initial Assessment of Patients With Anxiety

The assessment of a patient presenting with an anxiety state must consider 4 possible scenarios:

1. The anxiety disorder is primary, and there is no significant physical disorder (any physical symptoms are secondary to the anxiety).
2. The anxiety state is symptomatic of a primary physical illness (for example, hyperthyroidism).
3. The anxiety state has been triggered or exacerbated by a physical cause such as stimulant use.
4. Both an anxiety disorder and a physical disorder are present, but they are not causally related (Figure 2.1).

Assessment of the patient with anxiety should include a review of systems, prescribed medications, over-the-counter agents, alcohol use, caffeine intake, and illicit drug use, together with a focused evaluation of the anxiety symptoms, a physical examination focusing on areas of symptomatology, and a functional inquiry. The appropriate investigations will follow from the findings of the history and physical examination. Table 2.4 lists a range of general medical conditions that mimic anxiety disorders, and Table 2.5 lists potential investigations to be considered depending on the patient's presentation and specific symptoms (for example, breathlessness or vertigo).

Ideally, physical examination and baseline laboratory investigations should be performed before pharmacologic treatment for anxiety disorders is initiated. Patients with anxiety disorders should be monitored initially every 2 weeks and then every 4 weeks for weight changes and adverse effects of medication, including sexual dysfunction. Adverse effects are the major reason for patients' discontinuing medications. The suggested investigations shown in Table 2.5 should be performed at baseline; if no abnormalities are identified, repeat assessment should follow best-practice guidelines. Closer monitoring, initially weekly, is required in children younger than 10 years of age, seniors, medically ill patients, patients on medications associated with metabolic changes, and those on multiple medications.

Overview of Treatment

Treatment options for anxiety disorders include psychological and pharmacologic treatments (Figure 2.1). All patients should receive education from their physician that includes information about their disorder, treatment choices, and general prognosis. Physicians should identify alleviating and aggravating factors and signs of relapse for each patient. In addition, information on local self-help groups, self-help reading material describing evidence-based treatment strategies, and other resources, such as Web sites, may be helpful. To support informed decision making, patients should be informed about effectiveness, common side effects, uncommon but serious side effects, probable duration of treatment, any costs they might incur, and what to expect when treatment is discontinued.

The choice of psychological or pharmacologic treatment depends on several factors, such as patient preference and motivation, the ability of the patient to engage in one treatment compared with another (for example, asthma precludes the use of beta blockers; significant cognitive impairment may preclude certain cognitive-behavioural strategies), the skills and experience of the treating clinician, the availability of resources for psychological treatment, the patient's response to any prior treatment, and the presence of a comorbid medical and psychiatric disorder. Whatever course of treatment is chosen, an adequate trial should be administered, with appropriate monitoring and follow-up for 12 months or more. The question of whether to offer treatment to those who are anxious but whose symptoms do not meet the full diagnostic criteria for an anxiety disorder should be answered on a case-by-case basis; if there is sufficient suffering and impairment of function, treatment is justifiable even if the symptoms are subsyndromal.

A brief overview of psychological and pharmacologic treatments is provided below. More specific recommendations for each anxiety disorder are given in the following sections.

Overview of Psychological Treatment

Psychological treatments play an important role in the management of anxiety disorders; however, patient preference and motivation are extremely important when choosing treatment. Cognitive-behaviour therapy (CBT) is well accepted by patients (46); however, in a study of patients with depression, those who actively chose CBT rather than medications had better adherence to treatment and somewhat better outcomes than did those randomly assigned to CBT (47). Assisting patients to obtain their preferred treatment increases the likelihood of their continuing treatment (48). Regardless of whether formal psychological treatment is undertaken, patients with anxiety disorders should be encouraged to face their fears. For example, patients with SAD need to attempt to gradually participate in feared social interactions.

An increasing number of controlled trials of psychological treatments have been conducted in recent years, with the largest number examining various forms of CBT (49–53). A few studies have used other approaches, including interpersonal psychotherapy, which addresses relationship issues; supportive psychotherapy, which offers support and encouragement rather than specific instructions; and brief psychodynamically oriented therapy and hypnotherapy, which are aimed at uncovering and resolving unconscious conflicts (4,54). Data on these strategies are insufficient to consider them established alternatives.

No single form of CBT is suitable for all anxiety disorders. CBT can be delivered in different formats, including individual therapy, group therapy, self-directed therapy (that is, bibliotherapy), or minimal intervention therapy. Minimal intervention therapies include abbreviated treatments with a therapist (for example, a single session for a specific phobia), treatments offered via the Internet (for example, online group or individual therapy sessions), or interaction via telephone (telemedicine) (55–58). These strategies may be useful in cases where in-person therapy is not an option because of distance or other issues. Support group strategies are a form of mutual aid in which groups of individuals with common problems or experiences seek to help each other by offering emotional support and practical assistance. Groups can involve exposure therapy, in which individuals are instructed to engage in exposure practices on their own (4).

Figure 2.1 Key decision points in the management of anxiety disorders

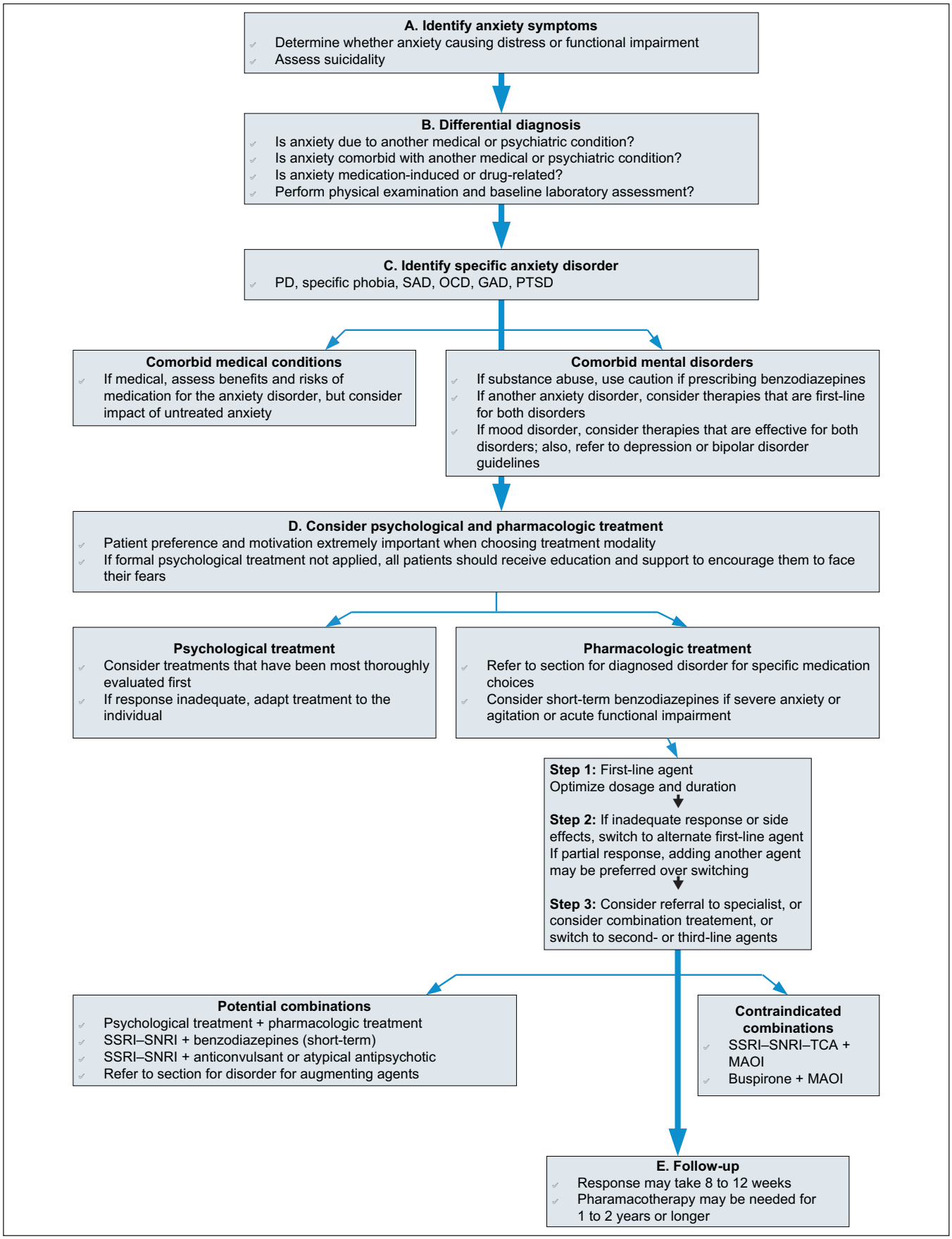

Table 2.4 General medical conditions that may aggravate or mimic anxiety symptoms

Physical condition	Examples
Endocrine conditions	Hyperthyroidism and hypothyroidism, hypoglycemia, adrenal insufficiency, hyperadrenocorticism, pheochromocytoma, menopause
Cardiovascular conditions	Congestive heart failure, pulmonary embolism, arrhythmia, mitral valve prolapse, angina pectoris
Respiratory conditions	Asthma, chronic obstructive pulmonary disease, pneumonia
Metabolic conditions	Diabetes, porphyria
Central nervous system and (or) neurological conditions	Vestibular dysfunction, temporal lobe epilepsy, migraines, early dementia neoplasms, encephalitis
Occupational chemical exposure	Lead poisoning
Gastrointestinal disorders	Peptic ulcers, irritable bowel syndrome
Hematological conditions	Vitamin B_{12} deficiency, anemia
Genitourinary conditions	Urinary tract infection (in elderly)
Other conditions	Chronic fatigue
Other serious and (or) terminal illnesses	Cancer
Medication-induced conditions	Many classes of drugs have side effects similar to anxiety or exacerbating anxiety (for example, SSRIs are associated with an increase in anxiety in the first 2 weeks); a medication history is necessary
Drug-related	Excessive stimulant intake (including caffeine and nicotine), excessive alcohol consumption, discontinuation symptoms, illicit drugs (for example, cocaine)

Adapted from New Zealand National Health Committee (34). The presence of any of the above conditions does not exclude a diagnosis of anxiety disorder.

Table 2.5 Baseline laboratory investigations in patients with anxiety disorders

- Complete blood count
- Fasting glucose
- Fasting lipid profile (total cholesterol, very low density lipoprotein, low density lipoprotein, high density lipoprotein, triglycerides)
- Electrolytes
- Liver enzymes
- Serum bilirubin
- Serum creatinine
- Urinanalysis
- Urine toxicology for substance use
- 24-hour creatinine clearance (if history of renal disease)
- Thyroid-stimulating hormone
- Electrocardiogram (if age > 40 years or if indicated)
- Pregnancy test (if relevant)
- Prolactin

Psychotherapies may be used to complement pharmacotherapy, but each approach may also be used independently. Direct comparisons of pharmacotherapy and various CBT approaches suggest they are about equivalent in their effectiveness for the average patient (59–61). Current evidence is limited but does not support the practice of routinely combining pharmacotherapy and CBT (as this generally does not increase the effectiveness of treatment) (62–64). At present, data are insufficient to support or contradict the use of combinations. For an individual patient, it is possible that combinations may be beneficial, and they are worth considering when a single method of treatment does not produce the desired degree of improvement. Adding CBT to medication

Table 2.6 Common components of CBT

Education	• May include workbooks and (or) self-help materials

Problem solving	• Collaboration between the patient and the clinician
	  • defines and describes the problem
	  • generates alternative solutions
	  • selects and implements initial approach
	  • schedules monitoring of implementation and results
	  • assesses results of problem-solving approach and revises as necessary

Exposure-based approaches	• Focus on overcoming avoidance associated with anxiety disorders and eliminating unhelpful coping strategies • Gradually face feared situations, which has a strong effect on reducing anxiety • Provide exposure to real-life situations if possible, but imagined exposure may also be helpful, particularly for patients who are fearful of experiencing particular thoughts (for example, repugnant obsessions in OCD, traumatic memories in PTSD) • Provide exposure to feared physical symptoms (for example, spinning to induce dizziness), which is a useful component of treatment for PD • May direct goals at improving relationships for difficulties in interpersonal relationships or avoidance of social interaction
Cognitive approaches	• Focus on identifying and evaluating negative automatic thoughts and on considering alternative views
Emotion-regulation approaches	• May involve relaxation approaches, exposure to strong emotions that have been avoided, acceptance-based approaches, and mindfulness-based meditation
Relapse prevention	• Develops a plan for coping with problems that may emerge in the future

may reduce the relapse rate when treatment is discontinued (65). Few data are available on the sequential use of psychological and pharmacologic treatments (almost all studies of combination treatments are based on starting both treatments concurrently).

Pharmacologic treatments are often conceptualized in terms of first-, second-, and third-line treatments; however, this approach is generally not used with psychological treatments. The forms of psychological treatment that have been most thoroughly evaluated should be used first. If a patient fails to progress, the next step is to adapt the treatment to the needs of the individual, staying within the CBT framework rather than changing to a different psychological treatment modality.

CBT is not a single approach to treatment but, rather, a sophisticated process that focuses on intervening in the thoughts and behaviours that have a strong influence on the experience of emotion. CBT may include education, problem solving, exposure-based interventions, cognitive restructuring, emotion regulation, social skills training, and relapse-prevention approaches (Table 2.6). Different aspects of treatment are emphasized for different disorders. Table 2.7 lists some books and Web sites that are useful for education about and psychological management of anxiety disorders. CBT is offered by various professionals who have training in this area, including family physicians, psychiatrists, psychologists, social workers, nurses, and others. See Appendix B for a brief overview of how to conduct exposure therapy.

Overview of Pharmacologic Treatment

This section provides a general overview of some of the strengths and weaknesses of the most commonly recommended pharmacologic agents. Evidence and recommendations for specific medications for each of the anxiety disorders are described in the sections on the specific disorders.

Various antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and reversible inhibitors of monoamine oxidase A (RIMAs), have demonstrated some degree of efficacy in the treatment of various anxiety disorders (Table 2.8) (66). (See Sections 3–9 for evidence and references.) Of these, SSRIs, SNRIs, and NaSSAs are currently preferred, being generally safer and better tolerated than TCAs or MAOIs. For most disorders, there is more evidence for SSRIs and, in some cases, SNRIs than for NaSSAs. The norepinephrine dopamine reuptake inhibitor bupropion has not been adequately evaluated in the treatment of primary

Table 2.7 Resources for psychological treatment of anxiety disorders

Books

- Andrews G, Creamer M, Crino R, and others. *The treatment of anxiety disorders: clinician guide and patient manuals.* 2nd ed. Cambridge (UK): Cambridge University Press, 2003.
- Antony MM, Ledley DR, Heimberg RG, editors. *Improving outcomes and preventing relapse in cognitive behavioral therapy*. New York (NY): Guilford Press; 2005.
- Antony MM, Swinson RP. *Phobic disorders and panic in adults: a guide to assessment and treatment.* Washington (DC): American Psychological Association; 2000.
- Barlow DH, editor. *Clinical handbook of psychological disorders*, 3rd ed. New York (NY): Guilford Press, 2001.
- Mclean PD, Woody SR. *Anxiety disorders in adults: an evidence-based approach to psychological treatment*. New York (NY): Oxford University Press, 2001.
- Nezu AM, Nezu C, Lombardo E. *Cognitive behavioral case formulation and treatment design: a problem solving approach*. New York (NY): Springer Publishing Company; 2004.

Web sites

- Anxiety Disorders Association of Canada: www.anxietycanada.ca
- Anxiety Disorders Association of America: www.adaa.org
- National Institutes of Mental Health (United States): www.nimh.nih.gov/anxiety
- Anxiety Research and Treatment Centre (Canada): www.anxietytreatment.ca
- Obsessive-Compulsive Foundation (United States): www.ocfoundation.org

Note: all web sites accessed 2006 May

anxiety disorders and therefore cannot be recommended. However, bupropion has been shown to be effective in the treatment of depression with comorbid anxiety (67,68).

Anxiolytics, including benzodiazepines and buspirone, have been extensively studied and found to be effective (although the effectiveness of buspirone appears to be limited to GAD). There is ample evidence of the efficacy of benzodiazepines in anxiety disorders, but the role of these agents as monotherapy is controversial. Benzodiazepines may be useful as adjunctive therapy early in treatment, particularly for acute anxiety or agitation, to help patients in times of acute crises or while waiting for onset of adequate efficacy of SSRIs or other antidepressants. Although benzodiazepine monotherapy has demonstrated efficacy in SAD, adjunctive therapy was not beneficial; in addition, there is some evidence of worsening in PTSD with the early use of benzodiazepines. Owing to concerns about possible dependency, sedation, cognitive impairment, and other side effects, benzodiazepines should usually be restricted to short-term use, with regular rather than as-needed dosing. Benzodiazepines should be used with great caution in the elderly and in those with a history of substance abuse. For some patients, benzodiazepines are the most effective agent and can be safely used with adequate monitoring.

Several anticonvulsants have demonstrated efficacy in some anxiety disorders, but owing to side effects with older agents and limited experience with newer agents, anticonvulsants are generally recommended as second-line therapy or as adjunctive treatment. (See Sections 3–9 for evidence and references.)

Early study results are available for the use of atypical antipsychotics in anxiety disorders; however, these agents are generally recommended as adjunctive therapy for treatment-resistant cases until more data become available. (See Sections 3–9 for evidence and references.)

The benefits of combination therapies, such as adjunctive medication and psychological treatment, continue to be unclear. When using medications in combination, clinicians are cautioned to use only safe combinations, such as an SSRI or SNRI with a short-term benzodiazepine, or an SSRI or SNRI with an anticonvulsant or atypical antipsychotic. Combining an MAOI with an SSRI, SNRI, TCA, or buspirone is contraindicated. Refer to the sections for each disorder for evidence and recommendations for specific augmenting agents.

The choice of treatment involves considering its efficacy in the specific disorder, its spectrum of action compared with patient pathology, and its safety and tolerability for both acute and long-term use (69). Patients should be educated to expect a delay of about 2 to 4 weeks in onset of symptom relief with antidepressants (69); full response may take 12 or more weeks. In general, patients who fail to respond to trials of 2 different first-line agents should be referred for specialist assessment. Longer-term

Table 2.8 Medications with Health Canada–approved indications for the treatment of anxiety disorders

	Anxiety disorders	PD	SAD	OCD	GAD	PTSD
Antidepressants						
SSRIs						
Fluoxetine (Prozac)				X		
Fluvoxamine (Luvox)				X		
Paroxetine (Paxil)		X	X	X	X	X
Paroxetine CR (Paxil CR)		X	X		X	
Sertraline (Zoloft)		X		X		
Other antidepressants						
Venlafaxine XR (Effexor XR)		X	X		X	
Azapirones						
Buspirone (BuSpar, Buspirex)					X	
Benzodiazepines[a]	X					

[a]Multiple generic and (or) brand name products, consult product monographs: alprazolam, bromazepam, chlordiazepoxide, clorazepate, diazepam, lorazepam, and oxazepam are indicated for anxiety disorders; alprazolam is also indicated for PD.

Data from *Canadian Compendium of Pharmaceuticals and Specialties* (66)

therapy has been associated with continued symptomatic improvement and the prevention of relapse, and therapy should be continued for 12 to 24 months for most patients (70–75).

Safety and Side Effects

Antidepressants. SSRIs and SNRIs are generally well tolerated, with gastrointestinal side effects and sleep disturbances being among the most commonly reported adverse events (76–78). Headaches and diaphoresis occur early in treatment and may fade over time, whereas weight gain and sexual side effects may continue to occur as treatment continues (79). Be aware that some patients may experience activating side effects such as insomnia, agitation, tremor, and anxiety with some SSRIs (76, 77). SSRIs, SNRIs, and NaSSAs are generally better tolerated than are TCAs, with reduced severity of anticholinergic effects, low levels of toxicity, and less psychomotor or cognitive impairment (80,81). MAOIs are generally reserved for second- or third-line treatment because of side effects, drug interactions, and dietary restrictions associated with these agents.

Anxiolytics. The use of benzodiazepines may be associated with dependence, rebound anxiety, memory impairment, and discontinuation syndrome (82). Memory impairment has been associated with high-potency benzodiazepines, particularly in older people (82). Elderly patients may experience more falls due to psychomotor impairment (83). Short- and intermediate-acting compounds carry greater risk of withdrawal reactions, rebound, and dependence than do long-acting agents (82). Buspirone is generally well tolerated; side effects are mild and may include dizziness, light-headedness, headache, nausea, sweating, and nervousness (66).

Atypical Antipsychotics. Atypical antipsychotics are associated with weight gain, diabetes, and other metabolic side effects, including alterations in glucose and lipid levels, which appear to occur more frequently with clozapine and olanzapine when compared with other atypical antipsychotics (84–87). Prolactin elevations have also been reported, particularly with risperidone (88). As well, cardiovascular side effects have been reported with atypical antipsychotics (89). Because of the risks of diabetes and weight gain and the fact that evidence for the efficacy of these agents in anxiety disorders is in its early stages, it is recommended that these agents generally be reserved for second- or third-line use. (See Sections 3–9 for evidence and references). Studies supporting the use of atypical antipsychotics in anxiety disorder have used these agents in combination with a first-line antidepressant.

