a useful option for patients with panic disorder who do not have ready access to a specialist.

The available data suggest that the benefits of a short-term course of CBT are long-lasting (for example, see reference 160). However, once patients have achieved a satisfactory reduction in symptoms and impairment, the focus of CBT shifts, and development of a specific relapse prevention plan becomes an integral part of treatment. The therapist normalizes fluctuations in anxiety and anticipates that the patient may experience periods of increased anxiety (including occasional panic attacks) in the future. The therapist and patient collaborate to anticipate potential triggers for these periods of increased anxiety (e.g., work stress, moving to an unfamiliar place) and to develop an individualized relapse prevention plan that the patient can follow if symptoms recur. This plan typically involves a return to more intensive practice of CBT skills that were previously helpful such as exposure and cognitive restructuring. If symptoms do not improve with the implementation of the practice plan, the therapist and patient can consider the option of "booster sessions" (i.e., a short course of CBT to help the patient reinstitute skills that were previously helpful). If efforts to boost response are unsuccessful, the psychiatrist should consider trying a different treatment modality or referring the patient to another qualified professional.

There is little evidence to suggest that CBT and commonly prescribed medications for panic disorder either enhance or counteract one another in the acute term. One randomized controlled trial found that fluvoxamine plus exposure therapy was superior to either alone in treatment of panic disorder with moderate to severe agoraphobia (68); however, this result has not been replicated. In contrast, another study found that, 6 months after treatments were withdrawn, patients who responded to a combination of imipramine and CBT for panic disorder displayed poorer maintenance of response than those who received CBT alone or CBT plus placebo (111). This finding raises some concern that simultaneously initiating medication and CBT may negatively affect the durability of the effects of CBT after treatments are withdrawn. This topic requires further study before firm conclusions can be drawn. Concern also exists about possible decreases in the efficacy of CBT if combined with benzodiazepines, although there is a dearth of systematic empirical data on this topic (190). One large randomized controlled trial showed that although adding alprazolam to exposure therapy marginally enhanced gains during acute treatment, patients who received the combination relapsed more after treatment withdrawal compared to those who received exposure plus placebo (149). Another small study showed that patients taking benzodiazepines had poorer memory for the educational material presented in CBT than patients who were taking no medications (161). Clinical experience suggests that p.r.n. ("as needed") use of benzodiazepines to block anxiety symptoms can be difficult to reconcile with certain components of CBT, and many CBT therapists discourage p.r.n. benzodiazepine use as soon as the patient has developed other anxiety management skills.

Cognitive-behavioral therapy for panic disorder has been shown to be effective in treating not only the targeted panic disorder but also in reducing the rates and severity of some co-occurring conditions (191–194).

2. Psychodynamic psychotherapy

The goal of psychodynamic psychotherapy is to achieve remission of panic disorder symptoms through a therapeutic process that encourages exploration of feelings and past and present traumatic experiences. The core principles of psychodynamic psychotherapy are 1) the appreciation that much of mental life is unconscious, 2) childhood experiences in concert with genetic and constitutional factors shape adult personality, and 3) individual symptoms and behaviors may serve multiple functions (195).

Many studies suggest that acute stressors, or "life events," occur just prior to panic disorder onset (196–198). According to psychodynamic theory, the psychological meaning of these events as well as symptoms, behaviors, and coping styles are determined by complex forces that may be unavailable to the patient's conscious awareness (199–201). In patients with panic disorder, one of the goals of psychodynamic psychotherapy is to uncover and understand the thoughts and feelings associated with panic symptoms as well as the unconscious psychological meanings of these panic symptoms, issues that are theorized to be related to separation, autonomy, self-esteem, anger, or aggression. Understanding of transference and interpretation are used to elucidate these issues as well as related interpersonal conflicts. In addition, the therapist attempts to identify and alter core conflicts in order to reduce vulnerability to future panic symptoms (145). Given the highly individualized nature of these thoughts, feelings, and conflicts, the length and intensity of most psychodynamic psychotherapy also tends to be individualized.

In psychodynamic psychotherapy, symptom relief or resolution is theorized to result from emotional growth and understanding of the various developmental and psychological issues that relate to the patient's symptoms. Examples include both conscious and unconscious problems of self-esteem and self-cohesion, unresolved developmental trauma, and psychic conflict (e.g., unacceptable impulses, unrealistic or harsh issues of self-esteem and conscience, unadaptive psychological defenses). The therapist places

the current symptoms in the context of the patient's life history and current realities. The therapist-patient relationship is often used as a vehicle to achieve insightful awareness by bringing the unconscious into consciousness, as well as to facilitate intrapsychic growth. Because psychodynamic therapies are rooted in various psychoanalytic and/or psychodynamic theoretical models, there are a variety of methods for conducting psychodynamic psychotherapy.

Panic-focused psychodynamic psychotherapy is a twice weekly, 12-week manualized treatment program developed by Milrod and associates (145) that has been tested in a randomized controlled trial (146). It focuses on the underlying psychological meaning of panic symptoms and on current social and emotional functioning. Panic-focused psychodynamic psychotherapy is based on the postulate that panic symptoms carry a specific emotional significance that the patient must confront before remission of the panic symptoms can occur. According to this theoretical model, patients with panic disorder are conceptualized as having difficulty separating from important attachment figures and perceiving themselves as autonomous, which is thought to motivate agoraphobic avoidance. The combination of perceiving their environment and relationships as overly dangerous and themselves as inadequate and lacking autonomy triggers high levels of anxiety that perpetuate panic and agoraphobic avoidance. Panic symptoms in turn are thought to reinforce conflicted interpersonal relationships in which the patient feels excessively dependent on significant others and frightened of losing them. Panic-focused psychodynamic psychotherapy focuses on the transference as a mutative therapeutic agent and does not require behavioral exposure to agoraphobic situations. It helps patients to confront the emotional significance of their physical symptoms and recognize that their fears of upcoming catastrophe reflect an internal emotional state rather than reality. Through these techniques, PFPP encourages patients to function more autonomously and may help patients with panic disorder to achieve a greater sense of personal efficacy, yielding improved function and symptomatic relief.

Compared to PFPP, other approaches to psychodynamic psychotherapy often have a wider focus on other psychological and interpersonal issues in the patient's life. These alternative approaches have not been the subject of rigorous research studies. Consequently, evidence for the use of other psychodynamic psychotherapy approaches in panic disorder is limited to case reports and opinions of psychodynamic psychotherapy experts. No studies have compared the efficacy of the different psychodynamic psychotherapy approaches or have compared psychodynamic psychotherapy with other psychosocial treatments in patients with panic disorder.

As with all psychiatric treatments, psychodynamic psychotherapy (including PFPP) should be conducted by appropriately trained therapists, and patients need to understand the rationale, goals, and potential risks and benefits of the treatment. The exploration of memories and important conflicted relationships and the surfacing of unconscious material may sometimes be associated with powerful affects and transient upsets in the therapeutic and other relationships. These occurrences tend to decline in both frequency and intensity as the patient experiences how they relate to and help resolve the symptoms and problems that brought the patient to treatment.

Many patients with panic disorder have complicating co-occurring Axis I and/or Axis II conditions. The broad focus of some forms of psychodynamic psychotherapy may be useful in reducing symptoms or maladaptive behaviors in these associated conditions. For example, some preliminary data showed that PFPP demonstrated superiority to applied relaxation therapy for patients with Cluster C personality disorders, compared to patients without Cluster C personality disorders (202).

Although evidence is limited, psychodynamic techniques have been used in combination with pharmacotherapies or with elements of CBT (145, 203, 204). For example, patients with agoraphobic avoidance may be encouraged to expose themselves to frightening situations and explore the feelings that the exposure aroused to gain a deeper understanding of the conflicts surrounding feared situations. In practice, psychodynamic therapies are often used adjunctively with medication to assist in the resolution of the panic symptoms (204, 205).

3. Supportive psychotherapy

The available evidence suggests that supportive psychotherapy is inferior to standard treatments for panic disorder. One controlled study compared the efficacy of emotion-focused therapy, CBT, imipramine, and pill placebo in patients with panic disorder (147). Emotion-focused therapy was described as a short-term psychotherapy that involved empathic listening and supportive strategies. Emotion-focused psychotherapy was based on the theory that unrecognized emotions (typically triggered by interpersonal situations) trigger panic attacks; therefore, patients were encouraged to explore and process their emotional reactions with the aim of resolving panic symptoms. Results suggested that emotion-focused psychotherapy was less effective than CBT and imipramine in treatment of panic disorder and that its effect was approximately equivalent to that of placebo. Therefore, emotion-focused therapy and other supportive psychotherapies that resemble it cannot be recommended as treatments for panic disorder.

4. Eye movement desensitization and reprocessing

Eye movement desensitization and reprocessing was originally developed as a treatment for posttraumatic stress disorder (206), but it has been studied as a possible treatment for panic disorder. Eye movement desensitization and reprocessing involves reprocessing distressing memories while engaging in guided eye movement. When applied to panic disorder, EMDR targets distressing memories such as the memory of the first panic attack and life events that the patient associates with panic disorder (207).

