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
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 3.4 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 |
**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
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.
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

| 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 |
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.