Anticonvulsants. Anticonvulsants are associated with gastrointestinal side effects, weight gain, and dermatologic and hematologic side effects. The use of divalproex requires

Table 2.9 Medications to avoid during pregnancy

Phase of pregnancy	Medication to avoid
First trimester	• Carbamazepine • Divalproex • Lithium • Conventional antipsychotics • Paroxetine (91) • Benzodiazepines can be used with caution (92)
Third trimester and labour–delivery	• High-dose benzodiazepines should be used with caution
All trimesters	• MAOIs

Adapted from Sivertz and Kostaras 2005 (90)

monitoring of blood levels, particularly at the initiation of therapy (66).

Special Considerations Concerning Pharmacotherapy in Women

Anxiety disorders generally have been found to occur more often in women (16%) than in men (9%) (4); thus, it is important to review the special issues surrounding the use of pharmacotherapy during pregnancy and breastfeeding. When pharmacotherapy is indicated for a pregnant or breastfeeding woman, the potential risks of medication exposure in the fetus and infant must be weighed against the risks inherent in untreated maternal illness (Table 2.9) (90).

Antidepressants. Generally, the use of most SSRIs and TCAs in pregnancy does not appear to be associated with an increased risk of adverse effects in the newborn. However, use of paroxetine during pregnancy has been associated with a risk of tremors at birth and soon after, owing to drug discontinuation through parturition (91). Although minor anomalies have been reported, no increased risk of major malformations has been reported with the use of antidepressants during pregnancy or lactation (90,93–98), with the exception of paroxetine, which has been associated with a twofold risk in major congenital malformations, particularly cardiac septal defects, compared with other antidepressants (91). Few data are available on bupropion, escitalopram, and mirtazapine (96).

Most antidepressants pass into breast milk (95,99–102); however, the advantages of breastfeeding likely outweigh the very low risk of an adverse event from drug exposure to the infant (99, 103). An individualized risk–benefit assessment with the goal of minimizing infant exposure while maintaining maternal emotional health is the ideal approach (93,103).

Mothers who have high anxiety late in pregnancy without necessarily having a diagnosable anxiety disorder are at risk of increased rates of behavioural or emotional problems in their children (104). While few data are available, prenatal exposure to antidepressants does not appear to be associated with changes in long-term neurocognitive or behavioural development in children (98,105).

MAOIs are contraindicated during both pregnancy and breastfeeding, according to animal studies that have reported increased rates of congenital abnormalities and profiles indicating extensive interaction with other medications (90).

Benzodiazepines. Exposure to high-dose benzodiazepines in utero has been associated with newborn withdrawal symptoms, including irritability and restlessness, apnea, cyanosis, lethargy, and hypotonia (90). A metaanalysis of exposure during the first trimester suggests a very small but significant increase in risk for cleft palate (absolute risk < 1 in 1000 cases) (92). No long-term effects have been reported, although data are limited (90). Case reports of benzodiazepine use during lactation report sedation, lethargy, impaired respiration, and withdrawal in exposed infants after prolonged use (90).

Atypical Antipsychotics. Data suggest that olanzapine and clozapine do not appear to increase teratogenic risk during pregnancy (106,107). Little or no information is available on aripiprazole, risperidone, quetiapine, and ziprasidone (90,106). Cases of gestational diabetes have been reported to occur with the use of atypical antipsychotics (106). These medications are secreted in breast milk, and adverse effects have been reported in infants; effects are not fully known but may be of concern (108).

Anticonvulsants and Mood Stabilizers. Lithium, divalproex, and carbamazepine used during pregnancy have been associated with an increased risk of major congenital malformations in humans (107,109–112). Data from a large pregnancy registry suggest no increased teratogenicity with lamotrigine (113).

Table 2.10 Health Canada–approved recommended daily doses of pharmacotherapy

	Initial daily dose (mg)	Maximum daily dose (mg)
SSRIs		
Citalopram (Celexa)	20	40–60
Escitalopram (Cipralex)	5–10	20
Fluoxetine (Prozac)	20	80
Fluvoxamine (Luvox)	50	300
Paroxetine (Paxil)	20	60
Paroxetine CR (Paxil CR)	25	62.5
Sertraline (Zoloft)	50	200
MAOIs and (or) RIMAs		
Phenelzine (Nardil)	15	90
Moclobemide[a]	300	600
TCAs		
Clomipramine[a]	25	200
Imipramine[a]	25	150
Other antidepressants		
Bupropion SR (Wellbutrin SR)	100–150	300
Bupropion SR (Wellbutrin XL)	150	300
Mirtazapine (Remeron)	15	45
Mirtazapine RD (Remeron RD)	15	45
Venlafaxine XR (Effexor XR)	37.5–75.0	225
Benzodiazepines		
Alprazolam[a]	0.25	1.5–3.0
Bromazepam[a]	6	30
Clonazepam[a]	0.25	4
Diazepam[a]	2.5	10
Lorazepam[a]	0.5	3–4
Azapirones		
Buspirone[a]	5	30
Anticonvulsants		
Gabapentin (Neurontin)	900	3600
Lamotrigine (Lamictal)	25	200
Pregabalin (Lyrica)	150	600
Topiramate (Topamax)	25	800
Atypical antipsychotics		
Olanzapine (Zyprexa)	5	20
Risperidone (Risperdal)	0.5	6
Quetiapine (Seroquel)	50	800

[a]Multiple generic and (or) brand name products; data from respective Canadian product monographs; dosages are for healthy adults, not necessarily for those with anxiety disorders (see Table 2.8 for approved indications) (66)

Follow-Up

Anxiety disorders are often chronic and are associated with significant functional impairment and reduced quality of life (1,4). A systematic approach to treatment that includes patient education, examination of potential comorbidities, and empirically proven pharmacologic and psychological interventions with adequate monitoring and duration will improve outcomes (69).

Initiation of medication should be at a low dosage (Table 2.10), and the patient should be seen at 1 week to assess tolerability of the medication, adherence to the regimen, and progress. Usually, medication increases can occur at 1- to 2-week intervals, but in PD particularly, the rate of increase may need to be slower to allow the patient to adapt to side effects. By 4 to 6 weeks, patients should be receiving medication in the recommended dosage range (Table 2.10). The need for high dosages of medication to achieve an adequate response in OCD is frequently overstated and can lead to increased dropout rates. Because anxiety disorders are very chronic, a few weeks spent in establishing a therapeutic dosage level is a better approach than starting at too high a dosage and producing intolerable side effects. Once the therapeutic range has been achieved, improvement is usually seen over the next 4 to 8 weeks. Follow-up should occur at 2-week intervals for the first 6 weeks and monthly thereafter. The Clinical Global Impression (CGI) scale can be used at each appointment to assess improvement (114). It is brief, comprehensive, and easy to use.

For a patient receiving CBT, treatment includes weekly contact with the therapist for about 12 to 20 weeks, although most CBT studies on OCD are based on more frequent sessions (at least twice weekly). A follow-up appointment 4 weeks later and then every 2 to 3 months is usually sufficient.

Table 2.11 Structured self-administered rating scales to assess anxiety disorders

Self-report rating scale	Description
Depression Anxiety Stress Scale	42-item, self-rated scale to assess symptoms of depression, anxiety, and stress. Items rated from 0–3 (a brief 21-item version is also available) Available without charge at www.psy.unsw.edu.au/dass/
Davidson Trauma Scale	17-item, self-rated scale to assess symptoms of PTSD in adults
Obsessive Compulsive Inventory	42-item, self-rated scale to assess symptoms of OCD (a briefer version is also available)
Anxiety Sensitivity Index	16-item, self-rated scale to assess anxiety sensitivity (anxiety about experiencing symptoms of fear)
Social Phobia Inventory	17-item, self-rated scale to assess symptoms of social anxiety
Sheehan Disability Scale	Self-rated score of disability in 3 areas: work, social life, and family life
Fear Questionnaire	24-item, self-rated scale to assess symptoms of agoraphobia, social phobia, and BII phobia

For reviews of scales used to assess anxiety disorders, see Antony and others (115) and Lam and others (116).

Table 2.12 Structured clinician-administered rating scales to assess anxiety disorders

Structured rating scale	Description
HARS	14-item, clinician-rated, 4-point scale
CAPS-2	Assesses frequency and intensity of symptoms with standard questions and behaviourally anchored rating scales; lengthy to administer
TOP-8	8-item, clinician-rated scale, highly correlated with CAPS, but shorter and easier to use
Y-BOCS	Interview-based, clinician-rated instrument; can be very time-consuming to administer
Leibowitz Social Anxiety Scale	24-item, clinician-rated instrument, measures both severity of fear and anxiety
PDSS	Clinician-rated, 4-point scale; assesses 7 dimensions of PD

For reviews of scales used to assess anxiety disorders, see Antony and others (115) and Lam and others (116).

Assessing Response to Treatment

The use of objective scales can better inform a physician about a patient's treatment progress than can more subjective measures of treatment goals. Patients who have been symptomatic for a long time may not have an adequate frame of reference to fully understand the limitations imposed by their anxiety (69); a structured scale can assist such patients to fully recognize their treatment progress and potential for fuller functioning. The clinician-rated Hamilton Anxiety Rating Scale (HARS) is a useful tool to assess response to therapy of anxiety in general and is often used in clinical trials. However, this scale takes some minutes to administer, its psychometric properties are not well established, and it does not assess features that are specific to individual anxiety disorders. Self-report scales to assess the specific anxiety disorders are listed in Table 2.11, and clinician-rated scales are listed in Table 2.12. The listed self-report scales are easy to use and take little time for clinicians to review. These scales can assist in assessing treatment response as indicated by the degree of reduction of the disorder's core symptoms, of comorbid symptomatology, and of functional impairments in work, social, and family activity (69,117). Many patients with anxiety disorders also suffer from depression; therefore, patients should also be assessed with the Hamilton Depression Rating Scale, the Beck Depression Inventory, or another scale for depression, because improvement of depressive symptomatology is an important part of recovery (69,117).

A response to therapy is often defined as a percentage reduction in symptoms (usually 25% to 50%) on an appropriate scale.

Although it might not be possible for all patients, remission should be the goal of therapy. Remission is often defined as loss of diagnostic status, a prespecified low score on an appropriate disorder-specific scale, and no functional impairment. Specific remission criteria for each anxiety disorder are outlined in the sections for each disorder.

Summary

Anxiety disorders are among the most common mental disorders, and they create a substantial burden for patients and their families. Treatment options for anxiety disorders include psychological and pharmacologic therapies. All patients should receive education that includes information about their disorder, treatment choices, prognosis, alleviating and aggravating factors, and signs of relapse.

No single form of CBT is suitable for all anxiety disorders, although exposure-based techniques form the core of effective treatment for many of them. CBT may include education, problem solving, exposure-based interventions, cognitive restructuring, emotion regulation, social skills training, and relapse-prevention approaches. Different aspects of treatment are emphasized for different disorders.

Pharmacotherapy for anxiety disorders may include various antidepressants. SSRIs, SNRIs, and NaSSAs are currently preferred, since they are generally better tolerated than are TCAs or MAOIs. Anxiolytics, including benzodiazepines and buspirone, and anticonvulsants have also been studied and may have a role for some patients.

Anxiety disorders are often chronic and are associated with significant functional impairment and reduced quality of life. A systematic approach to treatment should include patient education, examination of potential comorbidities, and empirically proven psychological and pharmacologic treatments with adequate monitoring and duration.

Future Directions

The purpose of these guidelines is to promote improved outcomes for people with anxiety disorders. The most effective steps that can be taken, given the information currently available, are early and accurate recognition of anxiety disorders, including early recognition in childhood, and the prompt administration of evidence-based treatment methods. With those changes, outcomes for many people would be markedly improved.

Many questions remain to be answered regarding the management of patients with anxiety disorders. Methods to help predict outcomes of specific treatment interventions for specific individuals would be helpful. For example, knowing that a certain percentage of people improve with a specific intervention does not help in choosing initial therapy for an individual. The development of predictors to reduce the odds of making the wrong choice would add enormously to reducing the impairment that results from anxiety disorders.

Surprisingly few studies compare psychotherapy with pharmacotherapy, and there are no studies assessing the sequential use of these therapies. Is it better in the long term for patients to begin with psychotherapy and add medication if needed, or is it more effective to gain symptomatic control with medications and use CBT for residual avoidance and relapse prevention? Future research needs to address these and other practical issues in the treatment of anxiety disorders.

New medications acting on different receptor and messenger systems will no doubt improve outcomes in the future. The development of these agents will be guided by imaging and genetic studies. In the meantime, management of anxiety disorders must focus on optimizing the treatments that are available.

3. Panic Disorder, With or Without Agoraphobia

Epidemiology

Panic disorder is a chronic and recurrent illness associated with significant functional impairment. The estimated lifetime prevalence of panic attacks is 15%, with a 1-year prevalence of 7.3% (118); however, the prevalence of PD is somewhat lower, at 4.7% (lifetime) and 2.7% (1-year) (2,3). It is estimated that about one-third to one-half of patients with PD also have symptoms of agoraphobia (118). In a Canadian study conducted in 2002, 1.5% of adults had current PD, and 2.1% had a history of the disorder (119). PD and agoraphobia are more common in women than in men (118,120) and generally begin in late adolescence or early adulthood (51,119).

Individuals with PD are less likely to work and more likely to be permanently unable to work, compared with those who have never had the disorder (119,121). Patients with PD have levels of mental health and daily functioning that are substantially lower than those of patients with other major chronic medical illnesses such as diabetes, heart disease, and arthritis (122). Negative coping behaviours, including alcohol or drug use and smoking, are about twice as common among those with PD compared with those without (119). Comorbid depression is common and has a negative impact on outcomes (121,123). Individuals with PD have more than double the risk of suicidal ideation and suicide attempts, compared with those with other psychiatric disorders, and almost 20 times the risk, compared with those with no psychiatric disorder (23).

Diagnosis

The assessment of PD involves evaluating 5 principal domains: panic attacks, anticipatory anxiety, panic-related phobic avoidance (for example, agoraphobia), overall illness severity, and psychosocial disability (71). For a diagnosis of PD, a patient must have had recurrent, unexpected panic attacks (Table 3.1) followed by at least 1 month of persistent concern about another attack, worry about possible implications or consequences of panic attacks, or significant behavioural change related to attacks (Table 3.2) (1). PD may or may not be associated with agoraphobia (anxiety about having a panic attack in certain situations, which are avoided or endured with marked distress). Interview questions that may be helpful in diagnosing PD in patients presenting with anxiety are shown in Table 3.3.

Patients with PD often have very specific and dramatic cardiac and nervous system symptoms that are worrisome to them as well as to their physicians (124). Key psychological symptoms that are typically specific to panic attacks are feelings of "going crazy" or of losing control. Many medical conditions produce symptoms similar to those of a panic attack, such as mitral valve prolapse, hyperthyroidism, hypothyroidism, diabetes mellitus, hypoglycemia, migraine headaches, temporal lobe seizure, vestibular dysfunction, myocardial dysfunction, hypertension, hypotension, asthma, and transient ischemia (124); thus, differential diagnosis is an important consideration. However, even once a diagnosis is established, many patients with PD fear they have a life-threatening illness, despite repeated negative medical tests (1).

In the National Comorbidity Survey, patients with PD sought medical help more often and more quickly than those with other anxiety disorders, which may have been owing in part to the somatic symptoms often seen in this disorder (6). Despite this, only 34% of patients sought treatment during the first year of the disorder, and the median duration of delay among those that subsequently made contact was 10 years (6).

Assessing Response to Therapy

The goals of therapy in PD are to decrease the frequency and severity of panic attacks and to reduce anticipatory anxiety, fear-driven avoidance, and impaired functioning related to anxiety (51,117). Treatment response in PD can be quantified and documented with the Panic Disorder Severity Scale (PDSS), a clinician-rated instrument assessing 7 dimensions of PD on 4-point scales (a self-report version is also available) (125).

Table 3.1 DSM-IV-TR criteria for panic attacks

A discrete period of intense fear or discomfort, in which 4 or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light-headed, or faint
9. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias (numbness or tingling sensations)
13. Chills or hot flushes

Adapted from DSM-IV-TR (1)

Table 3.2 DSM-IV-TR diagnosis of PD (with or without agoraphobia)

- The person has experienced both of the following:
  - Recurrent unexpected panic attacks
  - one or more of the attacks has been followed by 1 month or more of one or more of the following:
    - Persistent concern about having additional attacks
    - Worry about the implications of the attack or its consequences
    - A significant change in behaviour related to the attacks
- The presence (or absence) of agoraphobia
- The panic attacks are not due to substance abuse, a medication, or a general medical condition
- The panic attacks are not better accounted for by another mental disorder

Adapted from DSM-IV-TR (1)

Table 3.3 Interview questions to screen for PD (with or without agoraphobia)

PD

- Do you have times when you experience a sudden rush of symptoms or uncomfortable physical feelings such as racing heart or dizziness?
- Do you have feelings of fear or panic at these times?
- Have these spells ever occurred out of the blue, without any obvious trigger or cause?

Agoraphobia

- Do you avoid any situations because you might experience these spells of symptoms or feelings of fear or anxiety?
  - Crowds, enclosed places, driving, leaving the house alone, or other situations

Self-rating scales that are often useful in clinical practice include the Fear Questionnaire, the Mobility Inventory for Agoraphobia, the Agoraphobia Cognitions Questionnaire, the Anxiety Sensitivity Index, and the Panic and Agoraphobia Scale (PAS) (reviewed by Antony and others, 115). The PAS considers factors that impair patient quality of life (panic attacks, phobic avoidance, anticipatory anxiety, impairment in social relationships and work, and assumption of somatic disease) and was designed to assess response to therapy. The scale is available as observer-rated and self-rated, with matching items, and takes only about 10 minutes to complete (126).

PD is generally chronic, and relapse is not uncommon (127); therefore, the complete absence of panic attacks on a long-term basis may not be a realistic goal (117). According to the suggested criteria, PD is in remission when the patient is essentially free of panic attacks (PDSS ≤ 3, with no individual item score > 1) and has no or mild agoraphobic avoidance, no or minimal anxiety (HARS ≤ 10), no or mild functional disability, and no depressive symptomatology (117).

Psychological Treatment

Approach to Psychological Management

The onset of panic attacks often occurs during or following periods with increased stressful life events. Individuals who develop PD focus increasing amounts of anxious attention on the possibility of having another attack and on the bodily sensations that may signal an attack (128).

CBT is the most consistently efficacious psychological treatment for PD, according to metaanalyses (Level 1) (51,129,130). CBT can be effectively delivered in various settings, including individual, group (131,132), and minimal intervention formats such as self-help books (131,133) or treatment via telephone (56,57) or Internet (55,134). Courses of CBT often include one or more follow-up sessions. In long-term studies, the benefits of CBT were maintained for up to 2 years after treatment completion (135–138). Evidence is accumulating that CBT may be more effective than medication in preventing relapse (130,139). A long-term follow-up study of patients who had become panic-free with exposure therapy found that 93% remained in remission after 2 years and 62%, after 10 years (140).

Various CBT approaches to the treatment of panic attacks have been developed over the years (139). Table 3.4 shows common elements of CBT treatments for PD; the core components typically include education, cognitive strategies, and exposure to feared sensations and situations.

Several specific versions of CBT have been developed for PD, some placing more emphasis on exposure and others placing more emphasis on the cognitive aspects of treatment. Panic control treatment is one of the most widely known approaches and particularly emphasizes interoceptive exposure, in addition to

Table 3.4 Common components of CBT for PD

Education	• Explains the development of panic attacks • Informs about the panic cycle—typical bodily reactions, thoughts, and behaviours during panic attacks and related anxiety experiences • Presents a cognitive-behavioural model for panic attacks and PD • Recommends relevant self-help reading materials (see Table 3.5)
Cognitive approaches	• Illustrate the catastrophic thinking and other cognitive errors that often accompany panic attacks (for example, belief that rapid heart beat means an impending heart attack) • Demonstrates strategies for replacing anxious thoughts with alternative interpretations and coping thoughts • Offers behavioural experiments designed to challenge unrealistic anxious thoughts
Interoceptive exposure	• Exposure to feared bodily symptoms experienced during episodes of panic. Teaches strategies to produce the symptoms so that exposure may be practised repeatedly (for example, hyperventilation triggers feelings of dizziness, breathlessness, and racing heart)
Real-life exposure to avoided situations	• Offers graded and repeated exposure to situations that are feared and may be avoided because they have become associated with panic attacks • Typically, exposure occurs in the context of assignments between treatment sessions, although therapist-assisted exposure is common as well
Emotion-regulation approaches	• Comprise various relaxation approaches • Teach paced breathing to reduce hyperventilation • Recently developed approaches focus on acceptance and mindfulness, developing tolerance of periods of increased anxiety
Problem solving	• Practise coping with problems that were possibly involved in the development or maintenance of PD—conflict, loss, overwork, perfectionism
Relapse prevention	• Preparation for periods of increased anxiety or panic in the future

cognitive therapy and other behavioural strategies (141). This protocol typically includes 12 sessions; about one-half of patients show substantial benefit after 3 to 6 sessions, while patients with more severe agoraphobic avoidance may require more than 12 sessions (128). A protocol developed by David Clark and colleagues places more emphasis on cognitive change and involves a similar number of sessions for the treatment of PD with no more than mild agoraphobia (142). A brief form of this treatment, with only 6.5 hours of therapist time, has been shown to be as efficacious (136). It is generally accepted that more severe agoraphobic avoidance requires more intensive situational exposure.