Empirical data on the use of EMDR in treating panic disorder are limited. In one trial, six sessions of EMDR were superior to a waiting-list control at posttreatment; however, the investigators questioned the clinical significance of the treatment's effect because very few patients who received EMDR showed substantial functional recovery at 3-month follow-up (207). Another study found EMDR to be equivalent in its effects to a credible attention-placebo control (208). Eye movement desensitization and reprocessing therefore cannot be recommended as a treatment for panic disorder at this time.

5. Group therapy

Clinical experience suggests that possible benefits of a group format for treating panic disorder include 1) decreasing shame and stigma by providing experiences with others who have similar symptoms and difficulties; 2) providing opportunities for modeling, inspiration, and reinforcement by other group members; and 3) providing a naturally occurring exposure environment for patients who fear having panic symptoms in social situations. Most approaches to group therapy have not been empirically tested for panic disorder. However, group CBT for panic disorder has been shown to be effective in controlled studies and therefore can be recommended with confidence as a treatment for panic disorder (137, 176–179). When considering a patient for inclusion in a CBT group, the therapist should consider the severity of the patient's panic disorder, co-occurring disorders, level of insight, interpersonal skills, and the patient's preference for a group versus individual format.

There is limited evidence from a small uncontrolled trial for the effectiveness of group mindfulness-based stress reduction for patients with panic disorder (209, 210). This modality includes training in meditation and relaxation strategies. Other types of groups, such as medication support groups, may provide useful adjunctive experiences for patients with panic disorder but have not been tested empirically.

6. Couples and family therapy

Patients with panic disorder have symptoms that can disrupt day-to-day patterns of relationships and may place a family member in a caretaker or rescuer role. Increased dependency needs of patients with panic disorder may lead to frustration in family members, and relationships may be jeopardized. Results are mixed with regard to whether panic disorder is associated with increased incidence of relationship dysfunction or whether relationship dysfunction affects outcome of standard treatments for panic disorder (180).

The scant available literature suggests that marital therapy alone is less effective than established treatments in relieving panic symptoms (211). Based on the available data, couples or family therapy alone cannot be recommended as a treatment for panic disorder. In contrast, partner-assisted exposure therapy for panic disorder has been shown to reduce symptoms of panic disorder in several studies (180). Other studies have documented benefits of including patients' significant others in group-based CBT (177, 212, 213) and of adding couples-based communication training to exposure treatment (214). Therefore, including a significant other in CBT or exposure-based treatment may be a useful approach for some patients.

When pursuing other treatments for panic disorder (e.g., pharmacotherapy), educating significant others about the nature of the disorder and enlisting them to improve treatment adherence may also be helpful. However, no empirical studies of involving partners or family members in other types of treatment have been published.

7. Patient support groups

Patient support groups may be helpful for some patients with panic disorder. Patients who participate in support groups have the opportunity to learn that they are not unique in experiencing panic attacks and to share ways of coping with the illness. Family members of patients with panic disorder also may benefit from the educational aspects of patient support groups. In deciding to refer a patient or family member to a support group, it is important that the psychiatrist obtain information about the nature of the group and the credentials of its leader(s). Support groups are not a substitute for effective treatment; rather, they are complementary.

8. Complementary and alternative treatments

A review of research on a variety of self-help and alternative treatments for anxiety disorders concluded that there was no evidence for efficacy of most of these treatments for panic disorder (215). Treatments evaluated included natural products (e.g., kava, St. John's wort, inositol), other physical treatments (e.g., acupuncture, massage), and lifestyle treatments (e.g., yoga, relaxation). Most of the treatments had never been formally tested in patients with panic disorder. Very preliminary support is available

for the efficacy of the glucose isomer inositol in treatment of panic disorder; however, inositol is rarely used clinically, and more extensive clinical research is necessary to establish its efficacy (216, 217). Evidence of efficacy has also been found for relaxation training (215). Although one controlled study found applied relaxation to be as effective as CBT and exposure therapy (218), a recent meta-analysis suggested that relaxation training is less effective than CBT for patients with panic disorder (219).

H. SPECIFIC PHARMACOLOGICAL INTERVENTIONS

Because medications from four classes—SSRIs, SNRIs, TCAs, and benzodiazepines—are roughly comparable in efficacy, the decision regarding which medication to choose for panic disorder mainly involves considerations of side effects, cost, prior treatment history, the presence of co-occurring general medical and other psychiatric conditions, and the strength of the evidence base for the particular medication in treatment of panic disorder. Medication choice can also be influenced by pharmacological properties such as medication half-life, drug metabolism (e.g., effects of cytochrome P450 isoenzymes), and the potential for drug interactions. These latter factors are particularly important when treating older adults and individuals taking multiple medications.

Selective serotonin reuptake inhibitors or SNRIs are likely to be the best choice of pharmacotherapy for many patients with panic disorder, though SSRIs have a larger evidence base and are more likely to be chosen as a first-line treatment. Although SSRIs and SNRIs do carry a risk of sexual side effects, they lack the significant cardiovascular and anticholinergic side effects associated with TCAs, which are particularly troublesome for older patients and for patients with general medical conditions. Although cost was previously a concern, most SSRIs are now available in less expensive generic forms. For patients with co-occurring depression, SSRIs, SNRIs, and TCAs are preferable to benzodiazepines as monotherapies because, in contrast to benzodiazepines, these agents will likely alleviate the depressive symptoms. Because they have no liability for abuse, SSRIs, SNRIs, and TCAs are also preferable to benzodiazepines in individuals with current or prior substance use disorders.

Benzodiazepines are often used for treatment of panic disorder, and some studies suggest that these medications are still used with greater frequency than the SSRIs (220). Although consideration must be given to potential side effects of benzodiazepines (e.g., sedation, memory difficulties, increased rates of falls or motor vehicle accidents), one advantage of benzodiazepines is their earlier onset of action as compared to antidepressants (101, 221). Because demonstration of some improvement often takes 4–6 weeks with SSRIs, SNRIs, and TCAs, benzodiazepines may be useful for patients with very distressing or impairing symptoms in whom rapid symptom control is critical. Furthermore, several studies suggest that the short-term (4–6 week) addition of benzodiazepines (alprazolam and clonazepam) to antidepressants produces a more rapid therapeutic response (100, 222, 223). Consequently, benzodiazepines may be used along with antidepressants to help control symptoms until the antidepressant takes effect, followed by slow tapering of the benzodiazepine. With benzodiazepines, the benefit of more rapid response to treatment must be balanced against the possibility that the patient may have difficulty tolerating the tapering and discontinuation of benzodiazepine; with ongoing use, all benzodiazepines will produce physiological dependence in most patients. To reduce the possibility of physiological dependence, psychiatrists sometimes prescribe benzodiazepines on an as-needed (p.r.n.) basis. Unfortunately, this practice has a number of adverse effects. Irregular use promotes fluctuating blood levels that may aggravate anxiety. One study also showed worse CBT outcomes in participants using benzodiazepines on a p.r.n. basis compared to those taking benzodiazepines on a regular schedule and those not taking benzodiazepines (224). Because many individuals may end up taking as-needed medication on an almost daily basis, it may be preferable to encourage regular use rather than use linked to or associated with surges of anxiety.

Once an initial pharmacotherapy has been selected, patients are typically seen every 1–2 weeks when first starting a medication, then every 2–4 weeks until the dose is stabilized. After the dose is stabilized and symptoms have decreased, patients will most likely require less frequent visits.

When implementing treatment with SSRIs, SNRIs, and TCAs, it is helpful to educate patients about the likely time course of treatment effects. In addition, some patients with panic disorder may be hypersensitive to medication side effects at treatment initiation. Thus, it is recommended that starting doses of SSRIs, SNRIs, and TCAs be approximately half of those given to depressed patients (225). The low dose is maintained for several days then gradually increased to a full therapeutic dose over subsequent days and as tolerated by the patient.

Table 5 summarizes usual dosing for antidepressant and benzodiazepine pharmacotherapy for panic disorder.

With antidepressant medications, concerns have been raised about the potential for treatment-related increases in self-harming or suicidal behaviors. Based primarily on data in children and adolescents (226), the FDA has issued warnings that apply to all antidepressants, which indicate that the risk of increased suicidal thinking and behavior in patients under the age of 25 must be balanced with the clinical need for pharmacotherapy (227). No deaths from suicide oc-

TABLE 5. Dosing of Antidepressants and Benzodiazepines for Panic Disorder

	Starting Dose and Incremental Dose (mg/day)	Usual Therapeutic Dose (mg/day)[a]
SSRIs		
Citalopram	10	20–40
Escitalopram	5–10	10–20
Fluoxetine	5–10	20–40
Fluvoxamine	25–50	100–200
Paroxetine	10	20–40
Paroxetine CR	12.5	25–50
Sertraline	25	100–200
SNRIs		
Duloxetine	20–30	60–120
Venlafaxine ER	37.5	150–225
TCAs		
Imipramine	10	100–300
Clomipramine	10–25	50–150
Desipramine	25–50	100–200
Nortriptyline	25	50–150
Benzodiazepines		
Alprazolam	0.75–1.0[b]	2–4[b]
Clonazepam	0.5–1.0[c]	1–2[c]
Lorazepam	1.5–2.0[b]	4–8[b]

[a]Higher doses are sometimes used for patients who do not respond to the usual therapeutic dose.
[b]Usually split into three or four doses given throughout the day.
[c]Often split into two doses given morning and evening.

curred in any of the pediatric clinical trials, but pooled analyses of 24 placebo-controlled trials of nine antidepressants in pediatric patients with a variety of psychiatric disorders showed a risk of suicidal thinking and behavior during the first few months of antidepressant treatment that was approximately twice that of patients receiving placebo (4% in the active treatment groups vs. 2% in the placebo groups) (226, 228, 229). A more recent meta-analysis suggested that benefits of antidepressant treatment were greater than the risks of increased suicidal ideation or behaviors across indications, including anxiety disorders (230). In adults, antidepressant treatment does not appear to be associated with an increase in suicide risk per se (227, 231, 232).