More recently, evaluating which elements of these multicomponent treatments are most important has been emphasized (143,144). There has been some concern that procedures designed to reduce arousal, such as paced breathing, relaxation, distraction, and the use of safety behaviours, may detract from the effectiveness of exposure, and some approaches have eliminated these aspects of treatment (143,144). Recent studies of anxiety induction with carbon dioxide inhalation suggest there may be advantages to focusing more on symptom acceptance than on strategies to control arousal in challenging situations (145,146).

Not Recommended

Data are currently insufficient to recommend routine use of eye movement desensitization and reprocessing (EMDR) (147,148), applied relaxation (51,149,150), or psychodynamic therapy (151) for the treatment of PD.

Combined Psychological and Pharmacologic Treatment

There is considerable controversy over whether it is helpful to routinely combine CBT with pharmacotherapy (for example,

Table 3.5 Useful self-help books

- Antony MM, McCabe R. *10 simple solutions to panic: how to overcome panic attacks, calm physical symptoms, and reclaim your life.* Oakland (CA): New Harbinger Publications; 2004.
- Barlow DH, Craske MG. *Mastery of your anxiety and panic (MAP 3).* 3rd ed. (client workbooks for anxiety, panic, and agoraphobia). New York (NY): Oxford University Press; 2000.
- Zuercher-White E. *An end to panic: breakthrough techniques for overcoming panic disorder.* 2nd ed. Oakland (CA): New Harbinger Publications; 1997.

SSRIs or TCAs), and well-designed studies with medications currently in wide use are limited. Several studies and metaanalyses have found that combination therapy was superior to CBT or pharmacotherapy alone during the acute treatment phase and while medication was continued (50,60, 129,152–156). The most recent metaanalysis, which included 20 studies, reported a small beneficial effect on anxiety and depression of combined CBT and medication over CBT alone (157). Conversely, in a large study of imipramine and CBT, combined treatment had some advantages during the acute and follow-up phases, but, when the medication was discontinued after the follow-up phase, there was a considerably lower relapse rate in the CBT and CBT-with-placebo groups (18%), compared with the CBT-plus-imipramine group (48%) and imipramine-alone group (40%) (60).

Similarly, in a study of patients with PD with agoraphobia, combining alprazolam with exposure therapy marginally enhanced gains during treatment but impaired improvement thereafter (158).

Providing CBT sessions around the time of medication discontinuation appears to lower the relapse rate at the time of discontinuation and in the months following among patients treated with benzodiazepines or antidepressants (143,159). Both CBT and antidepressant medication have been found to be helpful for the comorbid depressive and anxiety disorders that frequently accompany PD (139,160).

Pharmacologic Treatment

Approach to Pharmacologic Management

The management of patients with PD should follow the principles discussed in Section 2 and mapped in Figure 2.1. Pharmacotherapeutic interventions that have demonstrated efficacy in treating PD include SSRIs, TCAs, MAOIs, and benzodiazepines. These treatments have been evaluated according to the criteria for strength of evidence (Tables 1.1 and 1.2) for their use (see Tables 3.6 and 3.7 for a summary).

Individuals with PD may interpret some side effects such as tachycardia, dizziness, dry mouth, and tremor as the physical symptoms of disorders other than anxiety or panic attacks (161). Their anxiety about physical illnesses may increase at the onset of treatment with antidepressants. Side effects are most common in the first weeks of pharmacologic treatment and generally subside; therefore, it is very important to counsel patients about potential adverse events to prevent premature withdrawal from treatment. Because PD patients are often highly sensitive to any physical experience, it is important to start medication treatment with very small doses of the chosen agent. This may be as low as 5 mg fluoxetine or 5 mg paroxetine. The dosage will need to be increased weekly or every 2 weeks to the usual therapeutic range, but the initial increases should be very small.

For patients with PD, therapy should be initiated with a first-line agent: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, or venlafaxine extended release (XR) (all Level 1) or escitalopram (Level 2) (Table 3.7). If response to therapy with one of the first-line agents is inadequate, dosing should be optimized and compliance assessed before switching to another agent. In patients who have an inadequate response to optimal dosages of a first-line agent or in whom the agent is not tolerated, therapy should be switched to another first-line agent before considering a second-line medication. Second-line choices include TCAs, clomipramine, imipramine, mirtazapine, and benzodiazepines (alprazolam, clonazepam, lorazepam, and diazepam). While benzodiazepines are a second-line treatment, they can be used at any time if agitation or anxiety is severe. Studies have shown that the addition of a benzodiazepine to an SSRI at the initiation of treatment can lead to a more rapid response (162, 163). In these studies benzodiazepines were completely discontinued by Week 7. Benzodiazepines should be used short-term according to the principles described in Section 2.

Treatment Nonresponse

Treatment-refractory 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 of at least 8 weeks with first- and second-line therapies used alone and in combination. Divalproex, gabapentin, phenelzine, atypical antipsychotics, pindolol, and moclobemide are third-line options (Table 3.6) that could be considered as adjunctive therapy for the treatment of refractory PD.

First-Line Agents

SSRIs. There is good evidence from randomized controlled trials (RCTs) supporting the use of the SSRIs fluoxetine (166–169), fluvoxamine (152,170–175), paroxetine (154,176–179), and sertraline (180–184) (all Level 1) and some evidence for citalopram (Level 1) (164,165) and escitalopram (Level 2) (164) for the treatment of PD. In metaanalyses, SSRIs and TCAs have

Table 3.6 Strength of evidence of pharmacotherapy for PD

Agent	Level of evidence
Antidepressants	
SSRIs	
Citalopram (164,165)	1
Fluoxetine (166–169)	1
Fluvoxamine (152,170–175)	1
Paroxetine (154,176–178)	1
Paroxetine CR (179)	2
Sertraline (156,180–184)	1
Escitalopram (164)	2
TCAs	
Clomipramine (165,176,178,185,186)	1
Imipramine (60,172,184,186–190)	1
MAOIs and (or) RIMAs	
Phenelzine (191)	2
Moclobemide (169,185,192,193)	2[a]
Other antidepressants	
Venlafaxine XR (194–197)	1
Mirtazapine (168,198,199)	2
Bupropion SR (200)	3
Other therapies	
Anxiolytics	
Benzodiazepines	
Alprazolam (187,201–203)	1
Clonazepam (202,204–207)	1
Lorazepam (203,208,209)	1
Diazepam (210–212)	1
Adjunctive clonazepam (162,163)	1
Azapirones	
Buspirone (213,214)	–1
Anticonvulsants	
Gabapentin (222)	2[a]
Divalproex (223–226)	3
Carbamazepine (227)	–2
Atypical antipsychotics	
Olanzapine (215,216)	3
Quetiapine (217)	3
Risperidone (217)	3
Other therapies	
Other agents	
Trazodone (218)	–2
Propranolol (211,219,220)	–2
Adjunctive pindolol (221)	2

[a]No significant superiority over placebo in overall group, but significant benefits in subgroup of more severely ill patients

demonstrated similar effect sizes, with a similar proportion of patients being panic-free (54% and 56%, respectively) (175, 228). Although the SSRIs demonstrated a significantly higher proportion of panic-free patients than did placebo, placebo response rates are high in some studies (20% to 60%). However, SSRIs also demonstrate significant improvements in panic severity, anticipatory anxiety, and agoraphobic avoidance, as well as improvements in outcomes such as disability and quality of life.

Citalopram (164,165) and escitalopram (164) have also demonstrated efficacy in RCTs. Citalopram relieved phobic symptoms more consistently than did clomipramine (165,229). Citalopram was less effective than escitalopram in a comparative trial, and although both drugs reduced PD severity, only escitalopram significantly reduced panic attack frequency, compared with placebo (164).

SNRIs. Venlafaxine XR has been shown to be useful in reducing the severity of PD symptoms in RCTs (Level 1) (194–197), although several studies did not show significantly greater rates of panic-free patients, compared with placebo (194,195). However, one study showed that venlafaxine XR was superior to paroxetine in terms of the proportion of panic-free patients and reduced symptom severity (194).

Second-Line Agents

TCAs. There is good evidence from RCTs to support the use of the TCAs clomipramine (165,176,178,185,186) and imipramine (60,172,184,186–190) in PD (Level 1). In a metaanalysis, TCAs were associated with a 60% reduction in the number of panic attacks, as well as with reductions in agoraphobia, overall anxiety, and depression (175). However, since these agents tend to be less well tolerated, have greater cardiotoxicity, are more toxic in overdose, and are associated with higher discontinuation rates than are SSRIs (30%, compared with 17%) (175), they are recommended as second-line options.

Table 3.7 Recommendations for pharmacotherapy for PD

First-line	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine XR
Second-line	Clomipramine, imipramine, mirtazapine, benzodiazepines (for example, alprazolam, clonazepam, lorazepam, diazepam), adjunctive clonazepam
Third-line	Divalproex, gabapentin, phenelzine, moclobemide, bupropion, adjunctive pindolol, olanzapine, risperidone, quetiapine
Not recommended	Buspirone, trazodone, propranolol, carbamazepine

Mirtazapine. There is evidence from open trials (198,199) that mirtazapine may be useful for the treatment of PD. In one small RCT, mirtazapine was as effective as fluoxetine in decreasing the number of panic attacks, with greater reduction in phobic anxiety levels (Level 2) (168).

Benzodiazepines. Alprazolam (187,201), clonazepam (202, 204–207), lorazepam (203,208,209), and diazepam (210–212) have demonstrated efficacy for the treatment of PD (Level 1). Short-term adjunctive clonazepam at the initiation of SSRI treatment can lead to a more rapid response (Level 1) (162,163). As mentioned above, benzodiazepines may also be used at any time for the short-term management of acute or severe agitation or anxiety.

Third-Line Agents

MAOIs and RIMAs. Despite the widespread use of phenelzine, only 1 RCT has assessed this agent and demonstrated that phenelzine was more effective than placebo and as effective as imipramine (Level 2) (191).

Placebo-controlled RCTs have demonstrated conflicting results with moclobemide for the management of PD. In comparative trials, moclobemide demonstrated efficacy similar to that of clomipramine and fluoxetine; the percentage of panic-free patients was 49% to 53%, respectively, with moclobemide (Level 2) (169,185). In placebo-controlled trials, moclobemide was not superior to placebo overall (192,193); however, in one study, it was beneficial in more severely ill patients (192), suggesting it may be useful in treatment-resistant patients.

Atypical Antipsychotics. Open-label studies suggest that the atypical antipsychotics olanzapine (215,216), quetiapine (217), and risperidone (217) (all Level 3) may have some benefits for the treatment of patients with refractory PD.

Other Therapies. In RCTs, pindolol added to fluoxetine therapy in patients with treatment-resistant PD was associated with significant improvement in PD symptoms, compared with fluoxetine plus placebo (Level 2) (221). In an RCT, gabapentin was not superior to placebo overall but demonstrated significant benefits in patients who were more severely ill (Level 2) (222). Divalproex (223–226) and bupropion sustained release (230) have shown some efficacy in open trials. However, until more data become available, these agents should only be tried as third-line therapy in patients with refractory PD. Referral to an anxiety disorders specialist should be considered.

Not Recommended

Buspirone (Level 1, negative) (213,214), trazodone (Level 2, negative) (218), propranolol (Level 2, negative) (211,219,220), and carbamazepine (Level 2, negative) (227) have not demonstrated efficacy and are not recommended for the treatment of PD.

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 (171), significant improvements should be seen within 6 to 8 weeks and may continue to accrue for up to 12 months (75). There is some evidence to suggest that completing at least 8 months of therapy is associated with better outcomes when compared with only 2 months of therapy (231). It is not advisable to discontinue medication until avoidance behaviour has been overcome, even if panic is controlled (51). Ceasing medication used to manage anxiety may cause rebound anxiety, a discontinuation syndrome, or relapse. All medication should be tapered gradually over at least 8 weeks. During discontinuation, patients should be encouraged to continue with exposure exercises and other cognitive-behavioural strategies and to avoid stimulant drugs (for example, caffeine and nicotine); relaxation may be helpful in dealing with brief exacerbations of anxiety symptoms. Specific CBT approaches have been developed for use when discontinuing benzodiazepines or antidepressants (143).

Long-Term Treatment

In long-term follow-up studies, citalopram (232), fluoxetine (169), paroxetine (233), sertraline (184), venlafaxine XR (234), and moclobemide (169) have demonstrated maintained benefits and continued improvements over 6 to 12 months of ongoing treatment. The TCAs clomipramine (232,233) and imipramine (184,235–237) have also shown ongoing benefits with maintenance therapy. However, in one study, there was no

difference in the proportion of panic-free patients treated with imipramine, compared with placebo, after 8 months of therapy (231). Several trials have demonstrated the benefits of alprazolam maintenance during up to 2 years of therapy (231, 235); there was no evidence of tolerance developing, but up to one-third of patients were unable to discontinue therapy (231). In long-term studies, the benefits of CBT were maintained for up to 2 years (135–138).

Venlafaxine XR (234) and imipramine (237) have been shown to prevent relapse in randomized, placebo-controlled discontinuation studies. After 3 months of acute treatment, the time to relapse was significantly prolonged with ongoing venlafaxine XR, compared with switching to placebo during 6 months of follow-up (234). In a small study, relapse rates during the discontinuation phase were only 3.4% with imipramine, compared with 37% with placebo, over a 1-year period (237). Evidence is accumulating that CBT may prevent relapse better than medication does (130,139).

Some data suggest that low dosages of medication can effectively maintain a panic-free state. In an open-trial, once-weekly fluoxetine effectively maintained 9 of 10 patients in a panic-free state for over 2 years; however, this could be related to the long half-life of fluoxetine (238). During a 12-month follow-up of responders to 6 months of imipramine treatment, no patient had relapse or worsening of symptoms with half-dose maintenance therapy (236).

Summary

PD is associated with significant disability, elevated rates of suicidal ideation and suicide attempts, and high rates of substance abuse and depression (23,119,121). CBT and pharmacotherapy should be considered as first-line options for the treatment of PD. Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine XR are first-line pharmacotherapeutic choices. Even when pharmacotherapy results in improvements, elements of CBT should usually be part of therapy, particularly in patients with substantial agoraphobic symptoms. Patients who do not do well with CBT may improve with pharmacotherapy and vice versa. When antidepressants are discontinued, there is substantial risk of relapse; therapy should be continued for 8 to 12 months. Many patients require long-term therapy to achieve full benefits and to prevent relapse.

4. Specific Phobia

Epidemiology

A specific phobia is an excessive or irrational fear of an object or situation and is usually associated with avoidance of the feared object. Spiders, bugs, mice, snakes, and heights are the most prevalent feared objects or situations (239). Specific phobia occurs frequently in the general adult population. Large epidemiologic surveys conducted in the United States report a lifetime prevalence estimate of 12.5% and a 12-month prevalence of 8.7% (2,3). Specific phobias begin at a young age, with a median age of onset of 7 years (range 5 to 12 years) (2). However, age of onset tends to vary depending on the subtype of specific phobia; animal and blood-injection-injury (BII) phobias generally begin in childhood and situational phobias (for example, driving phobia and claustrophobia) generally begin in late adolescence or early adulthood (240–242).

Diagnosis

Specific phobias tend to co-occur with other specific phobias (17), as well as with other anxiety disorders (243). However, when specific phobias co-occur with other anxiety disorders, the specific phobia is generally of lesser severity than is the comorbid condition, typically occurring as an additional diagnosis rather than as the primary diagnosis (243).

To meet the DSM-IV criteria for specific phobia, a patient must have excessive or unreasonable fear of a specific object or situation and must suffer marked distress or impaired functioning (Table 4.1) (1). Specific phobias are delineated into 5 subcategories: animal type, natural environment type, BII type, situational type, or other type (Table 4.2). Interview questions that may help to identify specific phobias in patients presenting with anxiety are shown in Table 4.3.

Because specific phobias may present with situationally bound panic attacks, panic disorder must be considered as a differential diagnosis. Individuals with panic disorder with agoraphobia may appear to have claustrophobia or a fear of flying because they avoid these situations for fear of having a panic attack, whereas patients with specific phobias generally have low levels of intercurrent anxiety because their fear is limited to a specific stimulus (1).

Assessing Response to Therapy

There are various structured tools for assessing specific phobias, which differ for each condition (see Antony, 244). Although response can be indicated by the absence of the phobic condition after therapy, it can also be quantified by using appropriate scales.

Psychological Treatment

Specific phobia is widely regarded as the most treatable of the anxiety disorders (245). Pharmacotherapy is used minimally; this is in large part owing to the high degree of success of exposure-based therapies in providing remission of specific phobias.

Primary treatment for specific phobia is exposure-based and provides the patient with relatively quick symptom resolution (246). Both in vivo exposure and virtual reality (VR) exposure can be effective (245), depending on the phobia type (VR has been evaluated primarily for phobias in regard to heights and flying). For patients experiencing BII phobias, exposure therapy is often combined with muscle tension exercises (referred to as applied muscle tension) designed to prevent fainting. This approach has been shown to be highly effective for this type of specific phobia (247). Cognitive strategies have not been well studied, but there is some evidence for beneficial effects in dental phobias (248).

Collectively, exposure-based therapy has been shown to be more effective if certain conditions are met. These include sessions grouped closely together, prolonged exposure, no avoidance in therapy, real exposure (not imagined), and some degree of therapist involvement (not entirely self-directed) (246). Compliance may be better with gradual exposure as opposed to a more rapid approach, although evidence regarding this issue is not clear.

A common approach to exposure-based therapy is that of graded exposure. For example, if an individual is afraid of snakes, the following hierarchy could be used to guide his or her exposure

Table 4.1 DSM-IV-TR diagnosis of specific phobia

- Excessive or unreasonable fear, cued by the presence or anticipation of a specific object or situation (for example, flying, heights, animals, receiving an injection, seeing blood)
- Exposure provokes an immediate anxiety response
  - May have situationally bound or situationally predisposed panic attack
- The fear is recognized as excessive or unreasonable
- The situation is avoided or else endured with intense anxiety or distress
- There is marked distress or interference with normal functioning
- Not due to a substance or medical condition or better accounted for by another mental disorder

Adapted from DSM-IV-TR (1)

Table 4.2 Specific phobia types in DSM-IV-TR

Phobia Type	Examples
Animal type	Insects, snakes, spiders, dogs, cats, birds, fish, mice
Natural environment type	Heights, being near water, storms
BII type	Seeing blood, receiving an injection, having blood drawn, watching surgery
Situational type	Public transportation, tunnels, bridges, elevators, flying, driving, enclosed spaces
Other type	Choking, vomiting, contracting an illness, space phobia

Adapted from DSM-IV-TR (1)

Table 4.3 Interview questions to screen for specific phobias in patients presenting with anxiety

- Do any of the following make you feel anxious or fearful:
  - Animals (for example, spiders, snakes, dogs, cats, birds, mice, bugs)?
  - Heights, storms, being near water?
  - The sight of blood, getting an injection or blood test?
  - Driving, flying in an airplane, enclosed places such as elevators or small rooms?
- Does this fear interfere with your life or cause you marked distress?

practices, depending on how difficult the individual finds each step: looking at pictures of snakes, holding a rubber snake, looking at a live snake through glass, touching the outside of a glass aquarium containing a live snake, standing 2 feet from a live snake being held by someone else, touching a live snake being held by someone else, and finally, holding a live snake. This approach provides a progressively more difficult exposure to the phobic object or situation.

Recently, computer-generated VR exposure has been shown to be effective for such phobias as fear of flying (249,250) and of heights (251,252). This approach is a promising alternative for treating these fears as well as others (for example, fear of storms) for which in vivo exposure is often not practical. Table 4.4 outlines various psychological treatment strategies found to be effective for each specific phobia (245). Useful self-help books targeted toward specific phobias are shown in Table 4.5.

Pharmacologic Treatment

There are few studies of pharmacologic treatment of specific phobias. The few studies of benzodiazepines have usually assessed their efficacy in combination with exposure therapy,

Table 4.4 Psychological treatments with demonstrated efficacy in specific phobias

Psychological treatment	Phobia
Exposure-based treatments	All specific phobias
Virtual reality exposure	Heights, flying
Computer-administered treatments	Spiders, dental, flying
Applied muscle tension (exposure combined with muscle tension exercises)	BII type
Cognitive therapy and exposure	Dental

Adapted from Antony and Barlow (245)

Table 4.5 Useful self-help books

- Antony MM, Craske M, Barlow D. *Mastery of your specific phobia: client workbook*. 2nd ed. New York (NY): Oxford University Press; 2006.
- Antony MM, McCabe R. *Overcoming animal & insect phobias: how to conquer fear of dogs, snakes, rodents, bees, spiders & more*. Oakland (CA): New Harbinger Publications; 2005.
- Antony MM, Watling M. *Overcoming medical phobias: how to conquer fear of blood, needles, doctors, and dentists*. Oakland (CA): New Harbinger Publications; 2006.
- Brown D. *Flying without fear.* Oakland (CA) New Harbinger Publications; 1996.

and these have found no additional benefit with medication (245). Benzodiazepines are often used in clinical practice to provide acute symptom relief when it is necessary for a patient with a specific phobia to face a feared situation (for example, a dental procedure, a magnetic resonance imaging session, or an unexpected flight).

Very few data are available on the use of antidepressants. There have been 2 reported cases of resolution of flying phobias with fluoxetine (253) and one case of successful treatment of storm phobia with fluvoxamine (254). In one small RCT (n = 11), paroxetine was significantly more effective than placebo in resolving anxiety in people with specific phobias, although the study had several methodological limitations (for example, outcome measures that were overly general and a greater number of situational-specific phobias in the paroxetine condition than in the placebo condition) (255).

In an RCT, D-cycloserine, a partial agonist at the *N*-methyl-D-aspartate receptor, combined with exposure therapy resulted in significantly larger reductions of acrophobia symptoms within virtual and real environments, compared with exposure therapy alone (256).

Long-Term Treatment

Long-term treatment of specific phobia is rare, as most treatment strategies are designed to achieve remission relatively quickly.

Summary

Treatment for specific phobia remains focused on various exposure-based techniques, and these treatments are highly effective.

5. Social Anxiety Disorder

Epidemiology

Social anxiety disorder affects 750 000 Canadian adults, or 3% of the population (2002) (257). With a lifetime prevalence of about 8% to 12%, SAD is one of the most common anxiety disorders (2,257). It is more common in women than in men (ratio about 3 to 2) (14,16,258). SAD has an early onset, peaking between ages 0 and 5 years, and again between ages 11 and 15 years; onset after age 25 years is rare (2,259,260). Behavioural inhibition, a personality style beginning in early childhood that involves a tendency to exhibit withdrawal and excessive autonomic arousal when presented with the unfamiliar, may be a precursor of SAD for some individuals (259). SAD is generally chronic, with a mean duration of 20 years or longer (257, 261,262).

SAD has been described as an "illness of missed opportunities" (263), because its early onset hinders future social success, making marital and job success less likely (257). Patients with SAD tend to be less well educated, of a lower socioeconomic status, and unmarried; they also tend to suffer greater functional, health, and physical impairment than individuals without SAD (16,20,257,260,263–266). It has a significant negative impact on quality of life, especially in social and emotional domains (20, 257,267–269). In the Canadian Community Health Survey, people with SAD were twice as likely to report at least 1 disability day in the past 2 weeks, compared with those without SAD (257). The presence of comorbid conditions dramatically increases the impairment and disability related to SAD (257,270).

Diagnosis

SAD is characterized by excessive anxiety and fear of scrutiny by others, often accompanied by anxiety symptoms such as tremulousness, blushing, palpitations, and sweating (Table 5.1) (1). This fear may lead to avoidance of social or performance situations and cause marked distress and interference with the person's daily life (1). However, apprehension and fear in social situations is very common. Most in the general population report a degree of discomfort with some social situation or other, and most individuals believe that they are more nervous than are others (258). A diagnosis of SAD should only be considered when the anxiety causes significant distress or functional impairment (271).

SAD can be generalized or nongeneralized, depending on the breadth of social and performance situations feared. Generalized SAD is anxiety precipitated by most social and performance situations, and nongeneralized SAD is limited to a restricted number of social or performance situations (for example, public speaking) (1). Patients with SAD rarely see a physician for symptoms related to social anxiety; more often, they seek help for comorbid substance abuse, depression, or another anxiety disorder, all of which are common in these patients (16,260). Table 5.2 sets out interview questions that may help in screening for SAD in patients presenting with anxiety.

Assessing Response to Therapy

Response to therapy can be assessed with standardized tools appropriate for SAD, such as the Liebowitz Social Anxiety Scale (LSAS) (273). The LSAS rates 24 potentially anxiety-producing situations for severity of fear and anxiety and frequency of avoidance. An LSAS score of 80 to 120 indicates severe illness, 60 to 80 indicates moderate illness, and 40 to 60 indicates mild illness. A proposed cut-off score for symptomatic remission is less than 30, as supported by data suggesting that scores of healthy people and those with SAD separated with good sensitivity and specificity at 30 (274). This rating scale can be administered by a clinician or used as a self-report measure (275,276). Another useful self-rating scale is the Social Phobia Inventory, which has a series of 17 questions, each scored from 0 to 4. Possible total scores range from 0 to 68, with a score of 19 or more typical of diagnosed SAD (277). Reviews of these and other empirically supported scales for measuring social anxiety may be found elsewhere (see Orsillo, 278; and McCabe and Antony, 279).

The use of validated rating scales in clinical practice may help to assess response to therapy. In addition, patients and physicians should set individualized treatment goals tailored to each

Table 5.1 DSM-IV-TR diagnosis of SAD (social phobia)

- Marked and persistent fear of social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others
  - Fear of embarrassment or humiliation
- Exposure to feared social or performance situation that provokes anxiety (for example, situational panic attack)
- Recognition that the fear is excessive or unreasonable
- Avoidance of feared situation or endurance with distress
- Avoidance or fear cause significant distress or impaired functioning
- Fear or avoidance are not due to another medical or mental disorder
- Specify "generalized" if the fears include most social and performance situations

Adapted from DSM-IV-TR (1)

Table 5.2 Interview questions to screen for SAD

- In general, are you overly anxious or concerned about embarrassing or humiliating yourself while doing things in front of people or interacting with others?

or

- Mini Social Phobia Inventory questions (272)
  - Consider social anxiety disorder in patients who appear reticent or shy and in all depressed or alcohol-dependent patients; ask 3 screening questions:
    1. Are you uncomfortable or embarrassed at being the centre of attention?
    2. Do you find it hard to interact with people?
    3. Do you blush and tremble when asked to do things in public, like speak, eat, or sign a cheque?

Adapted from DSM-IV-TR (1)

patient's fears and anxieties (for example, being able to enter a feared or avoided social or performance situation).

Psychological Treatment

Approach to Psychological Management

CBT has been associated with significant improvements in patients with SAD (52,280–287). One study showed that CBT is more effective for patients treated individually than in a group setting, possibly because the intervention may be more tailored to the individual's problem areas (284). However, at least 3 metaanalytic studies have failed to find an advantage for either individual or group treatment over the other (52,288,289). There is good evidence to support the effectiveness of exposure therapy alone (290,291), whereas evidence is mixed about the advantages of combining cognitive and behavioural elements, relative to exposure alone (292). In clinical practice and in many research protocols, cognitive and exposure aspects of treatment are combined.

Components of CBT for SAD include education, exposure, and cognitive restructuring, and some evidence-based protocols also include social skills training or relaxation procedures (Table 5.3) (52,293).

Combined Psychological and Pharmacologic Treatment

Although results vary, CBT and pharmacotherapy appear to have similar efficacy for the acute treatment of SAD (64, 281,283,285–287). There is controversy over whether it is helpful to use these agents in combination routinely, and there are few well-designed studies to answer this question.

A study comparing CBT, fluoxetine, combined CBT and fluoxetine, and placebo found similar results with medication and psychological treatment, but no additional benefits were

Table 5.3 Common components of CBT for SAD

Education	• Educates about the disorder and its treatment • Recommends self-help materials (see Table 5.4)
Exposure	• Offers imaginal exposure to situations that are difficult to practise regularly in real life • Offers in vivo (real life) exposure to situations that provoke social anxiety during treatment sessions and homework • Provides exposure role-play simulations (for example, simulated conversations or interviews) • Reduces safety behaviours in social situations
Cognitive restructuring	• Aims to reduce negative beliefs about self and others • Works to reduce the excessive self-focus that is characteristic of social anxiety disorder • Examines and changes perfectionist attitudes
Social skills training	• Deals with any areas of weak social skills, such as eye contact or conversation skills • Addresses any interpersonal problems, including lack of social contacts and friendships, improving social life, assertiveness, managing conflict, and dealing with romantic relationships or problematic relationships
Emotion-regulation approaches	• Offer relaxation approaches, acceptance of symptoms and anxiety

Table 5.4 Useful self-help books

- Antony MM. *10 simple solutions to shyness: how to overcome shyness, social anxiety, & fear of public speaking*. Oakland (CA): New Harbinger Publications; 2004.
- Antony MM, Swinson RP. *The shyness & social anxiety workbook: proven techniques for overcoming your fears.* Oakland (CA): New Harbinger Publications; 2000.
- Hope DA, Heimberg RG, Juster HA, Turk CL. *Managing social anxiety: a cognitive-behavioural therapy approach client workbook (treatments that work).* New York (NY): Oxford University Press; 2000.
- Stein MB, Walker JR. *Triumph over shyness: Conquering shyness & social anxiety*. New York (NY): McGraw-Hill; 2001.

seen with the combination (64). Depressive symptoms at baseline were related to a higher dropout rate and lower treatment response rates across all treatment groups (294). As in most other clinical trials involving pharmacotherapy for anxiety disorders, patients with major depression were not included in the study. In a trial evaluating CBT with or without medication, compared with placebo, fluoxetine treatment did not add to the benefits of CBT (281).

In general, the treatment gains seen with CBT appear to be maintained during 6 to 12 months of follow-up after the completion of treatment; however, these results are based on small sample sizes (52,281,284,290,292). It has consistently been found that, after treatment discontinuation, gains achieved with CBT persist longer than do gains achieved with pharmacotherapy (290,295). There is currently little research available on SAD to indicate whether adding CBT to pharmacologic treatment reduces the relapse rate when pharmacotherapy is discontinued, and this area warrants further study. This approach has been found to be helpful in some other anxiety disorders (62).

Pharmacologic Treatment

Approach to Pharmacologic Management

The management of patients with SAD should follow the principles discussed in Section 2 and mapped in Figure 2.1. Pharmacotherapeutic interventions that have demonstrated efficacy in treating SAD include SSRIs, SNRIs, MAOIs, RIMAs, anticonvulsants, and benzodiazepines. These treatments have been evaluated according to the criteria for strength of evidence (Tables 1.1 and 1.2) for their use, and these are summarized in Tables 5.5 and 5.6.

Therapy for patients with generalized SAD should be initiated with a first-line agent: escitalopram, fluvoxamine immediate release (IR) or controlled release (CR), paroxetine IR or CR, sertraline, or venlafaxine XR (Table 5.6). If response to therapy

Table 5.5 Strength of evidence of pharmacotherapy for SAD

Agent	Level of evidence
Antidepressants	
SSRIs (52,304)	1
Escitalopram (305,306)	1
Fluvoxamine IR (307,308)	1
Fluvoxamine CR (309,310)	1
Paroxetine IR (311–317)	1
Paroxetine CR (318)	2
Sertraline (319–323)	1
Citalopram (324,325)	2
Fluoxetine (64,281,326)	+1 to –1[a]
TCAs	
Imipramine (327,328)	–2
Clomipramine (329,330)	3
MAOI and (or) RIMA	
Phenelzine (285,286,296,331)	1
Moclobemide (299,331–334)	+1 to –1[a]
Other antidepressants	
Venlafaxine XR (312,314,335,336)	1
Bupropion (337)	3
Mirtazapine (338)	3
Other therapies	
Anxiolytics	
Benzodiazepines	
Alprazolam (286)	2
Bromazepam (339)	2
Clonazepam (52,283,340,341)	1
Adjunctive clonazepam (303)	–2
Azapirones	
Buspirone (287,342)	–1
Adjunctive buspirone (343)	3
Anticonvulsants	
Gabapentin (344)	2
Pregabalin (345)	2
Divalproex (346)	+3 to –3[a]
Topiramate (347)	3
Levetiracetam (348,349)	–2
Adjunctive tiagabine (350,351)	3
Antipsychotics	
Olanzapine (352)	2
Quetiapine (217,353)	3
Adjunctive risperidone (354)	3
Adjunctive aripiprazole (355)	3
Other agents	
Selegiline (356)	3
Atenolol (296,357)	–1
Propranolol (297)	–2
St John's wort (358)	–2
Pergolide (359)	–3
Adjunctive pindolol (360)	–2

[a]Conflicting data

with one of the first-line agents is inadequate, dosing should be optimized and compliance assessed before switching to another agent is considered. In patients who have an inadequate response to optimal dosages of a first-line agent or in whom the agent is not tolerated, therapy should be switched to another first-line agent.

In general, 2 different first-line agents should be tried before considering a second-line medication. Second-line choices include clonazepam, alprazolam, bromazepam, gabapentin, pregabalin, citalopram, and phenelzine. While benzodiazepines are a second-line treatment, they may be used at any time if there is an acute and severe exacerbation of agitation or anxiety in individuals with SAD who do not have comorbid alcohol and substance abuse. However, their use should be short-term, according to the principles described in the Section 2.

Few studies have examined the efficacy of psychotropic agents in nongeneralized SAD, as most published studies have been conducted predominantly in patients with generalized SAD. In practice, beta blockers (primarily propranolol and atenolol) have been used extensively for performance anxiety in nonclinical samples. In the 2 clinical trials (296,297) in which they were evaluated, the response was no better than that for placebo, although one study included only a small sample of patients with nongeneralized SAD (296).

In a post hoc analysis of an RCT, paroxetine was found to be equally effective in both subtypes (298). In another study, moclobemide was found to be equally effective in all subtypes (299). First-line pharmacologic treatment of the nongeneralized subtype should include either an SSRI or SNRI and a beta blocker (given their long history of successful use in nonclinical populations such as musicians and stage performers). Second-line therapy would include moclobemide. These recommendations are based on expert opinion; to date, there are no prospective studies to guide clinicians. Data support the use of CBT as a first-line treatment for this subtype (300–302).

Table 5.6 Recommendations for pharmacotherapy for generalized SAD

First-line	Escitalopram, fluvoxamine IR or CR, paroxetine IR or CR, sertraline, venlafaxine XR
Second-line	Clonazepam, alprazolam, bromazepam, gabapentin, pregabalin, citalopram, phenelzine
Third-line	Fluoxetine, bupropion, mirtazapine, moclobemide, divalproex, topiramate, levetiracetam, olanzapine, quetiapine, selegiline, clomipramine Adjunctive: risperidone, aripiprazole, tiagabine
Not recommended	Atenolol, propranolol, buspirone, imipramine, pergolide, St John's wort Adjunctive: pindolol, clonazepam

Treatment Nonresponse

Treatment-refractory 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 where appropriate. Fluoxetine, bupropion, mirtazapine, moclobemide, divalproex, topiramate, levetiracetam, olanzapine, quetiapine, selegiline, and clomipramine are third-line options that may be considered for use as adjunctive therapy or as alternative monotherapy for the treatment of SAD.

Although the combination of a benzodiazepine and an SSRI or SNRI is widely used in clinical practice, the available literature does not support it (303). Further investigations of this intervention are currently underway. Clinicians should use benzodiazepines with caution in patients with SAD because about one-quarter of these individuals suffer from comorbid substance abuse (12,260).

First-Line Agents

SSRIs. Two metaanalyses found that SSRI treatment, primarily with paroxetine, sertraline, and fluvoxamine, was effective in reducing total levels of social anxiety and improving overall clinical condition (Level 1) (52,304). The odds of responding were 3 times higher with SSRIs than with placebo (304). Escitalopram was significantly more effective than was placebo in 2 RCTs (Level 1) (305,306), with significantly more responders (54%, compared with 39% for placebo) (305). Some data suggest that escitalopram 20 mg was significantly superior to paroxetine 20 mg at 24 weeks (306); however, the dose equivalent of escitalopram was higher than the dose of paroxetine. Escitalopram also significantly reduced disability (305,306).

Fluvoxamine has demonstrated response rates ranging from 43% to 46 %, compared with 7% to 22% seen with placebo, in the treatment of SAD (Level 1) (307,308). Improvements in psychosocial disability are also seen (308). A CR formulation of fluvoxamine has also demonstrated efficacy for the treatment of SAD (309,310).

Paroxetine has significant efficacy in the treatment of SAD (311–317), demonstrating response rates ranging from 55% to 66%, compared with 24% to 32% for placebo (Level 1) (313,317). Paroxetine has demonstrated efficacy comparable to that of venlafaxine XR, with response rates ranging from 63% to 66%, compared with 59% to 69% for venlafaxine XR (312,314). A CR formulation of paroxetine has also demonstrated efficacy for the treatment of SAD (318).

In RCTs, sertraline-treated patients were significantly more improved than were patients treated with placebo (Level 1) (319–321), with one study reporting a response rate of 47% for sertraline, compared with 3% for placebo (321). In a longer, 20-week study, response rates for sertraline and placebo were 53% and 29%, respectively (322).

SNRIs. Venlafaxine XR has demonstrated efficacy for generalized SAD in 4 large, 12-week RCTs (Level 1) (312,314, 335,336), 2 of which included paroxetine (312,314). Response rates were significantly higher with venlafaxine XR (44% to 69%) and paroxetine (58% to 66%), compared with placebo (30% to 36%) (312,314,335,336).

Second-Line Agents

Citalopram. In an RCT, citalopram was significantly more effective than placebo (response rates were 50% and 8.3%, respectively) and as effective as a neurokinin-1 antagonist (41.7% response rate) (Level 2) (325). In a randomized single-blind study, response to citalopram was similar to that seen with moclobemide (324).

Benzodiazepines. In RCTs and a metaanalysis, the efficacy of the benzodiazepine clonazepam was superior to that of placebo and comparable to that of SSRIs or CBT (Level 1) (52,283,340,341).

Alprazolam (286) and bromazepam (339) have also demonstrated efficacy for the treatment of SAD (Level 2). These agents are recommended as second-line options because of their potential difficulties. These include anterograde amnesia and the risks of withdrawal, tolerance, and addiction, as well as their lack of efficacy in the more common comorbidities of MDD and OCD. They are contraindicated in patients with comorbid substance abuse.

Anticonvulsants. In RCTs, gabapentin and pregabalin, compared with placebo, have demonstrated efficacy in the treatment of SAD (Level 2) (344,345). These agents are recommended as second-line choices until the results can be confirmed in additional trials.

MAOIs. Although the efficacy of phenelzine has been established in multiple RCTs (Level 1) (285,286,296,331), these agents are a second-line option for the treatment of SAD because dietary restrictions, drug interactions, and adverse events limit their use.

Third-Line Agents

Fluoxetine. Results with fluoxetine have been mixed (64, 281,326). A small trial showed no benefit with fluoxetine over placebo (326). However, a larger RCT found that fluoxetine was as effective as CBT and more effective than placebo, with response rates of about 50% for active treatment, compared with 30% for placebo (Level 2) (64). There was no additional benefit when fluoxetine was added to CBT. Similarly, fluoxetine treatment did not appear to add to the benefits of self-exposure and was equal to the efficacy of placebo added to self-exposure (281).

NaSSAs. Preliminary evidence suggests that mirtazapine may be effective in the treatment of SAD (Level 3) (338).

Anticonvulsants. Preliminary open-label studies have demonstrated some efficacy with divalproex (Level 3, one positive and one negative) (346) and topiramate (Level 3) (347). Levetiracetam demonstrated efficacy in one open trial but showed no benefit on the primary outcome measure in a small, controlled trial; however, secondary outcomes revealed a good effect size of 0.5 on the LSAS with levetiracetam (Level 3) (348, 349). Therefore, levetiracetam may have a benefit as a third-line agent.

RIMAs. Results of controlled trials with moclobemide have been equivocal; some have demonstrated response rates for moclobemide that are significantly higher than those seen with placebo (Level 1) (299,331,332), whereas others have not (333, 334). However, on the basis of positive results of 2 large RCTs (299,332), moclobemide may be a third-line choice.

Atypical antipsychotics. Olanzapine was effective in a small RCT (Level 2) (352), and quetiapine has demonstrated efficacy in open-label trials (Level 3) (217,353). Open-label studies have demonstrated benefits with adjunctive risperidone (354) and aripiprazole (355) in patients with refractory anxiety disorders (Level 3).

Other Treatments. Bupropion (Level 3) (337), clomipramine (Level 3) (329,330), selegiline (Level 3) (356), adjunctive tiagabine (350,351), and adjunctive buspirone (Level 3) (343) have demonstrated efficacy in small, open-label trials; however, more data are needed on these agents.

Not Recommended

Atenolol (Level 1, negative) (296,357), propranolol (Level 2, negative) (297), imipramine (Level 2, negative) (327), buspirone (Level 1, negative) (287,342), pergolide (Level 3, negative) (359), St John's wort (Level 2, negative) (358), adjunctive pindolol (Level 2, negative) (360), and adjunctive clonazepam (Level 2, negative) (303) have failed to demonstrate efficacy in generalized SAD and are not recommended.

Dosing and Duration

Dosage for SSRIs is similar to the standard dosages used for depression (361). An initial response is usually seen after 6 to 8 weeks of treatment but may take 12 weeks or more. It is reasonable to switch medications if no benefit is seen during a 10- to 12-week initial trial. Dosage should be optimized to achieve maximal benefit; improvement may continue to accrue over months. Pharmacotherapy should likely be continued for 12 to 24 months.

Long-Term Management

Many patients with SAD may require long-term therapy; within 6 months of discontinuing pharmacotherapy, about 35% to 40% of patients will relapse (362,363). In one study, 88% of responders who completed 2 years of pharmacotherapy deteriorated after discontinuing therapy (364). There is no way to predict which patients will do well when medication is discontinued or which patients will require long-term treatment (361). The benefits of CBT are generally maintained during 6 to 12 months of follow-up (52,281,284,292) and are more enduring than those of pharmacotherapy after treatment discontinuation (290,295).