Although some evidence from meta-analyses of randomized controlled trials (primarily in patients with depression) suggests an increased likelihood of self-harming behaviors (231) or suicide attempts (233), these results may be confounded by the difficulty in calculating precise suicide risks from meta-analytic data (234). In a pooled analysis of placebo-controlled trials involving adults with major depressive disorder or other psychiatric disorders that included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in more than 77,000 patients, a reduction of suicidal thinking and behavior was seen in adults older than age 65 years who received antidepressants, compared to placebo, and adults between ages 25 and 65 years showed no change in risk with antidepressant treatment (227). Furthermore, studies using other methods showed no increases in the likelihood of suicide or suicide attempts with antidepressant treatment (235–237), and an additional study noted a small increase in the likelihood of self-harm but no increase in the risk of suicide (238). In addition, most, but not all (239, 240) studies of the relationship between antidepressant prescription rates and rates of suicide and suicide attempts suggest that increases in SSRI prescriptions are associated with decreases in suicide and suicide attempt rates in a variety of patient populations (241–248) and that decreases in SSRI prescriptions are associated with increases in suicide rates (249). Nevertheless, it is conceivable that side effects (e.g., anxiety, agitation, insomnia, irritability) may increase the chance of self-harming behaviors in some individuals (234, 250). Thus, careful monitoring for such side effects as well as for evidence of self-harming or suicidal thoughts or behaviors is important in adults as well, particularly in the early phases of treatment and after increases in antidepressant dose. Against

these small risks, the benefits of antidepressant treatment must always be considered (230, 251–253) and weighed against the corresponding risks and benefits of other options for the treatment of panic disorder. Additional information may be found at the web sites of the FDA (http://www.fda.gov/cder/drug/antidepressants/default.htm), the APA (http://www.psych.org), and the American Academy of Child and Adolescent Psychiatry (http://www.aacap.org).

1. Selective serotonin reuptake inhibitors

Six SSRIs are now available in the United States: fluoxetine, sertraline, paroxetine (immediate release [IR] and controlled release [CR] formulations), fluvoxamine, citalopram, and escitalopram. Numerous clinical trials have shown that each of them is effective for panic disorder, and three—fluoxetine, sertraline, and paroxetine (both IR and CR)—carry FDA approval for this indication. There is no evidence of differential efficacy between agents in this class, although differences in side-effect profile (e.g., potential for weight gain, discontinuation-related symptoms), drug half-life, propensity for drug interactions, and availability of generic formulations may be clinically relevant (254, 255).

Recommended starting and therapeutic doses are summarized in Table 5. As is the case with TCAs, some patients with panic disorder experience an initial feeling of increased anxiety, jitteriness, shakiness, and agitation when beginning treatment with an SSRI. For that reason, the initial dose should be lower than that usually prescribed to patients with depression. The recommended starting doses for SSRIs are as follows: 10 mg/day or less of fluoxetine, 25 mg/day of sertraline, 10 mg/day of paroxetine IR, 12.5 mg/day of paroxetine CR, 50 mg/day of fluvoxamine, 10 mg/day of citalopram, and 5–10 mg/day of escitalopram. Although some patients may respond to lower doses and some may require higher doses for response, clinical trials suggest that the following are therapeutic doses for the SSRIs: 10–20 mg/day of fluoxetine (74), 20–40 mg/day of paroxetine (73), 50–200 mg/day of sertraline (76), 100–150 mg/day of fluvoxamine (256), 20–30 mg/day of citalopram (71), and 10 mg/day of escitalopram (86). It is recommended that the initial low dose of the SSRI be maintained for approximately 3–7 days, then gradually increased (e.g., in weekly increments) to a more standard daily dose, adjusting the timing of titration to the individual patient's tolerability (257). Because elimination of SSRIs involves hepatic metabolism, doses may need to be adjusted for patients with liver disease.

Abrupt discontinuation of SSRIs (or SNRIs) can lead to a discontinuation syndrome with neurosensory (e.g., paresthesias, shock-like reactions, myalgias), neuromotor (e.g., tremor, unstable gait, visual disturbances), gastrointestinal (e.g., nausea, diarrhea), neuropsychiatric (e.g., anxiety, irritability), vasomotor (e.g., diaphoresis, flushing), and other manifestations (e.g., insomnia, fatigue, dizziness, headache) (85, 258). Selective serotonin reuptake inhibitors with very long half-lives (e.g., fluoxetine) are less likely to be associated with this discontinuation syndrome. Symptoms of SSRI discontinuation syndrome typically begin within 24 hours, peak about 5 days after withdrawal, and generally resolve within 2 weeks (67, 259). Tapering SSRIs over at least 7–10 days, or a longer period if clinical circumstances permit, can minimize the risk of SSRI discontinuation syndrome. If discontinuation symptoms do occur, reinstatement of the medication at the previous dosage level for a few days, followed by a return to an even slower taper schedule, is the preferred course of action.

In terms of significant side effects, SSRIs are safer than TCAs and MAOIs. They are rarely lethal in overdose and have few serious effects on cardiovascular function. Because they lack clinically significant anticholinergic effects, they can be prescribed to patients with prostatic hypertrophy or narrow-angle glaucoma. The most common side effects of SSRIs are headaches, irritability, nausea and other gastrointestinal issues, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness, and tremor. Some of these effects (e.g., nausea) are usually transient, lasting 1–2 weeks. Others (e.g., sexual dysfunction) commonly last for the duration of treatment. Side effects of SSRIs are highly individualized. For example, a particular SSRI may cause insomnia in one patient but somnolence in another. Thus, although comparative studies may tend to favor one medication over another for a particular side effect, a given patient may still experience that particular side effect. Fortunately, there are several SSRIs on the market, and it is usually possible to find one that the patient can tolerate well; this may require a process of engaging in several therapeutic trials until the optimal medication is found for a given patient.

There are scattered reports in the literature of extrapyramidal side effects, but these have not been observed in large multicenter trials and may be idiosyncratic. Some evidence suggests that SSRIs may be associated with an increased likelihood of upper gastrointestinal bleeding, particularly when taken in combination with NSAIDs or with aspirin (260, 261). Use of SSRIs also has been found to be associated with low bone mineral density in male patients age 65 years and older (262), increased rate of bone loss at the hip in older female patients (263), and increased risk of falls and of osteoporotic fractures in patients age 50 years and older (264, 265). In addition, as described earlier in Section II.H, the FDA has warned of the possibility that SSRIs and other antidepressants may increase the risk of suicidal ideation and behavior in patients age 25 years and younger (227).

2. Serotonin-norepinephrine reuptake inhibitors

Venlafaxine ER has been shown to be effective for panic disorder and has FDA approval for this indication (88, 89). Venlafaxine ER has been shown to be effective in the range of 75 to 225 mg/day. As with SSRIs and TCAs, venlafaxine and venlafaxine ER should be initiated gradually to reduce the likelihood of side effects: as described in Table 5, dosing is often initiated at 37.5 mg for the first 3–7 days, then increased to a minimum of 75 mg/day. Although increasing the dose after initial nonresponse or partial response to 150 mg/day is clinically recommended, the timing of such increase or the effectiveness of increasing the dose in those with initial poor or partial response has not been systematically studied. The level of initial response and tolerability should be taken into consideration. In clinical practice, some patients require and tolerate higher doses. Titration to these higher doses should be done gradually, and potential side effects, including blood pressure elevations should be monitored carefully.

Venlafaxine ER is generally well tolerated and has a side effect profile similar to the SSRIs. The most common side effects of SNRIs in studies of panic disorder include nausea, dry mouth, constipation, anorexia, insomnia, sweating, somnolence, tremor, and sexual dysfunction. Because a small proportion of individuals may develop sustained hypertension, an effect that may be dose related, it is reasonable to assess blood pressure prior to and during treatment, particularly when venlafaxine ER is titrated to higher doses. In addition to the concerns and debate regarding the relationship between antidepressants and increased suicidality, described earlier in Section II.H, some observational studies found that venlafaxine ER was associated with higher rates of lethal overdose than SSRIs (266–268). However, later studies suggested that this finding may be attributable to confounding patient factors (e.g., patients prescribed venlafaxine displayed more pretreatment suicide risk factors) (269, 270).