Long-term pharmacotherapy for SAD results in continued improvement and decreased relapse rates. Paroxetine (Level 1) (362,365,366), sertraline (Level 1) (363,367), escitalopram (Level 2) (306), fluvoxamine CR (Level 2) (368), and venlafaxine XR (Level 2) (369) have been associated with continued improvements over 5 to 6 months. Open follow-up of patients treated with moclobemide showed that benefits were maintained with ongoing therapy, and discontinuation of medication, even after 2 years of therapy, was associated with deterioration in most patients (Level 3) (299,364).

Paroxetine (362,365), sertraline (363), and escitalopram (370) have demonstrated significant reductions in relapse rates over 6 months in placebo-controlled discontinuation trials. Relapse

rates were 4% to 14% with ongoing SSRI treatment, compared with 36% to 39% for placebo (362,363).

These data suggest that, if a patient responds acutely to a medication, its continued use likely will effectively prevent relapse; long-term treatment can result in continued improvement.

Summary

SAD is one of the most common anxiety disorders and is associated with significant distress or disability. CBT and pharmacotherapy should be considered as first-line options for the treatment of SAD. Escitalopram, fluvoxamine, paroxetine, sertraline, and venlafaxine XR are first-line pharmacotherapeutic choices. Antidepressants may also have beneficial effects in those who suffer from a comorbid condition that is also responsive to antidepressants. However, the relapse rate is substantial when antidepressants are discontinued, and CBT may offer long-term advantages in this respect. Pharmacotherapy should likely be continued for 12 to 24 months, with many patients requiring ongoing, long-term therapy to achieve full benefits and prevent relapse.

6. Obsessive–Compulsive Disorder

Epidemiology

The estimated 1-year prevalence of OCD is 0.7% to 2.1% (2,371–373), with an estimated lifetime prevalence of 1.6% (2). A Canadian survey found a lifetime prevalence of 3.0% (13), although a more recent study suggests that this may be an overestimate (374). The median age of onset is about 19 years (range 14 to 30 years), although OCD also occurs in childhood (2). In women, OCD is not as prevalent as are other anxiety disorders; only about 60% of adults with OCD are female (15). Men with OCD are more likely to be chronically unemployed and to be receiving financial assistance, compared with men without a disorder (4). About 56% to 83% of patients with OCD will have at least one other mental disorder (4). OCD has also been associated with significant burden on the family members of those suffering from this illness (375).

Diagnosis

OCD is defined by the presence of obsessions (recurrent and intrusive thoughts, images, or urges that cause marked anxiety) or compulsions (repetitive behaviours or mental acts performed to reduce the anxiety generated by the obsessions) (Table 6.1) (1,4,376). These recurrent obsessions and compulsions cause impairment in terms of distress, the length of time the symptoms are present each day, or interference with functioning. The individual feels compelled to continue, despite an awareness that the thoughts or behaviours may be excessive or inappropriate, and feels distress if he or she cannot carry them out or if he or she stops them. This is in contrast to addictive behaviours and impulse control disorders that often produce pleasure or gratification (1). Concerns involving contamination, symmetry and exactness, safety, sexual impulses, aggressive impulses, and somatic and religious preoccupations are the most common obsessions, whereas checking, washing, repeating, ordering, counting, hoarding, and touching are common compulsions (4, 376,377). Table 6.2 lists interview questions that may help in identifying obsessions or compulsions in patients presenting with anxiety.

Assessing Response to Therapy

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) comprehensively measures the overall severity of obsessions and compulsions and is the most commonly used scale to assess OCD (378). The Y-BOCS, a clinician-rated scale in which 10 items are scored from 0 (nonexistent) to 4 (extreme), provides a total score that reflects the entire syndrome (a self-report version is also available). A score of 32 to 40 indicates extremely severe symptoms, 24 to 31 indicates severe symptoms, 16 to 23 indicates moderate symptoms, and 8 to 5 indicates mild symptoms. Response in clinical trials has generally been defined as a $\geq 25\%$ reduction on the Y-BOCS or a score of 1 or 2 (very much or much improved) on the CGI Improvement scale. Remission in OCD should be defined as no longer meeting the diagnostic criteria for the disorder, full functionality, and no or minimal anxiety and depressive symptoms (117); this has generally been interpreted as a Y-BOCS score of 8 or less.

Other empirically supported scales for measuring OCD symptomatology and severity include the Obsessive-Compulsive Inventory (379), the Clark-Beck Obsessive-Compulsive Inventory (380), the Vancouver Obsessive Compulsive Inventory (381), and the Padua Inventory–Washington State University Revision (382). Several studies support the reliability and validity of these as well as other instruments (for reviews see Antony, 383; and Taylor and others, 384).

Psychological Treatment

Approach to Psychological Management

OCD is a very disturbing condition that is often handled by the patient as a secret problem, not to be revealed to others. Traditional approaches to psychological treatment (for example, insight-oriented psychotherapies) have had limited impact on the symptoms of OCD. In 1966, Meyer described an approach to OCD called exposure with response prevention (ERP) (385). This approach was widely adopted by behaviour therapists and achieved positive results in numerous treatment-outcome studies (53,386). Later, researchers described cognitive processes in OCD and suggested that cognitive approaches to intervention

Table 6.1 DSM-IV diagnosis of OCD

Either obsessions or compulsions:

- Obsessions as defined by the following:
  - Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress
  - Not simply excessive worries about real-life problems
  - The person attempts to ignore or suppress the obsessions, or to neutralize them with other thoughts or actions
  - The obsessions are recognized as a product of his or her own mind
- Compulsions as defined by the following:
  - Repetitive behaviours (for example, hand washing, ordering, checking) or mental acts (for example, praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rigid rules
  - Compulsions are aimed at reducing distress or preventing some dreaded event; however, these compulsions either are not connected in a realistic way with what they are designed to neutralize or are clearly excessive
- At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable
- The obsessions or compulsions cause marked distress, are time consuming (take > 1 hour daily), or significantly interfere with the person's normal routine, or occupational, academic, or social functioning
- The obsessions or compulsions are not due to substance abuse, or another medical or mental disorder

Table 6.2 Interview questions that might suggest the presence of obsessions or compulsions

Obsessions

- Do you experience disturbing thoughts, images, or urges that keep coming back to you and that you have trouble putting out of your head?
  - For example, being contaminated by something, something terrible happening to you or someone you care about, or of doing something terrible?

Compulsions

- Do you ever have to perform a behaviour or repeat some action that doesn't make sense to you or that you don't want to do?
  - For example, washing or cleaning excessively, checking things over and over, counting things repeatedly?

could be helpful (387). Typical elements included in CBT for OCD are shown in Table 6.3.

As with the application of CBT to other anxiety disorders, there have been differences of opinion about the relative importance of the cognitive and behavioural elements in treating OCD. Protocols such as Foa's intensive ERP approach (63) have emphasized the behavioural elements of treatment that have been the most widely evaluated. Other approaches have emphasized cognitive components more strongly (387–389). Metaanalyses have shown that interventions with an emphasis on ERP produce results equivalent to interventions that also include cognitive elements (386) or that ERP produces stronger results than interventions that emphasize cognitive elements (53). ERP has been shown to produce cognitive change (388). However, a treatment using a cognitive intervention that includes no direct exposure and specifically designed to address fear of contamination with infectious substances ("danger ideation reduction therapy") was demonstrated to have better results than ERP (390,391). Cognitive interventions may be important when patients do not have overt compulsions, which can make ERP more difficult.

An important practical question concerns the intensity and pacing of treatment. The intensive ERP program described by Foa's group involves fifteen 2-hour sessions scheduled 5 days per week over 3 weeks (63,392). This intense approach was compared with a similar treatment involving the same amount of therapy time but administered as twice-weekly 2-hour sessions (a more practical approach for many patients and therapists) (393). Results showed that, while there was a trend for intensive treatment to yield greater symptom reduction at the end of the treatment, the interventions were equally effective at the end of follow-up.

Table 6.3 Common components of CBT for OCD

Education	• Educates about OCD, including typical obsessions, compulsions, and coping strategies • Describes the negative impact of some of the coping strategies • Explains the CBT procedures used to treat OCD • Recommends relevant self-help readings or manuals (Table 6.4)
Exposure	• Offers in vivo (real life) exposure to situations that provoke anxiety and compulsive behaviour (for example, touching contaminated objects, driving past a cemetery when there are concerns about death) • Offers imaginal exposure to feared obsessive thoughts (for example, especially concerning religious, aggressive, or sexual content) • Offers imaginal exposure to catastrophic consequences of feared thoughts and actions (for example, exposure to thoughts about becoming gravely ill after touching a garbage can) • Teaches response prevention, which is used at the same time as exposure so that exposure takes place without engaging in rituals or other safety behaviours • Teaches that exposure involves learning to tolerate, rather than avoid, anxiety experiences

Response prevention	• Gradually reduces and eliminates:
	  • Compulsive behaviour (for example, hand washing) including mental compulsions or rituals (for example, saying a prayer after having a harmful thought)
	  • Reassurance seeking (for example, asking a family member if a task has been completed correctly)
	  • Excessive safety behaviour (for example, wearing gloves or other protective clothing to avoid coming in contact with contaminated objects)

Cognitive interventions	• Reappraisal of beliefs concerning the danger involved in situations that provoke obsessions and compulsions. This involves estimation of likelihood of a negative outcome occurring and evaluation of the harm caused by these events • Reappraisal of beliefs concerning danger associated with the obsessions themselves • Reducing inflated sense of responsibility about creating harm • Addressing belief that the occurrence of a thought makes it more likely that the feared outcome will happen (for example, “If I think about harming someone, it is likely that I will harm them”) • Dealing with problems of intolerance of uncertainty and perfectionism (for example, “I must make absolutely sure that I never leave the door unlocked”)
Family involvement	• Informing family members about the problem and enlisting their cooperation with treatment • Family members are taught to stop their involvement in providing reassurance, safety behaviours (for example, excessive cleaning and checking), and assisting with compulsive behaviours
Problem solving	• OCD may cause severe disability; when there is improvement, there is often a need to rebuild work life, social interactions, and family relationships
Relapse prevention	• Preparing for periods of increased anxiety when exposed to threatening experiences that relate to the theme of the OCD (for example, exposure to a new illness or source of contamination)

Table 6.4 Useful self-help books

- Foa EB, Wilson R. *Stop obsessing: how to overcome your obsessions and compulsions*. Revised. New York (NY): Bantam Books; 2001.
- Grayson J. *Freedom from obsessive-compulsive disorder: a personalized recovery program for living with uncertainty*. New York (NY): Berkeley Publishing Group; 2004.
- Hyman BM, Pedrick C. *The OCD workbook: your guide to breaking free from obsessive-compulsive disorder.* 2nd ed. *Oakland (CA): New Harbinger Publications; 2005.*
- Purdon C, Clark DA. *Overcoming obsessive thoughts: how to gain control of your OCD.* Oakland (CA): New Harbinger Publications; 2005.

Table 6.5 Strength of evidence of pharmacotherapy for OCD

Agent	Level of evidence
Antidepressants	
SSRIs	
Fluoxetine (396–400)	1
Fluvoxamine (397,399–402)	1
Paroxetine (403–405)	1
Sertraline (396,397,399,400,406,407)	1
Citalopram (408,409)	2
Escitalopram	4
MAOIs	
Phenelzine (420,421)	3[a]
Tranylcypromine (422)	3
TCAs	
Clomipramine (63,397,399–402,410,411)	1
IV clomipramine (412–414)	2
Desipramine (406,415)	–2
Other antidepressants	
Bupropion (416)	–3
Venlafaxine XR (404,417,418)	2
Mirtazapine (419)	2
Adjunctive mirtazapine (409)	3
Other therapies	
Anxiolytics	
Benzodiazepines	
Clonazepam (423)	–2
Adjunctive clonazepam (424)	–2
Azapirones	
Adjunctive buspirone (425,426)	–2
Antipsychotics	
Adjunctive risperidone (436–439)	1
Adjunctive olanzapine (440,441)	2[a]
Adjunctive quetiapine (442–444)	2[a]
Adjunctive haloperidol (445)	2
Anticonvulsants	
Adjunctive topiramate (446,447)	3
Adjunctive gabapentin (448)	4
Opioids	
Tramadol (427,428)	4
Naltrexone (429)	–3
Adjunctive morphine (430)	–2
Other agents	
Adjunctive riluzole (431)	3
St John's wort (432)	3
Adjunctive pindolol	2[a]
Clonidine (433)	–2
Adjunctive lithium (434,435)	–2

[a]Conflicting data

CBT for OCD may be delivered individually or in a group format (389). A metaanalysis suggested that there was more improvement among patients who received individual CBT—possibly because this allowed greater individualization of the treatment (53).

Combined Psychological and Pharmacologic Treatment

There is strong evidence for the effectiveness of either CBT or pharmacotherapy with serotonergic agents (for example, SSRIs and clomipramine) when used alone; however, there is considerable controversy over whether it is helpful to routinely use these agents in combination, and there are few well-designed studies to answer this question. A review of the evidence as of 2002 concluded that there was no good evidence that the addition of medication enhanced or hindered progress with CBT (62). Conversely, the authors noted that combined treatment may have an advantage when less intensive forms of CBT are used. In one of the most comprehensive studies to date, Foa and others found response rates of 62% for ERP, 42% for clomipramine, 70% for ERP plus clomipramine, and 8% for placebo (63). During follow-up of treatment responders at 12 weeks after treatment discontinuation, the relapse rate was significantly lower among responders to ERP with or without clomipramine (12%) than among responders to clomipramine (45%), and the time to relapse was significantly longer (65). These findings suggest that adding CBT to pharmacologic treatment of OCD may reduce the relapse rate if medication is discontinued.

Both CBT and antidepressant medication have also demonstrated benefits for the treatment of comorbid depressive and anxiety disorders that frequently accompany OCD. There are limited data exploring whether the addition of pharmacotherapy improves the outcome of CBT for OCD among patients with severe depression, but this question warrants further investigation (394).

Pharmacologic Treatment

Approach to Pharmacologic Management

The management of patients with OCD should follow the principles discussed in Section 2 and mapped in Figure 2.1. Antidepressants (including TCAs, SSRIs, and SNRIs), anxiolytics, atypical antipsychotics, and other agents, as well as combinations of medications, have been examined for their efficacy in the treatment of OCD. 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 6.5 and 6.6).

For patients with OCD, therapy should be initiated with a first-line SSRI such as fluoxetine, fluvoxamine, paroxetine, or sertraline (Level 1) (Table 6.6). 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 with an inadequate response to optimal

Table 6.6 Recommendations for pharmacotherapy for OCD

First-line	Fluvoxamine, fluoxetine, paroxetine, sertraline
Second-line	Clomipramine, venlafaxine XR, citalopram, mirtazapine, adjunctive risperidone
Third-line	IV clomipramine, escitalopram, phenelzine, tranylcypromine Adjunctive: mirtazapine, olanzapine, quetiapine, haloperidol, gabapentin, topiramate, tramadol, riluzole, St John's wort, pindolol
Not recommended	Clonazepam, desipramine, bupropion, clonidine, buspirone, lithium, naltrexone, adjunctive morphine

dosages of a first-line agent or in whom the agent is not tolerated, therapy should be switched to another first-line agent. However, OCD can be difficult to treat, and it is often important to preserve even small gains achieved with initial therapy. Therefore, augmentation with second- or third-line agents may be important early in treatment.

If a trial of 2 different first-line agents has not produced the expected benefit, then clomipramine should be considered. While there is good evidence for the effectiveness of clomipramine in OCD, safety and tolerability concerns make it a second-line choice. If first-line agents and clomipramine are inadequate, consider using other second-line medications such as mirtazapine, venlafaxine XR, or citalopram (an SSRI) or adjunctive therapy with risperidone or mirtazapine.

Treatment Nonresponse

Treatment-refractory 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. Intravenous clomipramine and tranylcypromine are third-line options. Escitalopram has not yet been studied in OCD but may also be useful. Olanzapine, quetiapine, haloperidol, gabapentin, topiramate, tramadol, riluzole, phenelzine, St John's wort, and pindolol have demonstrated some efficacy in early studies and may be considered as adjunctive therapy for the treatment of OCD (Table 6.5). St John's wort should not be combined with SSRIs (395).

First-Line Agents

SSRIs. There is good evidence from RCTs and metaanalyses to support the use of SSRIs in the treatment of OCD. These include fluoxetine (396–400), fluvoxamine (397,399–402), paroxetine (403–405), and sertraline (396,397,399,400,406,407) (all Level 1). Metaanalyses have estimated that response rates are generally between 40% and 60%, whereas placebo response rates are lower than 20% (397,399,400,410,411). In head-to-head trials, the efficacy of the SSRIs fluoxetine, fluvoxamine, paroxetine, and sertraline was similar to that of clomipramine, but tolerability was better (397,399–403, 407,449).

Sertraline was superior to fluoxetine at Week 12, with a higher response rate (50% and 25%, respectively); however, both agents were equivalent by week 24 (396). Paroxetine and venlafaxine XR were equally effective, with response rates of about 40% for both treatments (404).

Second-Line Agents

Clomipramine. Clomipramine has been well studied in the treatment of OCD (Level 1) (397,399,400,410,411). However, because of safety concerns (convulsions, cardiotoxicity, cognitive impairment, anticholinergic side effects, drug interactions, and lethality in overdose; 450), it should usually be reserved for use after 2 first-line SSRIs have been tried. In metaanalyses of placebo-controlled studies, clomipramine appeared to be more effective than were SSRIs; in one analysis, the net improvements in Y-BOCS score between active drug and placebo were a decrease of 8.19 for clomipramine, 4.84 for fluvoxamine, 1.61 for fluoxetine, and 2.47 for sertraline (400). However, head-to-head trials show no significant difference between clomipramine and the SSRIs, and the SSRIs were generally better tolerated (63,397,399–402,407,410,411). Metaanalysis data suggest that clomipramine is superior to placebo in reducing both obsessive and compulsive symptoms considered together, as well as obsessions and compulsions considered separately (397). Response rates may be lower in patients with depressive symptoms (451,452).

Although clomipramine is associated with more side effects, studies showed that, if started at a low dosage of 25 mg daily, dropout rates were comparable to rates seen with SSRIs (453).

The use of clomipramine in combination with an SSRI has not been well studied, but both of these medications are beneficial. Because SSRIs affect the absorption of clomipramine, if used in combination, blood levels of clomipramine may be increased and dosing should be adjusted accordingly. The risk of serotonergic syndrome is also increased with this

combination (450,454). In general, if clomipramine is combined with an SSRI, clomipramine blood levels should be monitored.

Adjunctive Risperidone. Risperidone has demonstrated some efficacy as adjunctive therapy for OCD in patients refractory to SSRI treatment (Level 1) (436–439). In RCTs, 40% to 50% of nonresponders to SSRIs who were treated with adjunctive risperidone responded, compared with 0% to 20% of patients treated with placebo (436,437,439). Adjunctive risperidone was superior to placebo in reducing OCD, depressive, and anxiety symptoms (436).

Venlafaxine XR. There is some evidence to support the use of venlafaxine XR for the treatment of OCD (Level 2) (404, 417,418). A large RCT found that venlafaxine XR was as effective as paroxetine, with responder rates of about 40% in both groups (404). A single-blind trial comparing venlafaxine XR and clomipramine found no significant difference between the treatments; response rates were higher with clomipramine (50%, compared with 36% for venlafaxine XR), and venlafaxine XR was better tolerated (417). In a small RCT, 38% of patients responded to venlafaxine XR, compared with 0% treated with placebo; however, about 30% of patients treated with venlafaxine XR had a worsening of their condition (418).

Mirtazapine. In a double-blind discontinuation study, responders to mirtazapine who continued on the drug continued to improve, whereas those switched to placebo deteriorated (Level 2) (419).

Citalopram. In an RCT, response rates were 52% to 65% with citalopram, compared with 37% with placebo (Level 2) (408). A comparison of citalopram and the combination of citalopram plus mirtazapine found that response rates were higher with the combination at Week 4; however, there were no differences between groups by Week 8, and about 60% of patients in both groups responded by Week 12 (409).

Third-Line Agents

Adjunctive Atypical Antipsychotics. Results with adjunctive olanzapine have been inconsistent (Level 2) (440,441). In an RCT, 46% of patients responded to adjunctive olanzapine added to existing SSRI treatment, compared with 0% patients in the placebo group (440). However, another RCT reported no advantage to the addition of olanzapine in patients who were partial or nonresponders to fluoxetine (441). This may be due to the lower dosages used in the latter study (5 to 10 mg daily) (440), compared with the dosages used in the positive study (up to 20 mg) (441). Results with adjunctive quetiapine have also been inconsistent. RCTs have been very small, and results were positive in 1 trial (Level 2) (444) but negative in 2 others (442,443). There is some evidence to suggest that quetiapine may be useful for some patients, but more data are needed.

Intravenous Clomipramine. Intravenous (IV) clomipramine was found to be more effective than placebo, with 43% of patients responding compared with 0% treated with placebo (Level 2) (412). Studies evaluating IV compared with oral pulse loading have demonstrated contradictory findings; in one study IV pulse loading provided faster improvement (413), whereas in another, it did not (414). It was suggested that pulse loading itself, rather than IV or oral format, may induce more rapid and greater improvement than expected in OCD (414).

Adjunctive Mirtazapine. In a single-blind RCT, adjunctive mirtazapine was shown to hasten the onset of response when added to citalopram therapy, compared with citalopram alone, but there was no advantage of the combination over time (Level 3) (409).

Escitalopram. Data are not yet available on escitalopram for the treatment of OCD; however, the efficacy of its parent compound, citalopram, in OCD (408) and the efficacy of escitalopram in GAD (455,456), panic disorder (164), and SAD (305,306), as well as anecdotal experience in OCD, suggest that escitalopram may be effective for some patients (Level 4).

Adjunctive Haloperidol. Adjunctive haloperidol was found to be significantly better than placebo in reducing the severity of OCD in patients refractory to fluvoxamine (Level 2) (445). However, haloperidol is associated with extrapyramidal syndrome, tardive dyskinesia, and other side effects, and current clinical practice is to favour an atypical antipsychotic over a conventional antipsychotic if these agents are to be used.

Other Pharmacotherapies. Tranylcypromine (Level 3) (422), adjunctive riluzole (Level 3) (431), St John's wort (Level 3) (432), tramadol (427,428), adjunctive topiramate (Level 3) (446,447), and adjunctive gabapentin (Level 4) (448) have demonstrated some efficacy in open trials or case reports. Results with pindolol augmentation have been inconsistent; of 2 small RCTs, one was positive and the other was negative (Level 2) (457,458). Results with phenelzine have also been inconsistent. In one RCT, phenelzine was as effective as clomipramine (Level 3) (420). However, in a placebo-controlled trial, phenelzine was not significantly better than placebo in the overall group but was beneficial in a subgroup of patients with symmetry or other atypical obsessions (421). These treatments may be useful in refractory patients, although current data are inadequate to recommend their routine use.

Not Recommended

Clonazepam (Level 2, negative) (423,424), desipramine (Level 2, negative) (406,415), bupropion (Level 3, negative) (416), clonidine (Level 2, negative) (433), naltrexone (Level 3, negative) (429), buspirone (Level 3, negative) (425,426), and lithium (Level 2, negative) (434,435) have not demonstrated consistent efficacy and are not recommended in the treatment of OCD.

In a small trial, adjunctive morphine was effective in 1 patient who had failed 6 trials with SSRIs, 4 patients responded to lorazepam, and 0 patients responded to placebo (Level 2) (430). However, morphine is not a treatment of choice in light of the potential for abuse of this drug.

Dosing and Duration

It is important that patients receive adequate dosages (see Table 2.10), which at times may need to be higher than the usual recommended dosages, for an adequate duration before a therapeutic trial is deemed ineffective. Onset of efficacy of the antidepressants may be delayed for more than 6 weeks (376). Medication probably confers protection against relapse, as long as it is continued (450). Pharmacotherapy should probably be continued for a minimum of 6 months after acute treatment (74), with some guidelines recommending continuation of pharmacotherapy for 1 to 2 years (376,459). Discontinuation, if necessary, should be gradual to minimize discontinuation effects, and patients should be warned to look out for early signs of relapse; pharmacotherapy should be reinstated if needed (460). Lifelong medication may be necessary for many patients (450), particularly in the absence of psychological treatment.

Neurosurgical Therapy

When patients have shown no response to many trials of medication and an adequate course of CBT, neurosurgical approaches, including anterior cingulotomy, anterior capsulotomy, subcaudate tractotomy, and limbic leucotomy, as well as deep brain stimulation, may be useful. Early studies show that 40% to 60% of patients with refractory OCD may benefit from these treatments (Level 4) (454,461,462). Given the irreversible nature of neurosurgical procedures and the fact that such studies are unblinded, deep brain stimulation may prove to be a more prudent intervention in cases of treatment-refractory OCD. More data are needed before these procedures can be more widely recommended.

Long-Term Treatment

Few controlled studies have evaluated long-term pharmacotherapy for relapse prevention in patients with OCD, and most of the available maintenance data are from naturalistic follow-up studies.

Ongoing sertraline or fluoxetine therapy was associated with continued improvement over 6 months (396) to 2 years of treatment (463,464). Long-term clomipramine therapy demonstrated continued efficacy with more than one-half of patients no longer meeting full diagnostic status, compared with fewer than 5% of patients given placebo (465). Mirtazapine was associated with continued improvement from Weeks 12 to 20 of therapy, compared with a deterioration among patients switched to placebo (419).

Relapse-prevention studies in which responders to SSRI therapy are randomized to continued active treatment or placebo have demonstrated reductions in relapse rates with paroxetine, sertraline, and fluoxetine (405,466,467). Relapse rates were significantly lower with continued paroxetine treatment (38%), compared with placebo (59%) (405). Symptomatic relapse or exacerbation was significantly lower among patients who continued sertraline therapy, compared with those who were switched to placebo, and sertraline improved quality of life during the 18 months of follow-up (466). Relapse rates over 1 year were not significantly different among patients receiving fluoxetine overall, compared with placebo (21% and 32%, respectively), but were significantly lower among patients receiving fluoxetine 60 mg daily, compared with placebo (18% and 38%, respectively). Patients who continued with 20 or 40 mg daily had a relapse rate not significantly different from the placebo group (28.6% and 21.3%, respectively) (467).

Some evidence suggests that maintenance therapy may be effective at lower dosages, but medication should be reduced with caution to prevent relapses (464,468). Two-year open follow-up of patients who had previously responded to clomipramine, fluvoxamine, or fluoxetine found that continued therapy at full- or half-dosage was equally effective in reducing relapse rates, compared with discontinuation of therapy, with no differences between the active treatment groups (464). Similarly, in an RCT, gradual reduction of the dosage of fluvoxamine by as much as two-thirds (in previous responders) provided effective maintenance therapy without a worsening of OCD (468). Careful monitoring of patients is necessary as gradual dosage reduction is attempted.

Summary

OCD has a mean age of onset in the late teens and early 20s, although it may begin in childhood or later in life. A chronic condition, OCD is associated with a high prevalence of functional impairment and comorbid mental disorders. CBT and pharmacotherapy should be considered as first-line treatment options. Fluvoxamine, fluoxetine, paroxetine, sertraline, and clomipramine are first-line pharmacotherapeutic choices; however, SSRIs should usually be tried first because they are better tolerated and then followed by the addition of or switch to clomipramine. Only 40% to 60% of patients will respond to initial pharmacotherapy, and adding agents such as clomipramine or risperidone or switching to venlafaxine XR may be useful. CBT has demonstrated efficacy and may help maintain treatment gains after therapy is discontinued. When antidepressants are discontinued there is a substantial rate of relapse, and maintenance therapy for 1 to 2 years may be routinely required. Unfortunately, there are no data to indicate the length of pharmacotherapy that will reliably reduce relapse on discontinuation. Patients who do not do well with CBT may do well with pharmacotherapy and vice versa.

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.

8. Posttraumatic Stress Disorder

Epidemiology

PTSD has long been recognized as a potential consequence of combat exposure, and its significance in civilian populations is being increasingly recognized. In a community study in Canada, prevalence rates of PTSD were 2.4% (current and 1-month) and 9.2% (lifetime) (540). Traumatic exposure to events that frequently are sufficient to cause PTSD was reported by 75.7% of respondents. The National Comorbidity Survey in the United States reported rates of 3.5% (12-month) and 6.8% (lifetime) (2). As expected, the prevalence is much higher in areas where conflict has occurred, where it ranges from 16% to 37% (lifetime) (541). Onset is generally in the mid to late 20s (2), and prevalence is higher among women than men (542–544). The World Health Organization's Global Burden of Disease study predicted that exposure to traumatic events, such as motor vehicle accidents, war, and violence, will be the third, eighth, and twelfth leading causes of disability worldwide by the year 2020 (545), which suggests that the rate of PTSD will also increase (546). The risk of attempted suicide is increased sixfold among individuals with PTSD, compared with those not having any psychiatric disorder (547). Subthreshold PTSD is also a concern, with numerous subthreshold PTSD symptoms being associated with greater impairment, comorbidity, and suicidal ideation (25,543).

Differential Diagnosis

PTSD is characterized by intrusive reexperiencing of the event (reliving the memory), avoidance (attempts to escape recollections), and hyperarousal (difficulty concentrating or exaggerated startle response) (Table 8.1) (1). A DSM-IV-TR diagnosis requires that symptoms be temporally related to the stressor and must be present for more than 1 month (1). Symptom duration of less than 3 months is considered acute PTSD, and duration of 3 months or longer is considered chronic PTSD. Although symptoms usually begin within 3 months of exposure, a delayed onset is possible months or even years after the event has occurred. Table 8.2 lists interview questions that may help to screen for PTSD in patients presenting with anxiety.

Although PTSD is common after combat exposure, serious accidents represent a leading cause in the general population (548–550), with an estimated 9% of accident victims developing PTSD (542). Other potential PTSD patients include victims of physical attack, rape, sexual abuse, violent crimes, accidents, terrorist attacks, or natural disasters (542,549–551). In Canada, the most common forms of trauma resulting in PTSD include unexpected death of a loved one, sexual assault, and seeing someone badly injured or killed (540). Caregivers of trauma victims (552–554) and parents of children who die violent deaths (555,556) may also present with PTSD symptoms.

PTSD is frequently comorbid with other psychiatric disorders, including other anxiety disorders (SAD, OCD, and panic disorder), MDD, personality disorders, and substance abuse disorders, which may further complicate diagnosis and management (550,557,558). It is important to ask all patients with mental health symptoms about trauma, particularly women suffering from treatment-resistant depression (559) and those with general medical complaints, since patients with PTSD often present with somatic symptoms. Most individuals exposed to a traumatic event do not develop a psychiatric illness. In addition, PTSD is just one of the possible psychiatric outcomes of exposure to traumatic events; other outcomes include other anxiety disorders, depression, substance abuse disorders, and a range of other problems.

Assessing Response to Therapy

Response to therapy in PTSD may be assessed with standardized tools appropriate for PTSD, such as the Clinician Administered PTSD Scale (CAPS) or the Treatment Outcome PTSD Scale (TOP-8). The TOP-8 is shorter, is easier to use, and is highly correlated with the CAPS, which is more time-consuming and less practical for use in clinical practice. A TOP-8 score of 5 or less reflects no or minimal PTSD symptoms, a score of 7 equals mild symptoms, 15 indicates moderate symptoms, and 21 indicates severe symptoms. Remission in PTSD should be defined as no longer meeting the diagnostic criteria for the disorder, full

Table 8.1 DSM-IV-TR diagnosis of PTSD

- The person has been exposed to a traumatic event in which both of the following were present:
  - The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
  - The person's response involved intense fear, helplessness, or horror
- The traumatic event is reexperienced, including one (or more) of:
  - Recurrent and intrusive distressing memories, dreams or nightmares reliving the experiences (illusions, hallucinations, flashbacks), or physical or psychological distress when reminded of the trauma
- Persistent avoidance of stimuli or events associated with the trauma and numbing of general responsiveness, including 3 (or more) of the following:
  - Avoid thoughts, feelings, or conversations, avoid activities, places, or people, inability to recall aspect of the trauma, diminished interest or participation in activities, feeling of detachment or estrangement from others, restricted range of affect, sense of a foreshortened future
- Persistent symptoms of increased arousal including 2 (or more) of the following:
  - Difficulty falling or staying asleep, irritability, difficulty concentrating, hypervigilance, exaggerated startle response
- Duration of symptoms is more than 1 month
- Severity of symptoms must be sufficient to cause "clinically significant distress" or impaired functioning

Adapted from DSM-IV-TR (1)

Table 8.2 Interview questions to screen for PTSD in patients presenting with anxiety

Are you bothered by memories, thoughts, or images of a very upsetting event that happened to you or someone close to you in the past? For example:

- Being in a fire or serious accident?
- Being raped, assaulted, or abused?
- Seeing someone else badly hurt or killed?

functionality, and no or minimal anxiety and depression symptoms (117).

Prevention and Early Intervention

Given the high frequency of traumatic experiences and PTSD in the community, there has been great interest in developing pharmacologic and psychological strategies for prevention and early intervention (560). There has been considerable research on risk factors for PTSD, and social support at the time of the traumatic event seems particularly important (561). The most widely used psychological intervention involves a single session, individual or group, of critical incident stress debriefing after traumatic experiences (562). Unfortunately, reviews of the available research do not provide support for the position that this approach prevents or reduces the intensity of PTSD (563,564); in fact, there is some concern that it may interfere with the course of natural recovery, perhaps by developing unrealistic expectations concerning the experiences related to traumatic events (565). Conversely, early cognitive-behavioural interventions directed to individuals showing indications of acute stress disorder or high levels of distress after traumatic experiences show considerable promise. The interventions that have been evaluated include education about psychological effects of trauma, imaginal reliving of the event, cognitive restructuring, and reversal of avoidance behaviours (565,566). For example, a brief CBT program (5 or 6 sessions) for individuals with acute stress disorder following physical assault or a motor vehicle accident was significantly superior to supportive counselling on measures of PTSD symptoms, overall anxiety, and depression at posttreatment and follow-up when further accidents or traumatic events occurred (567–569). These differences were maintained 4 years after the completion of treatment (570). Researchers are very interested in what approaches may be taken at the community level after large-scale disasters, but to date, the research to guide interventions is limited (560). Clearly, a great deal of work remains to be done.

There are few data on the use of pharmacotherapy for the prevention of PTSD. In a cohort study and an RCT, the early use of benzodiazepines following trauma was not beneficial (571,572). In a cohort study and an RCT, by contrast, the beta blocker propranolol, administered immediately after trauma, was found to decrease the severity of PTSD symptoms and lessen the likelihood of developing subsequent PTSD (573,574).

Table 8.3 Common components of CBT for PTSD

Education	• Provides information about PTSD and its treatment • Considers recommending self-help book: Matsakis, A. *I can't get over it: a handbook for trauma survivors*. 2nd ed. Oakland (CA): New Harbinger Publications; 1996.
Exposure	• Helps patients to gradually confront feared situations, memories, emotions, and images associated with the traumatic experience until there is a significant reduction in distress • Imaginal exposure offers repeated review of the trauma based on memories of the experience and its aftermath, including the emotions accompanying the experience (either in imagination or by writing a trauma narrative) • In vivo exposure provides confrontations with avoided situations related to the event • Eliminates unrealistic safety behaviours
Cognitive approaches	• Identify dysfunctional thinking patterns associated with anxiety, depression, anger, and shame • Teach the patient to challenge irrational cognitions and replace them with functional, realistic beliefs • Reduce hypervigilance by refocusing attention
Emotion-regulation approaches	• Provide management skills to help cope with and reduce distress • Provide relaxation approaches such as muscle, breathing, or imagery relaxation • Refocus attention • Practise acceptance-based approaches to reduce avoidance of difficult emotions
Problem solving	• Practises overcoming any social withdrawal and negative impact on relationships • Addresses any excessive use of substances or other unhealthy coping approaches • Engages in positive activities and goals
Relapse prevention	• Practises preparation for trauma-related events that may occur in the future • Practises preparation for periods of increased distress related to reminders of the trauma

Psychological Treatment

Approach to Psychological Management

Compared with wait-list control groups, usual care, or supportive therapy, several CBT approaches have demonstrated efficacy in the management of PTSD (49). All the widely used protocols include education concerning PTSD and its treatment and exposure to cues related to the traumatic event (Table 8.3). The approaches differ in terms of the intensity of exposure, varying from gradually paced exposure using written accounts of traumatic events (575,576) to extensive exposure using vivid imagery and exposure to situations that resemble the trauma site (577,578). There is some controversy in the field concerning the importance of addressing cognitive aspects of PTSD (such as inappropriate guilt, low estimates of self-efficacy, or excessive estimations of danger in everyday situations). Some approaches emphasize these components (566,575,576,579,580), and there is some evidence that they add to the effectiveness of treatment (579).

The CBT approach has been used effectively in treating PTSD following sexual assault (575,576,578,581), civilian trauma (566,579), and military trauma (582). Military trauma may be more difficult to treat, possibly because of compensation issues and the relative frequency of comorbid disorders. In a metaanalysis of CBT studies, about 55% of those who started treatment and 65% of those who completed treatment no longer had symptoms meeting diagnostic criteria for PTSD at the end of the treatment period (583). With more stringent criteria for improvement with treatment (high end-state functioning in some evaluations), about 44% of intent-to-treat samples and 54% of completers were responders, compared with 10% in wait-list control groups.

Generally, follow-up after completion of treatment in studies has been limited to 6 to 12 months, and it appears that results are maintained over this time period (54,583). A metaanalysis of 10 studies with evaluations of 6 months or longer found that psychological treatments including exposure, CBT, and the combination were somewhat efficacious at follow-up, with 32% of patients considered improved, compared with their pretreatment status (583). Many researchers recommend planned follow-up contact to identify the return of any symptoms. CBT may have an

Table 8.4 Strength of evidence of pharmacotherapy for PTSD

Agent	Level of evidence
Antidepressants	
SSRIs	
Fluoxetine (591–593)	1
Paroxetine (594–596)	1
Sertraline (597–600)	1
Citalopram (600–602)	+3 to –3[a]
Fluvoxamine(603–607)	3
Escitalopram	4
MAOIs and RIMAs	
Phenelzine (610,611)	1
Moclobemide (618)	3
TCAs	
Amitriptyline (608,609)	1
Imipramine (610,611)	1
Desipramine (612)	–2
Other antidepressants	
Venlafaxine XR (613)	2
Mirtazapine (614–616)	2
Bupropion (617)	3
Other therapies	
Anxiolytics	
Benzodiazepines	
Alprazolam (619)	–2
Clonazepam (571,620,621)	–3
Azapirones	
Buspirone (622,623)	3
Atypical antipsychotics	
Adjunctive risperidone (637–640)	1
Adjunctive olanzapine (641)	2
Adjunctive quetiapine (642,643)	3
Olanzapine monotherapy (644–646)	–2
Anticonvulsants	
Lamotrigine (624)	2
Carbamazepine (625,626)	3
Valproate (627,628)	3
Adjunctive topiramate (629–631)	3
Adjunctive tiagabine (632–634)	4
Adjunctive gabapentin (635,636)	4
Other agents	
Adjunctive clonidine (647)	3
Fluphenazine (645)	3
Trazodone (648)	3
Naltrexone (649–652)	+3 to –3[a]
Prazosin (653–656)	3
Cyproheptadine (657)	–2

[a]Conflicting data

advantage during the long term, although very few data are available regarding return of symptoms following discontinuation of pharmacologic treatments. However, dropout rates in clinical trials have been high at up to 25% (575,579,584), similar to the rates typically reported in trials of pharmacologic treatments.

EMDR, a strategy that integrates elements of CBT and other therapies, is often encountered in clinical practice. This treatment includes exposure to memories of traumatic events, observation of eye movements, and recall of traumatic events and associations. Its use is controversial, not because it has any known harmful effects but because there is no clear evidence or theoretical basis for its method of action. Several studies have shown that the eye movement component of treatment does not contribute to successful outcomes and that other components of the treatment are likely responsible for change (585). EMDR demonstrated efficacy for PTSD in pre- and posttreatment analyses (54, 583,585) but was not significantly superior to wait-list or supportive therapy control groups in other studies (583). EMDR had smaller effects than conventional CBT in a metaanalytic study (54) and in some clinical trials (586–588).

Not Recommended

Supportive therapy alone has not been shown to be significantly more effective when patients receiving it are compared with wait-list control groups or patients in usual care in meta-analyses (49,583). However, a supportive therapeutic relationship may be invaluable following a traumatic event. Normalizing the distress that typically follows exposure to trauma, helping the patient to cope with some of the practical issues that arise after trauma (for example, dealing with an insurance company), and providing education to patient and family are probably important aspects of recovery.

Combined Psychological and Pharmacologic Treatment

Research evaluating combined treatment in PTSD is limited, and no controlled trials compare the results of combined treatment with monotherapy. There is preliminary evidence that patients with limited or partial response to medication benefit from the addition of CBT (589,590). In a small case series, exposure therapy after a partial response to medication was associated with improved outcomes (589). Similarly, in a pilot study of Cambodian refugees, symptoms improved when CBT was added to sertraline, which had a limited response when used alone (590). A trial of pharmacotherapy is also warranted in patients who experience a limited response to CBT alone.

Pharmacologic Treatment

Approach to Pharmacologic Management

The management of patients with PTSD should follow the principles discussed in Section 2 and mapped in Figure 2.1. Pharmacotherapeutic interventions that have demonstrated efficacy in treating PTSD include SSRIs, SNRIs, TCAs, MAOIs,

Table 8.5 Recommendations for pharmacotherapy for PTSD

First-line	Fluoxetine, paroxetine, sertraline, venlafaxine XR
Second-line	Fluvoxamine, mirtazapine, moclobemide, phenelzine Adjunctive: risperidone, olanzapine
Third-line	Amitriptyline, imipramine, escitalopram Adjunctive: carbamazepine, gabapentin, lamotrigine, valproate, tiagabine, topiramate, quetiapine, clonidine, trazodone, buspirone, bupropion, prazosin, citalopram, fluphenazine, naltrexone
Not recommended	Despipramine, cyproheptadine Monotherapy: alprazolam, clonazepam, olanzapine

anticonvulsants, atypical antipsychotics, and benzodiazepines, among other agents. 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 8.4 and 8.5).