No systematic data are currently available supporting the use of another SNRI, duloxetine, in panic disorder, although its mechanism of action, which is similar to that of venlafaxine, suggests it might be an effective agent.

Abrupt discontinuation of SNRIs can produce a discontinuation syndrome similar to that associated with SSRIs. Symptoms can include dizziness, headache, and nausea (271). Tapering the SNRI over at least 7–10 days, or a longer period if clinical circumstances permit, can minimize the risk of a discontinuation syndrome.

3. Tricyclic antidepressants

Imipramine is effective for panic disorder and is the most well studied of the TCAs (90–92, 94–102, 104, 105, 107, 108, 111). Clomipramine also has considerable empirical support (70, 72, 79, 93, 102, 103, 109, 110). Although few controlled studies have evaluated other TCAs for panic disorder, those that have are generally supportive of the efficacy of desipramine (106) and nortriptyline (112). Given the equivalency of TCAs in treating depression, there is little reason to expect other TCAs to work less well for panic disorder. However, TCAs that are more noradrenergic (e.g., desipramine, maprotiline) may be less effective than agents that are more serotonergic (272).

Psychiatrists have often noticed, and research studies have occasionally shown, that some patients with panic disorder are hypersensitive to both the beneficial and adverse effects of TCAs (91, 106). Patients sometimes experience a stimulating response, including anxiety, agitation, or insomnia, when treatment with antidepressant medication of any class is initiated. For this reason, it is recommended that, similar to the SSRIs and SNRIs, TCAs be started for patients with panic disorder at doses substantially lower than those for patients with depression or other psychiatric conditions. One common strategy is to begin with only 10 mg/day of imipramine or its equivalent and gradually titrate the dose upward over the ensuing weeks.

Few studies have rigorously addressed the optimum dose of TCAs for panic disorder. Results of clinical trials suggest that it is reasonable to titrate the imipramine dose of patients with panic disorder to approximately 100 mg/day and wait for at least 4 weeks to see whether there is a response. If tolerated, the dose can then be increased to as high as 300 mg/day if initial response is either absent or inadequate (108). Evidence suggests that clomipramine may be effective in somewhat lower doses than imipramine; clomipramine can generally be used effectively in doses ranging from 50 to 150 mg/day (93, 102). Although there is no evidence of a correlation between blood levels of TCAs and clinical response in panic disorder, blood level monitoring may be helpful for patients who display inadequate response despite seemingly adequate doses or for patients who display signs of toxicity despite doses that are in the therapeutic range.

The most common side effects of TCAs as reported in clinical trials for panic disorder are 1) anticholinergic effects, including dry mouth, constipation, difficulty urinating, increased heart rate, and blurry vision; 2) increased sweating; 3) sleep disturbance; 4) orthostatic hypotension and dizziness; 5) fatigue and weakness; 6) cognitive disturbance; 7) weight gain, especially for long-term users; and 8) sexual dysfunction (273). Higher doses of TCAs are associated with a higher dropout rate in research studies (108), and one naturalistic follow-up study found that one-third of patients prescribed TCAs discontinued them because of side effects (274).

Tricyclic antidepressants should not be prescribed for patients with panic disorder who also have acute narrow-

angle glaucoma or clinically significant prostatic hypertrophy. The risk of falls may be increased by TCAs, particularly among elderly patients, because of orthostasis. Because patients with preexisting cardiac conduction abnormalities may experience significant or fatal arrhythmia with TCA treatment (275), a baseline electrocardiogram should be considered before initiating a TCA. Overdoses with TCAs can lead to significant cardiac toxicity and fatality (275). For this reason and because of the concerns and debate regarding the relationship between antidepressants and increased suicidality (see discussion earlier in Section II.H), TCAs should be used judiciously in suicidal patients.

4. Benzodiazepines

Alprazolam has the largest number of clinical trials supporting its efficacy for treatment of panic disorder and is FDA approved for this indication (104, 116, 118, 122, 123, 126, 276, 277). The data support the efficacy of alprazolam in treating multiple dimensions of illness (i.e., preventing panic attacks, reducing anticipatory anxiety and avoidance) in patients with panic disorder. However, because of its short half-life, frequent (3–4 times daily) dosing is required, which creates practical difficulty for many patients and results in more rapid and profound withdrawal symptoms with missed doses. A sustained-release form of alprazolam is also FDA approved based on two placebo-controlled studies (125, 129). Although this formulation is approved for once daily dosing, clinical experience suggests that twice daily dosing of alprazolam, sustained release, may be required to maximize efficacy.

It is necessary to be flexible in choosing the alprazolam dose for an individual patient. Most patients require three to four doses per day to avoid breakthrough or rebound symptoms, although some may achieve symptom control with two doses of alprazolam per day. For patients who have not taken alprazolam in the past, the starting dose should be 0.25 mg three or four times daily. The dose should be titrated up to 2–3 mg/day over the first week or two, but an increase to as high as 5–6 mg/day may in rare instances be necessary to obtain symptom control. Although the literature on alprazolam, sustained release, is much more sparse, most studies have tested doses in the range of 2–4 mg/day. The manufacturer's recommendation for alprazolam treatment of panic disorder notes that doses above 4 mg/day are usually necessary and that doses up to 10 mg/day are sometimes required. However, very few studies have empirically evaluated dose requirements, and those studies that have been conducted have produced mixed results regarding the advantages of higher doses (e.g., 6 mg/day) over lower doses (e.g., 2 mg/day) (95, 278).

Clonazepam is also FDA approved for the treatment of panic disorder, and several clinical trials support its efficacy (122, 131, 132). Its longer half-life results in less severe withdrawal symptoms with missed doses and usually allows once or twice a day administration. These factors lead some psychiatrists to prefer clonazepam over other benzodiazepines for the long-term maintenance treatment of panic disorder, largely because of the ease of clonazepam dosing.

For patients without prior clonazepam treatment, starting doses are usually in the range of 0.5–1 mg/day and may be titrated to higher doses as needed. Studies of clonazepam suggest that daily doses of 1–2 mg offer the best balance of therapeutic benefits and side effects. These doses are the equivalent of 2–4 mg of alprazolam or less. Patients can usually be switched from alprazolam to clonazepam by taking the total daily alprazolam dose in milligrams and administering half that daily dose in milligrams of clonazepam (usually as twice daily or bedtime-only treatment).

Results of several studies suggest a relationship between alprazolam and clonazepam blood levels and treatment response (279–281). In patients who do not respond to usual dose titrations, dose adjustment may be facilitated by monitoring of alprazolam and clonazepam blood levels, although this is rarely done.

Additional studies suggest that other benzodiazepines (e.g., diazepam, lorazepam), when given in equivalent doses, may be as effective as alprazolam in the treatment of panic disorder (113–116, 119–121, 124, 127, 128, 130, 282).

In general, benzodiazepines seem to be well tolerated by patients with panic disorder, with very few serious side effects. When side effects of benzodiazepines do occur in patients with panic disorder, they appear similar to those reported when benzodiazepines are used for other indications. Side effects include primarily sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness. Geriatric patients taking benzodiazepines may be at higher risk for falls and fractures because of these side effects (283–287).

Because of an increased risk of motor vehicle accidents in association with benzodiazepine use (288), patients should be warned about driving or operating heavy machinery while taking benzodiazepines, particularly when these medications are started or with dose increases. Patients should also be advised about the additive effects of benzodiazepines and alcohol, in particular combined sedative and respiratory effects. Although patients may be able to safely drink small amounts of alcohol, they should consume alcohol slowly and exercise extra caution when doing so (e.g., avoid operating vehicles).

For patients in stable recovery from substance use disorders, there is not an absolute contraindication to benzodiazepine use, but the decision to use benzodiazepines should be made cautiously. In patients in early remission or with active substance use disorders, concerns regarding potential misuse of the benzodiazepine or relapse of the substance use disorder are greater; in these circumstances other treatments for panic disorder that have a lower abuse potential are recommended for first-line use (289–291). If benzodiazepines are felt to be necessary after careful consideration of other treatment options, the psychiatrist should closely monitor their use (e.g., dispense in limited quantities and on a time-limited basis, supervise medication administration, track prescription refills or use pill counts to assess medication adherence, increase office visit frequency to monitor the ongoing medical necessity for and the patient's response to the medication). In addition, selection of an agent that is more slowly absorbed (e.g., oxazepam, clorazepate) may limit the potential for abuse (291).

Cognitive effects of benzodiazepines have been the subject of debate and some empirical research (292–294). It is clear that benzodiazepines at higher doses can cause memory impairment (101). One meta-analysis concluded that long-term benzodiazepine users performed worse than control participants on numerous domains of cognitive functioning (295). However, another review concluded that the literature as a whole does not provide convincing evidence of cumulative long-term cognitive effects of benzodiazepines in anxious patients (296). Nevertheless, patients should be monitored for the development of cognitive impairment, which may be more problematic at higher doses and in patients performing complex information-processing tasks at work. Caution is indicated when prescribing benzodiazepines to elderly patients or those with preexisting cognitive impairment.

5. Other antidepressants

Monoamine oxidase inhibitors are widely regarded as effective for panic disorder. However, there have been virtually no studies involving the use of MAOIs for panic disorder since the introduction of the panic disorder diagnosis in DSM-III in 1980. One study included patients with what would now be called panic disorder and found phenelzine to be effective (297). The commonly held belief that MAOIs are actually more potent antipanic agents than TCAs has never been convincingly proven in the scientific literature and is only supported by clinical anecdote. There has been considerable clinical interest in medications that are reversible inhibitors of monoamine oxidase A, because these medications do not generally require adherence to the low-tyramine diet that is mandatory for patients treated with phenelzine, tranylcypromine, or isocarboxazid. However, none of these medications is currently approved for use in the United States in either oral or patch form, although moclobemide is available in other countries, including Canada. Four studies have examined the effectiveness of moclobemide in panic disorder, and the results are mixed and only modestly encouraging (298–301). Although the monoamine oxidase B inhibitor selegiline is available in the United States, there are no data to support its efficacy for the treatment of panic disorder.

Doses of phenelzine in controlled trials for illnesses that resemble panic disorder have tended to be low, often no higher than 45 mg/day (297, 302). Some authors have commented that higher doses may be more effective. Doses of phenelzine up to 90 mg/day and of tranylcypromine up to 60 mg/day are said by experienced psychiatrists to be necessary for some patients with panic disorder. Patients rarely get significant benefit before several weeks have elapsed, and periods up to 12 weeks may be necessary before the full effectiveness of the medication can be judged. No maintenance studies of MAOIs for panic disorder have been published. Hence, the optimal length of treatment that provides the least chance of relapse has not been established.

Adverse effects are a major concern with MAOIs, and these medications are generally reserved for use when a patient has not responded to several other treatments. The complexity of these medications suggests that they should be prescribed by physicians with experience in monitoring MAOI treatment. A major risk of taking an MAOI is the induction of a hypertensive crisis with ingestion of tyramine. Hence, patients taking phenelzine or tranylcypromine must adhere to a special low-tyramine diet (303). Certain medications, including but not limited to sympathomimetic amines and decongestants, can also precipitate a hypertensive crisis and must not be used with MAOIs. Another serious drug-drug interaction to be avoided is the "serotonin syndrome," which can be fatal and is characterized by confusion, agitation, hyperthermia, and other autonomic unstable vital signs (e.g., shivering, diaphoresis, nausea, diarrhea) and neuromuscular signs (e.g., tremor, hyperreflexia, clonus, myoclonus, ataxia) (304). Serotonin syndrome can occur when MAOIs are used with other antidepressants (particularly SSRIs); the antibiotic linezolid; the analgesics meperidine, fentanyl, and tramadol; the over-the-counter medication dextromethorphan; and other medications acting on serotonin such as buspirone, fenfluramine, sibutramine, and the anti-migraine triptan medications (305, 306). Even when the risks of hypertensive crises and serotonin syndrome are obviated by strict adherence to dietary and medication restrictions, MAOIs have substantial adverse effects. These

include hypotension (sometimes leading to syncope), weight gain, sexual dysfunction, paresthesia, myoclonic jerks, dry mouth, edema, and a paradoxical syndrome of excessive daytime sleepiness, nocturnal insomnia, and shorter sleep length.

There is minimal support for the use of trazodone in panic disorder. It appears less effective than imipramine and alprazolam and does not enhance outcome when used to augment CBT (221, 307, 308). Although there are a few small uncontrolled studies showing benefits of nefazodone in some patients with panic disorder (309–311), its use has been limited by concerns about liver toxicity (312). Thus, neither trazodone nor nefazodone can be recommended as a first-line treatment for panic disorder.

Bupropion (including extended release formulations) was effective in one small trial (313) and ineffective in another (314). Although it might be useful in some cases, given the limited and mixed systematic data regarding its efficacy, bupropion cannot be recommended as a first-line treatment for panic disorder.

A few open short-term studies support the potential efficacy of mirtazapine for panic disorder (315–319), and a comparison of mirtazapine and paroxetine in a very small randomized controlled trial involving 27 patients suggested similar efficacy of the two medications (320). However, mirtazapine should not be considered a first-line treatment for panic disorder because tolerability issues have been noted, with common side effects including somnolence and weight gain. In addition, there are no available data from large controlled studies supporting its efficacy in panic disorder.

The concerns and debate regarding the relationship between antidepressants and increased suicidality have been reviewed earlier in Section II.H and may apply to the other antidepressants discussed in this section.

6. Other agents

a. Anticonvulsants

There are limited data concerning the use of anticonvulsant medications in the treatment of panic disorder. One randomized controlled trial of gabapentin provided partial support for its efficacy and safety in panic disorder (321), but no further research has been conducted. Thus, gabapentin should not be considered a first-line treatment but may be useful in individual circumstances, either alone or as an adjunct to antidepressants. Small open-label studies have suggested that valproic acid may benefit some patients with panic disorder (322–324), but this medication has significant side effects (325), and controlled investigations are needed before it can be recommended. One small open-label study of levetiracetam (326) and very preliminary case report data for tiagabine (327) and vigabatrin (327) suggest that these agents may be worthy of further study in panic disorder. However, controlled trials are needed before any of these medications can be recommended as treatments for panic disorder. A small placebo-controlled trial suggested that carbamazepine was not effective for panic disorder (328).

b. Antipsychotic agents

First-generation (i.e., typical) antipsychotic medications are rarely appropriate in the treatment of panic disorder. There is no evidence that they are effective, and the risk of neurological side effects outweighs any potential benefit. Among the second-generation (i.e., atypical) antipsychotics, there is limited positive evidence for olanzapine (329) and adjunctive risperidone (330), suggesting the possibility that second-generation antipsychotics may be useful for patients with severe, treatment-resistant panic disorder. At present, however, evidence for efficacy is limited, and there is growing concern about side effects of second-generation antipsychotics, including weight gain, poor glycemic control, and metabolic syndrome (331). Consequently, at this time these agents cannot be broadly recommended for patients with panic disorder, although they may have a role in individual circumstances.

c. Antihypertensives

The available scant literature suggests that beta-adrenergic blocking agents (e.g., propranolol, atenolol) are ineffective for panic disorder (115, 332, 333). However, these agents continue to be used occasionally by psychiatrists who have observed that they can help reduce somatic sensations (e.g., palpitations) in some patients. There is limited evidence supporting the potential efficacy of a particular beta-blocker, pindolol, as augmentation for patients with SSRI-resistant panic disorder (334). Given the frequent side effects associated with beta-adrenergic blocking agents (e.g., fatigue, sleep disturbance, and possibly, the worsening of depression), these agents should not be considered in the routine treatment of panic disorder.

Although historically there was interest in treating panic attacks with calcium channel blockers, they are rarely used clinically, and efficacy data are very limited (335). Similarly, there are limited data suggesting clonidine may have mild and/or transient effects only (336, 337). Thus, calcium channel blockers and clonidine cannot be recommended as first-line or adjunctive treatments for panic disorder.

d. Buspirone

The available data suggest that buspirone monotherapy is not effective for panic disorder (338, 339) and does not enhance the efficacy of CBT (340). Although it is some-

times used clinically in individual circumstances as an augmentation strategy for patients with panic disorder, there are no published data except case reports (341) to support this practice.

I. MAINTAINING OR DISCONTINUING TREATMENT AFTER RESPONSE

There are few data on optimum length of treatment following response. Studies of acute treatment for panic disorder have been conducted over 6–12 weeks, with some studies including long-term follow-up periods of 1 to 2 years. Studies of CBT (which include some of the longer follow-up intervals) suggest that the majority of patients maintain benefits derived from a short-term course of CBT. Some clinical trials have included several months of maintenance CBT (i.e., monthly "booster sessions" focused on relapse prevention), which may have helped sustain positive response to CBT. However, the incremental benefit of periodic booster sessions has yet to be empirically proven. In general, CBT can be discontinued after 10–15 sessions (or sooner if the patient responds quickly) with specific instructions for continued independent practice of CBT skills. Many clinicians and patients also find addition of several monthly booster sessions useful.

With each of the antidepressant medications, therapeutic effects are generally maintained for as long as medication is continued. For responders to an SSRI or a TCA, clinical experience and some data suggest that continuing treatment for 6 months or more after acute response can lead to further symptom reduction and decreased risk of recurrence (70, 85, 99, 104, 342, 343). Although no empirical data are available addressing this question, clinical experience suggests patients with treatment-resistant panic disorder or prior relapse with treatment discontinuation may require longer term treatment. For venlafaxine ER, there are minimal systematic data addressing the optimum length of treatment following response, although discontinuation of venlafaxine ER after only 12 weeks of treatment has been shown to result in an increased likelihood of relapse (344).

Before advising a taper of effective medication, the psychiatrist should consider whether the patient is currently motivated to discontinue the medication as well as the duration of the patient's symptom remission. The timing of medication discontinuation is often influenced by factors such as the presence of psychosocial stressors or supports, the stability of co-occurring conditions, and the availability of alternative treatment options. Discussion of medication taper should also include the possible outcomes of tapering, which include the potential recurrence of panic symptoms, potential withdrawal symptoms, or both. If medication is tapered, it should be done in a collaborative manner with continual assessment of the effects of the taper and the patient's responses to any changes that emerge. Similarly, discontinuation of psychosocial treatment should be planned collaboratively with the patient. Before terminating treatment, clinicians providing CBT help patients develop personalized relapse prevention plans. They also frequently offer patients the option of scheduling "booster sessions" focused on maintaining and enhancing treatment gains.