For patients with PTSD, therapy should be initiated with a first-line agent such as fluoxetine, paroxetine, sertraline, or venlafaxine XR (Table 8.5). 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 with an inadequate response to optimal dosages of a first-line agent or in whom the agent is not tolerated, therapy should be switched to another first- or second-line agent, or a second-line agent should be added. Patients with PTSD may make few gains during treatment, and it is important to preserve even small gains achieved with initial therapy. Therefore, augmentation with second- or third-line agents may be important early in treatment. Second-line choices include fluvoxamine, mirtazapine, moclobemide, and phenelzine, as well as adjunctive risperidone or olanzapine.

Treatment Nonresponse

Treatment-refractory 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. The TCAs amitriptyline and imipramine are third-line options for monotherapy. Other options should be reserved for use as adjunctive treatments. These include carbamazepine, gabapentin, lamotrigine, valproate, tiagabine, topiramate, quetiapine, clonidine, trazodone, buspirone, bupropion, prazosin, and citalopram.

First-Line Agents

SSRIs. There is good evidence from RCTs supporting the use of the SSRIs fluoxetine (591–593), paroxetine (594–596), and sertraline (597–600) for the treatment of PTSD (Level 1). Fluoxetine has demonstrated efficacy in 3 randomized, placebo-controlled trials in PTSD (Level 1) (591–593). One trial reported significantly higher CGI response and remission rates with fluoxetine (85% and 59%, respectively), compared with placebo (62% and 19%, respectively) (592). Paroxetine demonstrated efficacy in three 12-week randomized, placebo-controlled trials in PTSD, with response rates of 56% to 62%, compared with 37% to 38% for placebo (Level 1) (594–596). Randomized, placebo-controlled trials in patients with PTSD have demonstrated the efficacy of sertraline, with response rates of 53% to 60%, compared with 20% to 38% for placebo (Level 1) (597–600).

Trauma from different origins may not respond similarly to each agent (591,599,658). This should be considered when interpreting the data. Several studies have suggested that results among combat veterans may be less robust than results in civilian populations (591,599,658). Improvements in depression scores have also been reported with these agents (591,593–596,598).

SNRIs. Venlafaxine XR was effective in a large, 12-week RCT in patients with PTSD, with remission rates of 30.2%, compared with 19.6% for placebo (Level 2) (613). This study also included a sertraline group, and there were no significant differences between venlafaxine XR and sertraline in efficacy or tolerability. This trial and considerable clinical experience support its use as a first-line agent.

Second-Line Agents

NaSSAs. Mirtazapine demonstrated efficacy in one small RCT (Level 2) (615) and 2 open trials (615,616). In an open study, response rates were significantly higher with mirtazapine than with sertraline (616).

Adjunctive Atypical Antipsychotics. RCTs demonstrated that risperidone significantly reduced not only psychotic symptoms and aggression but also core symptoms of PTSD in studies in combat veterans (Level 1) (637–639) and women who had experienced childhood abuse (640). Early results with adjunctive olanzapine also suggest significant improvements in PTSD symptoms, depression, and sleep (Level 2) (641). Since up to 40% of patients with combat-related PTSD experience psychotic symptoms (659,660), adjunctive antipsychotics may be beneficial in managing these symptoms as well.

Second-Line SSRIs. Open trials suggest that fluvoxamine is effective for PTSD, but it is recommended as a second-line agent because more data are needed (Level 3) (603–607).

RIMAs and MAOIs. A small open trial suggested that moclobemide was effective for PTSD (Level 3) (618). Serotonin syndrome may occur with coadministration of moclobemide and SSRIs, and this combination should be used with caution (661). Phenelzine was more effective than placebo and may be more effective than imipramine in RCTs in veterans with PTSD (Level 1) (610,611). However, MAOIs are recommended as a second-line treatment because of the dietary restrictions and potential adverse drug interactions associated with these agents. Phenelzine should not be used in combination with an SSRI or an SNRI.

Third-Line Agents

TCAs. Amitriptyline (Level 1) (608,609) and imipramine (Level 1) (610,611) have demonstrated efficacy as monotherapy in RCTs in patients with PTSD. However, results were not as robust as those reported in trials with SSRIs or MAOIs, and given the toxicity in overdose, these agents should be reserved for third-line use.

Adjunctive Anticonvulsants. Lamotrigine demonstrated efficacy in the treatment of PTSD in a small RCT, with response rates of 50%, compared with 25% for placebo (Level 2) (624). Data on other anticonvulsants, including carbamazepine (Level 3) (625, 626), valproate (Level 3) (627,628), topiramate (Level 3) (629–631), gabapentin (Level 4) (635,636), and tiagabine (Level 4) (632-634), are from open trials or case series in which these agents were primarily used as adjunctive therapy. Because of the lack of data, these agents are currently recommended only as adjunctive treatments in treatment-refractory patients.

Adjunctive Quetiapine. Adjunctive quetiapine has shown encouraging results in an open trial (643) and in case reports (642) (Level 3). However, unlike risperidone and olanzapine, controlled data are not yet available, and while the efficacy of the atypical antipsychotics may be a class effect, controlled data for quetiapine are needed before it can be recommended as a second-line agent.

Other Therapies. Open trials have suggested benefits with several agents, including clonidine (647), fluphenazine (645), trazodone (648), buspirone (622,623), bupropion (617), and prazosin (653–656) (all Level 3). Citalopram demonstrated efficacy in small open trials (Level 3) (601,602), but in a double-blind RCT, citalopram was not associated with significant improvements, compared with sertraline or placebo (600). Data are not yet available on escitalopram for the treatment of PTSD; however its efficacy in GAD (455,456), panic disorder (164), and SAD (305,306), as well as anecdotal experience in PTSD, suggests that escitalopram may be effective for some patients (Level 4). More data are needed to determine the usefulness of citalopram and escitalopram in PTSD. In open trials and case series, naltrexone has been shown to reduce flashbacks and improve other symptoms, including emotional numbing (Level 3) (650–652). However, in another small open-label study, it was not associated with a clinically significant improvement, and patients exhibited hypersensitivity to its side effects (649).

Not Recommended

In small controlled trials, alprazolam and clonazepam failed to show significant benefits over placebo (571,619–621) as monotherapy for the treatment of PTSD. Clinically, these drugs might be beneficial in combination with other agents for treating acute exacerbations of anxiety in patients with PTSD. Olanzapine monotherapy was effective in several open trials (645,646) but failed to differentiate from placebo in an RCT (Level 2, negative) (644) and therefore should not be used as monotherapy. Desipramine (612) and cyproheptadine (657) were not effective for PTSD symptoms in RCTs (both Level 2, negative).

Dosage and Duration

Patients must receive adequate dosages for an adequate duration before a therapeutic trial is deemed ineffective. Response to SSRI therapy should be apparent within 2 to 4 weeks; however, an adequate treatment trial length is at least 8 weeks (637), during which the drug should be actively titrated. Some data suggest that antidepressant benefits continue to accrue for up to 36 weeks of treatment (662).

Long-Term Management

One study indicated that about 25% of patients with PTSD who responded to treatment relapsed within 6 months of discontinuing pharmacotherapy, suggesting that long-term treatment is often needed (662). It has been recommended that patients with chronic PTSD (that is, symptoms lasting 3 months or longer) continue medication for at least 1 year (73). As discussed above, open follow-up data of psychological treatments suggest that benefits can be maintained for 6 to 18 months after treatment (54, 583,663,664). Benefits were sustained and continued to accrue with long-term SSRI therapy. Long-term treatment with

sertraline improved response rates; one-half of patients who had not responded to 12 weeks of treatment went on to respond during an additional 24 weeks (665). Quality of life improved progressively and was sustained over more than 1 year of treatment (666). Improvement in psychosocial functioning tends to lag behind symptom improvement, highlighting the need to continue medication well after the symptoms remit.

Fluoxetine (667,668) and sertraline (662) have been shown to prevent relapse of PTSD symptoms, compared with placebo, in randomized, controlled discontinuation trials of up to 6 months. Relapse rates were about halved by active therapy (5% to 22%, compared with 16% to 50% for placebo) (662,667,668).

Summary

PTSD is prevalent in primary care and is associated with significant morbidity. Comprehensive management of PTSD should incorporate both psychoeducational and pharmacologic components. CBT is the most effective choice for psychological treatment. According to current evidence, the SSRIs sertraline, paroxetine, and fluoxetine, as well as the SNRI venlafaxine XR, are recommended as first-line pharmacotherapy for PTSD. An adequate treatment trial is likely to be at least 8 weeks, with benefits continuing to accrue with longer duration of therapy. Many patients require long-term therapy to prevent relapse.

9. Special Populations

Children and Adolescents

Epidemiology

Anxiety disorders are the most common mental disorders in children and adolescents (669,670), with lifetime prevalence rates of 14% to 17% (671–673). In the National Comorbidity Survey, the median age of onset for anxiety disorders was 11 years (range 6 to 21 years), which was much younger than for substance use disorders (20 years) and mood disorders (30 years) (2). Separation anxiety disorder and specific phobias had very early ages of onset (7 years), followed by SAD (13 years), whereas other anxiety disorders had much later median ages of onset (range 19–31 years) (Table 9.1) (2), although earlier onsets are not unusual in anxiety disorders in children.

A survey in primary care found that, among children with a current anxiety disorder, 31% had received counselling or medication treatment during their lifetime, compared with 40% of children with depression and 79% with attention-deficit hyperactivity disorder (ADHD) (674). This is also the case for children who have high levels of anxiety but whose symptoms do not meet the full criteria to be diagnosed with the disorder (675). Early diagnosis and treatment of an anxiety disorder may have a positive impact on long-term outcomes, including chronic anxiety, depression, and substance abuse (676,677).

Psychiatric comorbidity is common among children with anxiety disorders, with up to 79% having at least one comorbid diagnosis (678,679). Most comorbidity consists of other anxiety disorders, but comorbid ADHD occurs in up to 25% of cases and comorbid depression is common in adolescents (680).

Diagnostic Issues

Diagnosis of anxiety disorders in children must consider developmentally appropriate levels of normal anxiety. Anxiety and worry are common phenomena in normal children, with anxiety symptoms generally being more common in younger than in older children and in girls more than in boys (681,682). An exception is early-onset OCD, which is more common in boys than in girls. Common anxiety symptoms in children include fear of the dark, fear of harm to a family member, overconcern about competence (for example, in school), excessive need for reassurance, somatic complaints, worries about dying and health, and worries about social contact (682,683). Regardless of the specific fear or anxiety, children with anxiety disorders are distinguished from their peers by the persistence of symptoms and the impairing effect of symptoms on day-to-day functioning (1).

Early signs of anxiety (such as persistent behavioural inhibition), family history of anxiety disorders (especially in parents), and environmental factors (such as parenting style) have been linked to the development of anxiety disorders and may help increase the index of suspicion for disorders in children (681). Behavioural inhibition, a temperament style characterized by shyness and avoidance of novelty, has been linked prospectively to multiple anxiety disorders in middle childhood and social phobia in adolescence. It is important to obtain information from multiple informants, including the child, the parents, and the teacher (if available), because reports of anxiety symptoms often differ among informants and anxiety may manifest more in some environments than in others (684). Standardized questionnaires such as the Multidimensional Anxiety Scale for Children (685) are not diagnostic, but they may be useful as an adjunct to diagnostic interviews and to monitor symptomatic response to therapy.

With the exception of separation anxiety disorder, which by definition begins in childhood, anxiety disorders are seen in both children and adults; thus, the DSM-IV-TR provides modifications to adult criteria for those disorders (Table 9.2) (1). An important difference to note when diagnosing anxiety in children rather than in adults is that anxiety may be expressed by crying, nightmares, physical symptoms (for example, headaches or upset stomach), or through play themes. In addition, unlike adults, children may not recognize that the fear is excessive or unreasonable, and this criterion is not necessary to make diagnoses in the case of SAD and specific phobia (1).

Although not currently considered an anxiety disorder in the DSM-IV-TR (13), selective mutism is also thought to be an anxiety-related condition. In this condition, the child fails to

Table 9.1 Age of onset of anxiety disorders in National Comorbidity Survey

Anxiety disorder	Median age (years)	Range (years)
Any anxiety disorder	11	6–21
Separation anxiety disorder	7	6–10
Specific phobia	7	5–12
Social phobia	13	8–15
OCD	19	14–30
PTSD	23	15–39
PD	24	16–40
GAD	31	20–47

Adapted from Kessler and others (2)

speak in specific environments, despite normal speech in others, often with debilitating effects on school and social functioning. Substantial evidence supports the role of social anxiety in this disorder (686), but immigration and certain developmental problems may also be contributing factors (687,688). In addition to psychiatric assessment, developmental and speech or language assessments are also indicated in these children (689). Some spontaneous resolution has been reported, especially in community samples, but more than one-half of children in clinical samples show persistent selective mutism over several years (690). Home- and school-based behavioural interventions have been advocated (691,692), and there is some evidence for the efficacy of SSRIs in this condition (693,694).

Treatment Issues

Although anxiety, particularly separation anxiety disorder, will resolve in some children, many will have a protracted course or will develop a new anxiety disorder (672,695). For example, a

Table 9.2 DSM-IV-TR diagnostic criteria specific in children

Anxiety disorder	DSM-IV-TR diagnosis specific to children
Separation anxiety disorder	• Developmentally inappropriate and excessive anxiety concerning separation from home or from those to whom the individual is attached, as evidenced by ≥ 3 of the following: • Distress when separation occurs; worry about loss or separation; reluctance to leave home, be alone or go to sleep because of fear of separation; nightmares involving separation; complaints of physical symptoms (for example, headaches, upset stomach) when separation occurs • Duration of at least 4 weeks • Onset before 18 years of age • The disturbance causes clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning
	Changes to adult DSM-IV-TR diagnostic criteria specific to children
Specific phobia	• Response to the phobic stimulus may be expressed by crying, tantrums, freezing, or clinging • May not recognize that the fear is excessive or unreasonable • Other phobias seen in children: avoidance of loud sounds or costumed characters • In individuals < 18 years, the duration is at least 6 months
SAD (social phobia)	• There must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults • The anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people • May not recognize that the fear is excessive or unreasonable • In individuals < 18 years, the duration is at least 6 months
OCD, PD	• No changes
PTSD	• Response to the event may be expressed by disorganized or agitated behaviour • Reexperiencing may be expressed through repetitive play in which themes or aspects of the trauma are expressed, dreams may be frightening without recognizable content
GAD	• Less stringent criteria for symptom response than in adults

Adapted from DSM-IV-TR (1)

Table 9.3 Useful self-help books for parents of anxious children

- Manassis K. *Keys to parenting your anxious child*. New York (NY): Barron's Educational Series, Inc; 1996.
- Rapee R, editor. *Helping your anxious child: a step-by-step guide for parents*. Oakland, (CA): New Harbinger Publications; 2000.

young child whose separation anxiety disorder resolves may show evidence of GAD several years later (695). Many children seem to have persistent anxious tendencies but report symptoms meeting criteria for different disorders over time as the manifestations of anxiety and strategies for coping with it change with development (696). Children with anxiety disorders, particularly those who are untreated, are at higher risk later in life for chronic problems related to anxiety, depression, and substance abuse (672,677,697). This is also the case for children who have elevated levels of anxiety but whose symptoms do not meet the full criteria for a disorder (675).

Psychiatric comorbidity does not appear to affect response to CBT (678,698). Evidence suggests that family dysfunction is related to less favourable treatment outcome in children with anxiety disorders who are receiving CBT (699).

Treatment of anxiety in children and adolescents should be psychological, with or without pharmacotherapy, and should include general support and education for the child and parents about the disorder and its treatment (681,700). Attention must be given to family matters, abuse issues, substance abuse, the use of peer support groups, and the encouragement of healthier lifestyle choices, such as exercise (700).

Psychological Treatment

Unlike adults, children are often brought to a physician by their parents and are not there entirely voluntarily. Children require help to recognize their anxiety states, and therapy may need to be adapted to address multiple comorbid disorders. Psychological treatments need to be simpler, more concrete, and adapted to the age and developmental level of the child. Outcomes appear to be enhanced by parental involvement. Adolescents may require less didactic models to engage them in therapy. Books that may be helpful for the parents of children or adolescents with anxiety disorders are shown in Table 9.3.

An example of a CBT protocol for anxiety disorders in children is the "Coping Cat" program developed by Kendall (701,702). This program has demonstrated efficacy in RCTs, and benefits were maintained at 12-month follow-up (701,702). The program involves 16 sessions designed to promote coping skills for dealing with anxiety (701). The child uses the Coping Cat workbook, in which he or she answers questions, using problem-solving strategies to address problems. In a 7-year follow-up, positive responders to the Coping Cat program had a decreased incidence of substance use and related problems and maintained significant improvements in anxiety (677). It is important to note that while this treatment is adaptable to GAD, SAD, separation anxiety, specific phobias, or a combination of these disorders, other specific CBT protocols are required for OCD and PTSD. The generalizability of Coping Cat to community samples also requires further study, but evaluations of other CBT approaches for children's anxiety in community studies describe long-lasting results (703,704).

A systematic review of CBT in the treatment of anxiety disorders in childhood and adolescence, including 10 RCTs, found remission rates of 56.5% with CBT, compared with 34.8% in the control groups (705). The pooled odds ratio was 3.3 (95%CI, 1.9 to 5.6), suggesting that CBT has a significant effect. More recent trials have confirmed the efficacy of CBT, given as both individual and group therapy, compared with a control group, in children with anxiety disorders (706) that included SAD (707,708), PTSD symptoms related to sexual abuse (709,710), and school refusal (711,712). A combination of imipramine and CBT was more effective than CBT alone in treating school-refusing adolescents with comorbid anxiety disorders and MDD (713). Most trials demonstrate greater efficacy for approaches that include family and (or) parental involvement (714–717). Such approaches may be particularly effective when parents suffer from an anxiety disorder themselves (718).

Pharmacologic Treatment

In general, pharmacotherapy alone should not be used in children and adolescents. Although the combination of pharmacologic and psychological treatments has not been adequately studied, behavioural and psychological interventions that help promote mastery are important to prevent recurrence after discontinuation of medication (719). In addition, using the medication in combination with CBT may make pharmacotherapy more acceptable to families that are reluctant to try SSRI therapy. The safety and suicide risk (see Safety Issues below) associated with antidepressants should be weighed against the potential benefits of therapy. In milder cases, while psychological treatments are being attempted, a wait-and-see approach to medication may be warranted. However, antidepressants may be important in children or adolescents with OCD or in those who are severely impaired by anxiety symptoms or less likely to respond to CBT (for example, because of cognitive limitations). Youths have highly variable dosage needs, so it is best to "start low and go slow," but note that final dosages may be in the adult range.

Benzodiazepines have not been well studied in children and adolescents with anxiety disorders, and children may be more prone to the side effects of disinhibition and aggression (681). In

Table 9.4 Strength of evidence of treatments for anxiety disorders in children and adolescents

Disorder	Treatments
OCD	Fluoxetine (Level 1) (721–723) Fluvoxamine (Level 2) (724) Sertraline (Level 2) (725) Clomipramine (Level 1) (726–728) Paroxetine (Level 2) (729) Citalopram (Level 3) (730) Clonazepam (Level 4) (731)
PD	Clonazepam (Level 4) (732,733) Alprazolam (Level 4) (734)
SAD	Alprazolam (Level 2, negative) (735) Fluoxetine (Level 2) (736) Fluvoxamine (Level 2) (737) Paroxetine (Level 2) (738) Sertraline (Level 3) (739) Venlafaxine XR (Level 2) (740)
Separation anxiety disorder	Fluoxetine (Level 2) (736) Fluvoxamine (Level 2) (737)
GAD	Fluoxetine (Level 2) (736) Fluvoxamine (Level 2) (737) Sertraline (Level 2) (741) Alprazolam (Level 2, negative) (735)
School refusal	Citalopram (Level 4) (742) Imipramine + CBT (Level 2) (713) Alprazolam (Level 2, negative) (743)

addition, because of the potential for abuse and dependency, these agents should be used sparingly in youths. Short-term use may be warranted for specific anxiety-provoking situations (for example, the first few days of school for a child with school phobia) or while waiting for an antidepressant to take effect.

SSRIs and TCAs have been studied in youths with anxiety disorders. Table 9.4 shows the strength of evidence of these medications in the treatment of children and adolescents. However, since SSRIs are associated with fewer side effects, they are generally preferred therapy in children and adolescents. The use of medication for the treatment of anxiety disorders in youths is best studied in OCD: a metaanalysis of 12 studies including 1044 youths found a significant effect size (0.46) with treatment (specifically, with paroxetine, fluoxetine, fluvoxamine, sertraline, or clomipramine) (720), indicating a moderate clinical benefit. There were no significant differences among the SSRIs.