If an SSRI, SNRI, or TCA is to be discontinued, most psychiatrists and patients prefer to taper medications over a period of several weeks or months. This both allows for an opportunity to monitor for the possible reemergence of panic symptoms as well as decreases the likelihood of discontinuation effects, particularly for those patients who are taking higher doses or after prolonged use. However, under more urgent conditions (e.g., the patient is pregnant and wants to discontinue medications immediately), these medications can be discontinued much more quickly.

There are fewer data examining the issue of benzodiazepine discontinuation, but existing studies support continuing benzodiazepine treatment to prevent recurrence (99, 104). Clinical experience also suggests that many patients can be maintained with stable doses of benzodiazepines for many years with no recurrence of symptoms. Although major concerns about benzodiazepine tolerance and withdrawal have been raised, there is no evidence for significant dose escalation in patients with panic disorder or with long-term benzodiazepine use (294, 345–347).

The approach to benzodiazepine discontinuation also involves a gradual tapering of dose. Withdrawal symptoms and symptomatic rebound are commonly seen with benzodiazepine discontinuation, can occur throughout the taper, and may be especially severe toward the end of the taper. This argues for tapering benzodiazepines very slowly for patients with panic disorder, probably over 2–4 months and at rates no higher than 10% of the dose per week (348–350). Although is it commonly believed that benzodiazepines with shorter half-lives produce more severe withdrawal symptoms than those with longer half-lives, most studies suggest that half-life is less of a factor than the use of a gradual taper schedule (126, 351). In addition, withdrawal symptoms can occur after relatively short-term periods of treatment and have been observed after as little as 6–8 weeks of treatment with alprazolam (352). The likelihood of discontinuation effects may be increased in patients with panic disorder who have traits such as high anxiety sensitivity and high levels of avoidance (353); for such patients, close monitoring should be performed and special care should be taken during the discontinuation process. Cognitive-behavioral therapy, which counteracts tendencies to

amplify bodily sensations and catastrophize discontinuation symptoms, has been found to effectively facilitate withdrawal from benzodiazepines (354–357).

There is also some evidence for the utility of concurrent psychotherapy to maintain response after discontinuation of antidepressants. One small controlled study showed that combining brief psychodynamic psychotherapy and clomipramine reduced the likelihood of relapse of panic disorder after clomipramine discontinuation (156). Furthermore, in a meta-analysis of antidepressant pharmacotherapy and psychotherapy (in which nearly all psychotherapy studies administered CBT), combination treatment was more effective than antidepressants alone after treatment had been withdrawn (160).

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

The following sections review data pertinent to the treatment of individuals with panic disorder who have specific clinical features that may alter the general treatment considerations that are discussed in Sections II.B through II.I. These sections are necessarily brief and are not intended to stand alone as a set of treatment recommendations. The recommendations reviewed in Sections II.B through II.I, including the use of psychiatric management, generally apply unless otherwise indicated.

A. PSYCHIATRIC FACTORS

1. Suicidality

The relationship between panic disorder and suicide is a controversial topic. Determining whether specific suicide risks are associated with panic disorder has been complicated by the frequency of co-occurring disorders that are themselves associated with increases in suicide risk. From a logical perspective, it can be difficult to reconcile how a patient with panic disorder who manifests a strong fear of dying could also experience a wish to die. However, panic disorder can be a severely distressing condition that motivates suicidal thoughts and behaviors in some patients. Evidence exists that panic disorder may contribute to an increased risk of suicidality. Because risk factors for suicide may differ from those for suicidal ideation and suicide attempts, we will review these areas separately.

Early studies, summarized in a meta-analysis by Harris and Barraclough (358), demonstrated that panic disorder was associated with a 10-fold increase in mortality due to suicide. However, individuals with panic disorder are identified in a relatively small proportion of suicides. For example, a psychological autopsy study of 1,397 suicides in Finland found that only 1.22% met the criteria for DSM-III-R panic disorder (359). These low rates may relate to an underreporting of panic disorder symptoms in such studies, because of masking of panic disorder symptoms by substance use (360) or by affective symptoms. Even in individuals identified in psychological autopsies as having panic disorder, co-occurring mood, substance use, and personality disorders are the norm (359, 361). In individuals with panic disorder who are studied longitudinally, co-occurring disorders are almost always present in those who die by suicide (362, 363). Additional evidence suggests that the presence of co-occurring panic attacks may be associated with an increase in suicide risk among individuals with major depression, particularly early in the course of illness (364). In summary, the evidence is mixed as to whether panic disorder and panic attacks are associated with an increased risk of suicide in and of themselves or whether the apparent increase in associated risk is related to co-occurring mood and substance use disorders.

It is similarly controversial whether panic disorder is independently or uniquely associated with suicidal ideation or suicidal attempts (i.e., after adjusting for co-occurring mental disorders, especially major depression) (365, 366). Some studies have noted an association of panic disorder with suicidal behavior even after adjusting for effects of co-occurring mental disorders (44), whereas other studies have not found these results (365, 366). Overall, however, most (44, 367–371) but not all (372) research with cross-sectional clinical and community samples has demonstrated that panic disorder and panic attacks are associated with suicidal ideation and suicide attempts. Substantial rates of suicidal ideation and attempts as well as high frequencies of co-occurring disorders have also been observed in smaller studies of patients with panic disorder in a variety of settings (369, 373–376).

The association between panic disorder and suicidal behavior is of considerable clinical significance, even if most or all of the increased risk is attributable to lifetime comorbidity. The vast majority of patients with panic disorder have current or past co-occurring Axis I or Axis II disorders. Thus, uncomplicated panic disorder is rela-

tively uncommon. Furthermore, co-occurring conditions may go undetected in busy clinical settings. Thus, it is important to be aware that patients presenting with panic disorder are at high risk for lifetime suicidal ideation and attempts. All patients presenting with panic attacks should be asked about suicidal ideation, past suicide attempts, about access to firearms and other means of suicide, and about co-occurring conditions likely to increase risk and to require specific treatment (e.g., bipolar disorder, major depressive disorder, or substance use disorders). When significant mood disorder and/or suicidal ideation exist, treatment should be initiated that is appropriate for the co-occurring diagnosis and a decision should be made about whether the patient can safely be treated as an outpatient. When a substance use disorder is present, it must also be monitored closely and addressed in treatment.

2. Co-occurring substance use disorder

In clinical and epidemiological studies, patients with panic disorder with or without agoraphobia have higher than average rates of cocaine, alcohol, and sedative abuse and dependence (377–383). Approximately 50% of people with panic disorder and substance use disorder have the onset of the substance use disorder prior to the onset of panic symptoms (378). Other individuals develop substance use disorders after the onset of panic disorder. Although the two problems may or may not be functionally related, some individuals may attempt to decrease panic and anxiety symptoms by using alcohol or other substances. In a recent epidemiological study, for example, 23% of subjects with a diagnosis of panic disorder reported using alcohol or drugs to reduce their anxiety symptoms (384).

Despite the anxiolytic effects perceived by some patients, use of many substances can trigger or worsen panic symptoms. Heavy alcohol use, acute alcohol withdrawal, and more prolonged subacute withdrawal may cause or exacerbate panic symptoms (382, 385). Cocaine, other stimulants, and marijuana have been reported to precipitate panic attacks in adolescents and adults (386–388). Panic attacks may also be triggered or worsened through the use of a number of legal substances, such as caffeine, sympathomimetics (e.g., nasal decongestants), and nicotine (389–393).

Psychiatrists should be certain to screen for substance use in patients with panic disorder. Substance use may play a role in causing or exacerbating panic symptoms, and patients with co-occurring panic disorder and substance use disorder have a poorer prognosis than those with either disorder alone (382, 385). It may be useful to incorporate formal drug screens into the treatment plan for patients with co-occurring substance use disorder (291). Psychiatrists also should consider referring the patient to community resources (e.g., Alcoholics Anonymous) and may need to coordinate care with addiction specialists who are providing concurrent care for the patient.

When the patient reports both problematic substance use and panic symptoms, treatment of the substance use disorder is essential. It is unclear whether specific antipanic treatment is necessary for patients with primary substance abuse (i.e., where it is clear that the panic attacks are a result of the substance use or withdrawal). The occurrence of several panic attacks in decreasing frequency during the early weeks of abstinence often warrants no treatment other than support and reassurance until the attacks abate (394, 395). However, if the panic attacks and other symptoms of panic disorder continue after several weeks of abstinence, making a diagnosis of panic disorder and initiating treatment is warranted. A return to substance use is common in patients who have ongoing symptoms of panic disorder in the period following substance use cessation (396–400). A controlled trial suggested that combined CBT and SSRI treatment significantly reduced anxiety symptoms in patients with co-occurring anxiety disorders (including agoraphobia) and alcohol dependence (401). However, there were no differences in relapse rates when patients who received anxiety treatment plus relapse prevention were compared to those who participated in relapse prevention alone. This study provides preliminary evidence that standard treatments for panic disorder can be effective for individuals who are in early stages of remission from substance use disorders, though effective treatment of anxiety does not necessarily translate into decreased relapse potential.

When panic symptoms persist after the initial period of detoxification, the psychiatrist must decide whether to pursue integrated or sequential treatment. Empirical data that provide guidance on this matter are lacking, and therefore this decision must be based on clinical judgment. Although integrated treatment is generally recommended (291), there are some individuals in whom the substance use disorder should be the primary target of the first phase of treatment. For example, most forms of CBT involve deliberately provoking anxiety symptoms or confronting anxiety-provoking situations. If these temporary increases in anxiety are likely to trigger compensatory substance use, a decision could be made to delay CBT until the patient has the support and skills to maintain sobriety even in the face of stress or discomfort.

In treating panic symptoms in patients with co-occurring substance use disorder, benzodiazepines should be avoided whenever possible in favor of CBT and/or antidepressants. A history of abuse of other substances, both licit and illicit, is associated with a higher prevalence of benzodiazepine abuse, a greater euphoric response to benzodi-

azepines, and a higher rate of unauthorized use of alprazolam during treatment for panic disorder (289, 402). If antidepressant treatment is indicated, SSRIs or SNRIs are preferred because the side effect and safety profiles of TCAs (e.g., increased risk of cardiac toxicity and seizures; greater lethality of TCAs in overdose) are of increased concern in the context of a co-occurring substance use disorder (403). More information about treating co-occurring panic disorder and substance use disorders is available in APA's *Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition* (291).

3. Co-occurring mood disorder

Substantial evidence from clinical and epidemiological studies demonstrates that panic disorder and panic attacks frequently co-occur with unipolar and bipolar mood disorders (14, 17, 33). Many studies indicate that patients with panic disorder and co-occurring mood disorders exhibit greater impairment, more hospitalizations, and generally more psychopathological symptoms than patients with panic disorder who do not have a co-occurring mood disorder (404, 405). As described in Section III.A.1, a co-occurring mood disorder can also augment the risk of suicidality in individuals with panic disorder. In treating patients with co-occurring panic disorder and mood disorder, the psychiatrist should select treatments that can target both disorders (e.g., psychosocial treatment and/or antidepressants rather than benzodiazepines alone for a patient with panic disorder and major depressive disorder).

With regard to CBT, most studies suggest that co-occurring major depressive disorder does not adversely affect response to CBT for panic disorder (191, 406). In some individuals major depressive disorder may occur as a reaction to the impairment created by the panic disorder (e.g., the patient feels depressed because panic symptoms limit his or her participation in activities). When the depression appears to be secondary, focusing on panic disorder in CBT and monitoring changes in depressive symptoms is a reasonable strategy. Some evidence suggests that if panic disorder is targeted using CBT, depressive symptoms may spontaneously improve (193, 194). For individuals who still have significant symptoms of depression after a course of CBT for panic, the therapist can shift focus and target the depression directly. If depressive symptoms are severe, associated with suicidality, or interfering with adherence to the treatment for panic disorder, the emphasis of the CBT should be shifted so that the depression becomes the primary focus of treatment.

Treatment of mood disorders may also be prioritized during pharmacological treatment for panic disorder; this is especially true for patients who present with suicidal ideation. When panic disorder co-occurs with bipolar illness, the psychiatrist should consider that antidepressants commonly used for treating panic disorder might exacerbate the bipolar disorder. Patients with co-occurring panic disorder and bipolar disorder should generally be treated with a mood stabilizing medication before the addition of an antidepressant is considered for treatment of the panic disorder. Careful monitoring is required whenever an antidepressant is added to the treatment regimen of an individual with bipolar disorder (407).

4. Other co-occurring anxiety disorders

Although spontaneous or unexpected panic attacks are a hallmark of panic disorder, panic attacks can occur in other anxiety disorders. Consequently, the psychiatrist must perform a detailed assessment to ensure that panic disorder is an appropriate diagnosis (see Section II.A.2). In many individuals presenting for treatment, panic disorder occurs concomitantly with other anxiety disorders (for example, see reference 408), and in these circumstances multiple disorders may need to be targeted in treatment.

Treatment with SSRIs, SNRIs, or CBT is appropriate for most individuals with co-occurring anxiety disorders. Medications commonly used to treat panic disorder often have a positive effect on the symptoms of other anxiety disorders. In addition, psychotherapy for panic disorder may have a positive effect on other symptoms even when co-occurring anxiety disorders are not directly targeted in treatment (191–194, 409). However, in some cases where panic disorder is part of a more complicated pattern of co-occurring conditions, a highly tailored and multimodal therapy may be required for optimal recovery. Although the first-line treatments may be similar under these conditions, specificity of treatment (e.g., addition of specific CBT modules, or other psychotherapeutic modalities, focused on co-occurring disorders) may make the difference between full response, partial response, and perceived treatment resistance.

5. Co-occurring personality disorders

Studies have shown that 40%–50% of patients with panic disorder additionally meet the criteria for one or more Axis II disorders (410–413). The personality disorders most frequently observed in panic disorder patients are three from the anxious cluster: avoidant, obsessive-compulsive, and dependent (414–416). In addition, patients with panic disorder often show traits from other personality disorders, such as affective instability and/or impulsivity (from borderline personality disorder), impulsivity (from antisocial personality disorder) (417, 418), and hy-

persensitivity to people (from paranoid personality disorder) (411). Longitudinal data suggest that panic attacks early in life predict the subsequent onset of personality disorders (419).

Results of studies examining the impact of co-occurring personality disorders on the course of panic disorder have been mixed. Several studies have shown that presence of co-occurring personality disorders predicts worse long-term outcome for patients with panic disorder (413, 420, 421). However, a large-scale, prospective, naturalistic study showed that, in contrast to social phobia and generalized anxiety disorder, the presence of a personality disorder did not predict longer time to remission in patients with panic disorder (422).

The majority of studies suggest that co-occurring personality disorders are associated with poorer response to standard treatments for panic disorder. A review of studies that examined the impact of co-occurring personality disorders on CBT outcome suggested that presence of a personality disorder at baseline was associated with poorer treatment outcome (423). Patients with co-occurring personality disorders also show less improvement and seem more likely to relapse following medication treatment for panic disorder (411, 414–416, 424, 425).

In working with patients who have co-occurring panic disorder and personality disorder, the therapist may need to devote more time to strengthening the therapeutic alliance and developing a hierarchy of specific treatment goals. One recent study provided preliminary evidence that a psychodynamic approach to treating panic disorder was effective for patients with co-occurring personality disorders (146).

B. CONCURRENT GENERAL MEDICAL CONDITIONS

Panic attacks are associated with prominent physical symptoms and may be misinterpreted as general medical conditions by patients and/or physicians. Moreover, panic symptoms may be an acute manifestation of a general medical condition (notably thyroid disease) or may result from the effects of prescribed medications to treat such conditions. An additional possibility is that a general medical condition is co-occurring with panic disorder. Studies show that panic and other anxiety disorders are more prevalent in medically ill patients than in the population at large, with physical conditions that have been specifically associated with panic disorder (426) including thyroid disease (427), cancer (428), chronic pain (429), cardiac disease (430), irritable bowel syndrome (431), migraine (432), mitral valve prolapse (36, 38, 39), vestibular disorders (433), and allergic and respiratory disease (434–436). To distinguish among these possibilities and to identify unrecognized general medical conditions that contribute to the clinical presentation requires a general medical evaluation as delineated in APA's *Practice Guideline for the Psychiatric Evaluation of Adults, Second Edition* (8). Even when results are negative, a careful assessment can provide needed reassurance to patients who fear that their panic attacks represent serious physical illness. In addition to the initial evaluation, assessments for general medical conditions may be indicated at other points in the treatment course. For example, among patients whose symptoms worsen or do not respond to initial treatments, a contributory general physical condition is worth considering.

Whenever a general medical condition is identified, the postulated relationship between that condition and the panic disorder will determine the approach to the patient. If the medical condition (e.g., hyperthyroidism) or treatment (e.g., oral corticosteroids) appears to be the primary cause of the panic symptoms, the specific treatment of panic disorder may be delayed until the general medical condition is treated or the precipitating medication discontinued. In some instances, medications that cause or worsen panic symptoms may be essential and cannot be discontinued; in these cases, concurrent treatment of panic disorder should be initiated. In other instances, a general medical condition or its treatment is not directly causing panic disorder (e.g., asthma) but may be worsening it. For example, data from some studies suggest that panic disorder and agoraphobic anxiety may increase the risk of mortality in patients with cardiovascular disease (362, 437, 438). Thus, with co-occurring general medical conditions and panic disorder, a simultaneous focus on optimizing treatment of the medical condition and the panic disorder may be indicated.