Safety Issues

The most important issue in regard to the use of antidepressants in children and adolescents is the potential risk of suicidality. A statement for the Canadian Psychiatric Association on antidepressant prescribing found that, when SSRIs other than fluoxetine were used for MDD in children and adolescents, there was an estimated 1 to 3 excess cases of suicidality for every 100 patients; fluoxetine carried a lower risk (744). Suicidal thoughts occurred in about 5% of SSRI-treated children and 2% to 3% of placebo-treated children, but all the studies concerned treatment of depression. The risk of suicidality with these medications has not been systematically examined in anxiety disorders, but it may be lower than in MDD. The analysis of suicidality by the US Food and Drug Administration found a higher rate of suicidal events with active drug treatment in data from MDD trials; although data from non-MDD trials also showed a higher rate of events, the attributable risk for serious events was much smaller than for MDD trials, and the data were not statistically significant (745).

Including parents as well as the anxious child in discussions of this potential risk is important. Discussion with the patient and family about potential side effects (such as anxiety, agitation,

Table 9.5 Lifetime prevalence of anxiety disorders in the National Comorbidity Survey by age

Disorder	Overall Age ≥ 18 years	Age ≥ 60 years
PD	4.7	2.0[a]
Specific phobia	12.5	7.5[a]
SAD	12.1	6.6[a]
GAD	5.7	3.6[a]
PTSD	6.8	2.5[a]
OCD	1.6	0.7
Any anxiety disorder	28.8	15.3[a]

[a] $P \leq 0.05$ for age-related differences in prevalence; adapted from Kessler and others (2)

hypomania, and activation syndrome) that may affect suicidality is also recommended, and early reassessment (weekly for the first month) after initiation of therapy should take place (744). The potential consequences of not providing medication should also be discussed and weighed against medication risks.

In general, SSRIs are better tolerated than TCAs; as well, sudden deaths have been reported with TCAs (681). However, parents and patients should always be educated on the safety and side effect profile of the medication, and therapy should be initiated at a low dosage and increased slowly. Gastrointestinal complaints represent the most common side effect with SSRIs, with agitation and restlessness being less frequently reported (681).

Elderly

Epidemiology

Older adults represent the fastest-growing segment of the population, but research on the course and treatment of anxiety in older adults lags behind that of other mental disorders (746). Most anxiety disorders meeting full DSM-IV syndromal criteria do not commonly begin in older adults, and most cases are chronic conditions with onset in young adulthood. However, late-onset generalized anxiety and agoraphobia are observed, with notable differences in presentation (747). The core symptom of uncontrolled worry is often absent in GAD, commonly presenting with "tension," anxious mood, and various somatic complaints superimposed on depression or dementia, which become the primary focus of therapy. Agoraphobia is often not recognized after a serious medical condition or is dismissed as "normal" in an older adult who is not engaged in school or employment.

The lifetime prevalence rates of most anxiety disorders, with the exception of SAD and OCD, are highest in people aged 45 to 59 years and diminish in older age (≥ 60 years) (Table 9.5) (2, 748–751). However, some data show that the prevalence of GAD does not decline with age and may actually increase (750, 752), although this is not a consistent finding (2). It has been suggested that age bias in diagnostic assessment may account for some of the apparent decline in prevalence with age (751,753). As in other age groups, the prevalence of anxiety disorders in older populations is generally higher in women than in men (748,750,754).

Anxiety in older patients may have a significant negative impact on psychosocial functioning (755) and on cardiac function and heart disease (756,757). Anxiety has been reported to be more common among individuals who have a fear of falling, urinary incontinence, hearing impairment, and hypertension, as well as among those with poor sleep, poor psychosocial functioning, or a need for more emotional support (758). In one survey of elderly adults with anxiety, 10% had 2 or more anxiety disorders. Major depression, benzodiazepine use, and chronic somatic diseases were significantly more prevalent in the anxious group than in those without anxiety disorders, although excessive alcohol intake and cognitive impairment were not (759). Other studies have reported that anxiety is associated with cognitive impairment and may be a predictor of cognitive decline (760,761). Adults at risk for restless leg syndrome (RLS) are more likely than those without risk of RLS to report additional physical and psychiatric conditions, including depression and anxiety. Additionally, they are also more likely to be overweight, unemployed, and daily smokers and to have issues with work attendance and performance (762).

The cooccurrence of anxiety and depression represents more severe and chronic illness (763,764), and anxiety has been shown to increase the risk of suicidality in older patients with

depression (765). Long-term outcomes of late-life anxiety show persistence of the disorder in 23% and subclinical anxiety in 47%, with high use of benzodiazepines (43%) but low use of antidepressants (7%) and mental health services (14%) (766). Self-perceived poor health is predictive of incidence and chronicity of anxiety. Suffering from more than one chronic disease predicts becoming anxious and anxiety chronicity (767).

Diagnostic Issues

Recognition of anxiety disorders, particularly differentiating between medical conditions and the physical symptoms of anxiety disorders, is more complicated in older adults (768,769). Older adults have a high prevalence of medical conditions and prescription medication use. However, late-onset anxiety disorders are quite rare, and a full investigation of potential causes, including depressive disorder, physical illness, or side effects of medications, should be done in any first presentation in late life (2,770) (see Table 2.4).

The decreasing prevalence of anxiety disorders in older individuals may be related to a decrease in diagnosis with age (751,753). Many older adults who experience clinically significant psychopathology do not fit easily into existing classifications and yet are disabled (753). Medical comorbidity, difficulty differentiating anxiety from depression, falsely high anxiety scores caused by overendorsement of cardiac and respiratory problems, and the tendency of older patients to resist psychiatric evaluation confound diagnosis of anxiety disorders in older patients (769).

Physical and psychosocial changes associated with aging possibly make it difficult to distinguish between phobias and nonpathologic avoidance behaviours in elderly patients (753). Social phobias may be attributed to diminished physical abilities, including visual problems, which may make elderly adults afraid to go out at night. New-onset agoraphobia may be difficult to diagnosis in elderly individuals who are less mobile and who tend to leave their houses less frequently.

Data suggest that late-onset PD is characterized by lower symptom severity and associated distress (771), whereas symptom presentations in younger and older adults are quite similar for OCD (772) and PTSD (773).

Treatment Issues

The high prevalence of comorbid medical conditions, including cardiovascular disease, diabetes, renal disease, hepatic disease, and cognitive decline, as well as the extensive use of prescription medications, may complicate the treatment of anxiety disorders in older patients.

Aging is associated with several neuroendocrine changes (774), and there is early evidence that some older patients with deficits in executive skills may respond poorly to antidepressant treatment, compared with those with intact executive functions (775). Comorbid depression and anxiety are common among older patients and are associated with poorer treatment outcomes, including delayed or diminished response and increased likelihood of dropout from treatment (763,764).

When treating older patients, a strong doctor–patient relationship is essential, and interventions should include environmental, social, recreational, supportive, and spiritual programs, as well as psychoeducational programs that include the patient's family.

Psychological Treatment

Clinical trials, most of which have been conducted in patients with GAD, have demonstrated the efficacy of CBT in elderly patients with anxiety (776–780). Compared with a minimal-contact control group, CBT for patients with GAD resulted in significant improvements in worry, anxiety, depression, and quality of life, and most gains were maintained or enhanced over a 1-year follow-up (778). However, although response rates were higher with CBT (45%), compared with a control condition (8%), and gains were maintained at 12-month follow-up, mean anxiety scores at posttreatment continued to be elevated, indicating considerable room for improvement (778). This finding of residual anxiety at the end of treatment is typical of psychological and pharmacologic intervention trials for GAD (479). Several studies have suggested that supportive therapy is as effective as CBT (280,780). Small pilot studies using enhanced versions of CBT in the elderly showed positive results in the treatment of GAD (777,779).

Overall, CBT has not been widely studied in the elderly; most studies have been small; and in many studies, CBT was only modestly more effective than supportive therapy (781). While most of the available information is based on studies in GAD, it likely can be applied to other disorders. CBT may need to be adapted for use with elderly patients; strategies using cross-modal repetition, frequent summarizing, and provision of examples in session may be useful. Age-appropriate learning principles may need to be included because CBT largely depends on the patients' acquisition of new skills. The addition of learning and memory aids appeared to bolster the efficacy of CBT treatment (777,779,781). Including a medical component may also be helpful in those with health-related concerns that contribute to, or result from, their anxiety disorder (781). Administration of therapy in the patient's own home, with familiar and comfortable surroundings, may facilitate the learning and use of individual CBT (280,779).

A group format may be particularly useful when treating some older adults, since it may offer positive aspects that individual therapy does not, including increased social contact and support, social reinforcement, decreased inactivity and isolation, and less stigma attached to treatment (781).

Modest behavioural changes may sometimes have a substantial functional impact for older individuals (781). Attrition rates are high, so it may be important to address retention strategies early in treatment or to focus therapy on the most effective components. The presence of serious medical conditions does not appear to compromise the efficacy of psychosocial treatments (781).

Pharmacologic Treatment

Evidence specific to the treatment of the elderly population with anxiety disorders is scarce. Small RCTs in elderly patients have demonstrated the efficacy of citalopram (782) and buspirone (783). Fluvoxamine was effective in older patients in an open trial (784). While some data report on the efficacy of benzodiazepines in older patients (785,786), older patients are more sensitive to both the therapeutic and toxic effects of these agents, and they should generally be avoided or used in low dosages (see Safety Issues below) (83,769,787). In some patients with Alzheimer's disease, treatment with acetylcholinesterase inhibitors may help reduce neuropsychiatric symptoms, whereas others may not benefit (788). With acetylcholinesterase inhibitors, anxiety, delusions, depression, and irritability are specific behaviours that show the greatest change, compared with baseline (789).

In the absence of studies of pharmacotherapy for anxiety disorders in elderly patients, treatment choices should follow the recommendations for younger adults while considering prior treatment response, the nature of the targeted symptoms, concurrent medications, and the safety and side effect profiles of the medications (769).

Safety Issues

Age-related alterations in physiology, renal disease, cardiac insufficiency, and decreased body fat may alter plasma drug concentrations, which may increase the number of adverse events (769,790,791). The elderly may be more sensitive to adverse events such as somnolence, orthostatic hypotension, and cognitive or extrapyramidal symptoms. In addition to the dependence and withdrawal issues associated with benzodiazepines, older patients may also experience daytime sedation, increased risk of falls, and impaired cognitive function with continued use (83,769,787).

Older individuals use multiple medications (≥ 2 prescription drugs) 3 times more frequently than do younger persons, which increases the potential for drug interactions (792). Therefore, the risk of drug interactions should be considered when choosing pharmacotherapy. In general, initial dosages for the elderly should be lower, and increases should be slow and individualized (790,791).

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Appendices

Appendix A
Interview questions to screen for anxiety symptoms and specific anxiety disorders

Questions	Responses
Part 1: Identify anxiety	
"How have things been going for you recently?" "Any problems with excessive stress, worry, or anxiety?"	[IF YES] Could you tell me about that? When did the extra difficulty seem to start? Were there any major changes or stresses in your life at that time?
Part 2: Explore positive responses above with the following types of questions. Modify questions to patient's responses	
"Do you have times when you experience a sudden rush of symptoms or uncomfortable physical feelings such as racing heart or dizziness? Do you have feelings of fear or panic at these times? Have these spells ever occurred out of the blue, without any obvious trigger or cause?"	[IF YES] Could you tell me about that? **See section on PD**
"Do you avoid any situations because you might experience these spells of symptoms or feelings of fear or anxiety?" (for example, crowds, enclosed places, driving, leaving the house alone, or other situations)	[IF YES] Could you tell me about that? **See section on PD**
"Do any of the following make you feel anxious or fearful: animals (for example, spiders, snakes, dogs, cats, birds, mice, bugs), heights/storms/being near water, the sight of blood/getting an injection or blood test, driving/flying in an airplane/enclosed places such as elevators or small rooms? Does this fear interfere with your life or cause you marked distress?"	[IF YES] Could you tell me about that? **See section on Specific phobias**
"In general, are you overly anxious or concerned about embarrassing or humiliating yourself while doing things in front of people or interacting with others?"	[IF YES] Could you tell me about that? **See section on SAD**
"Do you experience disturbing thoughts, images, or urges that keep coming back to you and that you have trouble putting out of your head?" (for example, being contaminated by something, something terrible happening to you or someone you care about, or of doing something terrible)	[IF YES] Could you tell me about that? **See section on OCD**
"Do you ever have to perform a behaviour or repeat some action that doesn't make sense to you or that you don't want to do?" (for example, washing or cleaning excessively, checking things over and over, or counting things repeatedly)	[IF YES] Could you tell me about that? **See section on OCD**
"What kinds of things do you worry about? Do you worry excessively about everyday things like your family, your 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?"	[IF YES] Could you tell me about that? **See section on GAD**
"Are you bothered by memories, thoughts, or images of a very upsetting event that happened to you or someone close to you in the past?" (for example, being in a fire or a serious accident, being raped, assaulted, or abused, seeing someone else badly hurt or killed)	[IF YES] Could you tell me about that? **See section on PTSD**
Part 3: If an anxiety problem is identified, explore whether the problem causes interference or a high level of distress	
Does this problem with [THE SYMPTOMS DESCRIBED BY THE PATIENT] bother you a lot? Does it interfere with your work, activities, or relationships?	

Appendix B
How to conduct exposure therapy

Avoidance of situations, thoughts, bodily sensations, and emotions that provoke anxiety has been identified as a central feature of most anxiety disorders. This is understandable because avoidance is one of the most common ways of dealing with threatening situations. Approaches that involve exposure to these avoided experiences have been found to be effective in overcoming anxiety problems. Patients often feel more confident managing exposure experiences gradually—facing moderately anxiety-arousing situations at first and then situations of increasing difficulty. To be effective it is important that exposure be practised repeatedly. There is also evidence that exposure is more effective if it occurs regularly (for example, at least several times weekly) rather than being too spread out over time. Exposure is most effective when practices are prolonged, ideally lasting until the fear has decreased to no more than a mild level. Generally, each exposure episode should last for about 30 minutes, or until subjective discomfort drops by 50%, whichever comes first (less time for children).

Often patients who are struggling with anxiety also do little in the way of problem solving because they avoid thoughts or feelings about the difficult situation. Encouraging them to take some problem-solving actions may also be very helpful. Difficulty may also arise in interpersonal relationships when patients avoid contact or avoid problem solving with someone close because of past conflicts or disappointments. Action by the clinician during regular office visits to encourage exposure and problem solving and to follow up on these recommendations in future visits is important in helping patients overcome anxiety problems. The patient handout that follows may be a helpful way to introduce the patient to the concepts involved in exposure treatment. The self-help resources for the various anxiety disorders described elsewhere in this publication provide much more detailed information about exposure and problem solving.

Patient handout (side 1)

Overcoming fears through exposure therapy

You have probably heard the expression, "What is the thing to do when you fall off a horse?… Get back on and ride." This saying is supported by a wealth of psychological research. Avoiding the situations you fear prevents you from overcoming the fear. The most powerful way to overcome an excessive or unrealistic fear is to face your fear in gradual steps. Facing your fears repeatedly will lead to a decrease in fear by teaching you that you are able to handle the situation better than you think and that the unpleasant anxiety thoughts and feelings subside over time. This treatment is also called exposure therapy. By starting small and gradually increasing the difficulty of the situations you practice you can overcome even very severe fears.

Points to remember about facing your fear practice

- Focus on one or two feared situations at a time. Many people have a number of different fears. Rather than trying to tackle them all at once, it is often best to pick one or two situations that cause most difficulty in your everyday life and work on them first.
- Break difficult problems into smaller and easier steps. Before starting to practise think of ways of breaking a difficult situation down into smaller steps. The goal is to make a list of about 10 steps each representing a situation you fear. Start with mildly anxiety-provoking situations and move gradually to situations that trigger higher levels of anxiety, as you work toward your final goal. For example, if you are nervous about speaking in public, think about similar situations that are also challenging for you that you can practise regularly to build up your confidence. Your list might include asking a question in class or a meeting, giving your opinion at a class or meeting, leading a small meeting, giving a presentation in a small class, and giving a presentation in a large class. Any situation that is related to your goal can be on your list as long as it produces anxiety. Situations that you can practise regularly are best. When you are ready to start your practice you can use this list of situations as your guide, starting with practice of lower anxiety situations and when these are going well moving to higher anxiety situations.
- Practice should be predictable and under your control. Plan practices in which you have a good idea of what might happen. For example, if you are trying to overcome a fear of dogs, be sure to practise with a dog that is relatively calm, particularly at the beginning of your treatment.
- Practice should be prolonged. Practice is most effective when it lasts long enough for your fear to decrease. Occasionally this takes just a few minutes, but often it may take up to several hours. So, plan practices when you have some time to spare. For example, if overcoming a fear of driving, practise driving for an hour or more – until your fear has decreased. If you are fearful of elevators, practise riding up and down until your fear has decreased.
- Practice works best when it is repeated frequently. Daily practice works better than weekly practice. Weekly practice works better than monthly practice. In most cases, it is recommended that practice occur at least three to five times per week, if possible. When the fear has improved, the frequency of practice can be decreased.
- Don't fight your fear during practices. It is normal to feel nervous or anxious when you are facing your fear. In fact, feeling this anxiety and finding that you can cope with it is part of the process of overcoming fear. Just accept the uncomfortable feelings. In time, your fear will decrease by taking charge and facing it repeatedly.

Patient handout (side 2)

Judge success based on what you do, not how you feel. Expect to feel uncomfortable during exposure practices, particularly at the beginning. Over time, the situations will become less anxiety-provoking.

Include a helper, if you prefer. Sometimes it is useful to include a friend or family member in your exposure practices, particularly at the start of your treatment. Later it will be important to practise facing your fear on your own.

Safety strategies. Some strategies may help you feel safer or more comfortable when you start your practice. Examples of safety strategies are spending a long time preparing for every question or comment you make in a meeting, taking a mobile phone with you to call someone if you become anxious, and only going into a difficult situation if you feel you have a person with you who can be relied upon to help in case of a problem. As you make progress, you will go further in overcoming your fear if you gradually let go of any safety strategies that most other people do not require.

Overcoming the fear of fear. Many people are frightened by the feelings their body produces when they are anxious. These feelings are part of the body's normal reaction to feared situations. If you are fearful of certain physical sensations, such as racing heart, dizziness, or sweating, you may benefit from practising exposure to these sensations using particular exercises. For example, to get dizzy and light-headed, try spinning in a chair or hyperventilating (very fast breathing) for 60 seconds. For exposure to a racing heart, try running on the spot. Practise wearing warm clothing and exercising if you are afraid of feeling overheated or sweating in front of others. Your doctor can let you know if any of these exercises are potentially dangerous for you. For example, you probably shouldn't practise hyperventilation if you have asthma or a chest cold. Note that if you are not frightened of the physical symptoms of fear and anxiety, it is not necessary to expose yourself to these sensations using these symptom exposure exercises.

For realistic fears, don't use exposure. Exposure is meant to help people to overcome excessive and unrealistic fears. If your fear is realistic (for example, a fear of driving fast in freezing rain, a fear encountering poisonous snakes), your fear is probably helping you avoid trouble. Exposure is not recommended for overcoming fears of situations where the chances of danger are high. In dangerous situations, fear and anxiety are helpful emotions.

Record your experiences in a Practice Diary. As in learning many other new skills, people who practise regularly make a lot more progress. Most people find it challenging to find the time and energy for regular practice. Using a notebook to keep track of regular practice, to describe your experiences, and to plan future practice will help motivate you to practise regularly and to keep making progress.

Examples of practice exercises for particular fears

Feared situation	Practice exercise
Public speaking	Ask questions in meetings, make comments in meetings, speak in front of very small group; join Toastmasters for training in speaking, presentations for larger groups
Dating situations	Go out more socially with friends, ask acquaintances (preferred sex) for coffee or lunch, respond to personal ads, ask person who interests you for coffee, ask person who interests you for movie
Crowded places	Spend time in crowded places such as malls, loaded buses, busy restaurants, sports events, concerts
Driving	Drive in situations that cause you mild anxiety, once that is going well practise driving in situations that are more and more challenging (highways, rush hour, bridges)
Dogs	Read book about dog behaviour and handling dogs, visit pet store and watch small dogs from a distance, get closer and closer until you are touching dogs, visit friends who have dogs and ask to play with the animal

List of Abbreviations

ADHD	attention-deficit hyperactivity disorder
BII	blood-injection-injury
CAPS	Clinician Administered PTSD Scale
CBT	cognitive-behavioural therapy
CGI	Clinical Global Impression
CR	controlled release
EMDR	eye movement desensitization and reprocessing
ERP	exposure with response prevention
GAD	generalized anxiety disorder
HARS	Hamilton Anxiety Rating Scale
IR	immediate release
IV	intravenous
LSAS	Liebowitz Social Anxiety Scale
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
NaSSA	noradrenergic and specific serotonergic antidepressants
OCD	obsessive–compulsive disorder
PAS	Panic and Agoraphobia Scale
PD	panic disorder
PDSS	Panic Disorder Severity Scale
PTSD	posttraumatic stress disorder
RCT	randomized controlled trial
RIMA	reversible inhibitor of monoamine oxidase A
RLS	restless leg syndrome
SAD	social anxiety disorder
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TOP-8	Treatment Outcome PTSD Scale
VR	virtual reality
XL	extended release
XR	extended release
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

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