To date, there are no systematic evaluations of psychological or pharmacological treatment in patients with co-occurring panic disorder and general medical disorders. As far as pharmacological treatment, it is important for psychiatrists to choose medications that have the fewest drug-drug interactions. Adverse drug interactions may occur between medications utilized for panic disorder and medications used for general medical conditions. Furthermore, panic disorder patients with concurrent medical conditions may have difficulty differentiating symptoms of the general medical condition (e.g., migraine, asthma attack, angina) from those related to panic attacks. Thus, they may not be clear whether to take medication for their general medical conditions or to take medication for their anxiety. In the specific example of co-occurring panic disorder and asthma, patients often encounter difficulties knowing whether to utilize asthma treatment medications (i.e., beta-agonists) or anxiolytic medications. If they misinterpret a panic attack as an asthma attack, utilizing a

beta-agonist is likely to worsen the panic attack symptoms. On the other hand, an asthma attack that is interpreted as being a panic attack would not resolve with an anxiolytic medication. However, because the symptoms of panic attacks and asthma may be very difficult to differentiate, a therapeutic trial of the various strategies is often required.

Psychosocial treatments for panic disorder may need to be adapted depending on the presence and severity of a co-occurring general medical condition. It is often necessary to adapt the psychosocial treatment to the physical or medical realities in the patient's life. However, the clinician also must be alert to the possibility that the patient is viewing the dangers of the medical condition as more threatening than they truly are or is incorrectly interpreting panic symptoms as signs of another medical illness. In any form of psychosocial treatment, learning to differentiate anxiety symptoms from those related to the general medical condition often becomes an important goal. This work can be done through careful self-monitoring. Adaptation of other aspects of treatment may also be required. For example, physically challenging interoceptive exposure exercises that are used in CBT may need to be modified for patients with co-occurring panic disorder and medical conditions (e.g., asthma, heart disease).

C. DEMOGRAPHIC VARIABLES

1. Children and adolescents

This section contains a brief overview of formal clinical trial data regarding the treatment of children and adolescents with panic disorder. Given the limited data in the child and adolescent literature, many treatment plans will necessarily include components that are not well studied. Unless otherwise stated, the general considerations outlined in Sections II.B through II.I apply to children; this is especially true of the importance of psychiatric management. In addition, treatment plans for children and adolescents frequently require attention to developmental issues (from psychological and physiological perspectives) and involvement of multiple systems (e.g., schools, family, and community). Information and recommendations regarding the etiology, diagnosis, and assessment of pediatric panic disorder are beyond the scope of this section. The reader is referred to the American Academy of Child and Adolescent Psychiatry's *Practice Parameter for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders* (439) for a more detailed discussion.

Although empirical data are limited, expert opinion generally suggests that treatment of panic disorder in children and adolescents consists of CBT and, when necessary, pharmacotherapy (439). Depending upon the age and the physiological and psychological maturity of the patient, adjustments in the treatment plan may be needed. For example, a developmental adaptation of CBT that is appropriate for adolescents with panic disorder has been described in the literature (440). One randomized controlled trial of this treatment has been completed, but the results have not yet been published. Several published randomized controlled trials have shown CBT to be effective for other pediatric anxiety disorders (441–443). In addition, one randomized controlled trial showed that CBT was effective in a sample of pediatric patients with various anxiety disorders, including some who were diagnosed with panic disorder (444). Thus, the early available evidence suggests beneficial effects of CBT in adolescents.

No randomized controlled trials have been conducted that evaluate the efficacy of pharmacotherapy for panic disorder in pediatric samples; therefore, medication recommendations are based on uncontrolled studies in patients with pediatric panic disorder and some controlled studies demonstrating efficacy for other pediatric anxiety disorders. In pediatric patients with panic disorder, one open trial treated 12 patients with various SSRIs (some in combination with a benzodiazepine) and found significant improvement in 75% of patients (ages 14–17 years, except for one 7-year-old patient) (445). Another study based on chart review of 18 pediatric patients (ages 7–16 years) showed that paroxetine was well tolerated and significantly reduced panic disorder symptoms in approximately 80% of the patients in the study (446). The findings from these uncontrolled studies, as well as evidence from randomized controlled trials showing SSRIs to be effective for other pediatric anxiety disorders (447, 448), suggest that SSRIs are a reasonable treatment option for children and adolescents with panic disorder. However, such treatment must be undertaken with full consideration of potential risks and benefits of antidepressant use in pediatric patients (see Section II.H).

A few case reports (449, 450) and case series (451) suggest that imipramine and the high-potency benzodiazepines alprazolam and clonazepam also may have some use in treating pediatric panic disorder; however, these medications would not be considered first-line treatment options.

2. Geriatric patients

Although anxiety symptoms and disorders are among the most common psychiatric ailments experienced by older adults, epidemiological studies suggest that the prevalence of panic disorder in later life may be lower than that in midlife (452). When panic disorder does occur, it is more likely to be preexisting rather than new in onset (453) and is more likely to be associated with co-occurring

general medical or psychiatric disorders, especially depression (454) or emerging dementia. Thus, for elderly patients presenting with new panic symptoms, a vigorous search for alternative and co-occurring diagnoses should be undertaken, with particular attention to general medical conditions (e.g., hypercalcemia due to malignancy) and effects of general medical pharmacological agents. When panic disorder is present without other co-occurring psychiatric disorders, elderly patients often have less severe symptoms and less anxiety sensitivity than younger patients (455).

There have been few systematic prospective clinical trials to determine the efficacy of standard medications and/or psychosocial treatments for anxiety disorders among the elderly. Some evidence suggests that elderly patients with panic disorder may benefit from cognitive-behavioral treatments, although there are no randomized controlled trials with samples comprised exclusively of geriatric patients with panic disorder (456). Less is known about the efficacy of other psychosocial treatments or medication for treating panic disorder in elderly patients. If medication is used, however, general principles of psychopharmacology would suggest that the starting doses and therapeutic doses of medication may be lower than those for younger patients and that dose titration should occur more slowly than in younger adults. Medications with longer half-lives will eventually reach higher steady-state blood levels and toxicity may develop more slowly than anticipated, confounding interpretation of adverse effects and potentiating interactions with other medications. Given the high rates of co-occurring mood disorder in elderly patients with panic disorder, an antidepressant is recommended as first-line pharmacotherapy (457). Selective serotonin reuptake inhibitors or SNRIs are preferred because of their lesser side effect burden relative to other antidepressant medications in geriatric patients. Benzodiazepine use should be avoided whenever possible, since use of long half-life benzodiazepines and long-term benzodiazepine use can be problematic in geriatric patients (295, 458).

3. Gender

Panic disorder is more common in women for reasons that are not yet fully understood. In epidemiological surveys, the lifetime prevalence of panic disorder is approximately twice as high in women as in men (33, 459). This gender difference appears to decrease in elderly cohorts (460). Despite numerous studies, few consistently replicable differences have been found between men and women in panic disorder phenomenology, course of illness, or treatment responsivity. However, women with panic disorder are more likely to have severe agoraphobia than are men with panic disorder. The proportion of female patients increases as the level of agoraphobia intensifies (461–463), even though, after controlling for level of agoraphobia, few sex differences emerge in self-reported panic disorder symptoms (464–466).

Several studies have explored the relationship between panic disorder and the perinatal period, an important issue in light of the high rate of panic disorder in younger women. The limited available data suggest that the course of panic disorder is highly variable during pregnancy and the postpartum period (467–469). It is also not clear whether uncontrolled symptoms of panic disorder affect the course or outcome of pregnancy (470).

The treatment of pregnant and nursing women raises certain specific concerns regarding the use of antipanic medications (471, 472). With women of childbearing age, the risks of treatment during pregnancy and nursing should be discussed actively and preferably before conception (473). Treatment with SSRIs during pregnancy (reviewed in references 474 and 475) may be associated with increased rates of spontaneous abortion (476) and with a greater risk of low birth weight and respiratory difficulties in the neonate (477). Older reports generally failed to find associations between antidepressants and risk of congenital malformations; however, more recent findings suggest an increase in the rate of cardiac malformations with paroxetine treatment, raising increased caution about its use during pregnancy (475, 478). In addition, SSRI exposure in the third trimester has been associated with a rare but increased likelihood of persistent pulmonary hypertension of the newborn (479) and, more commonly, a neonatal behavioral syndrome suggestive of antidepressant discontinuation that typically resolves with supportive care (480–483). A comparable discontinuation syndrome appears to occur with SNRI treatment and may be more pronounced in preterm neonates (483). The effects of benzodiazepines on fetal development are unclear; a meta-analysis of pooled case-control study data showed an increased relative risk of major malformations and oral clefts with benzodiazepine treatment whereas meta-analysis of cohort studies showed no such effect (484). When used near term, however, benzodiazepines have been associated with neonatal lethargy, sedation, and weight loss; these findings suggest that their use should be minimized whenever possible (485). In considering the literature on prenatal exposure to psychotropic medications for anxiety and mood disorders, it is also important to note that many studies have not controlled for potentially confounding factors (e.g., rates of smoking in women taking psychotropic medications during pregnancy).

The benefits of breast-feeding for women and their infants are well documented (486). However, antidepres-

sants and benzodiazepines are secreted into breast milk in measurable quantities, and their central nervous system effects on the nursing infant are unknown (471, 487–489).

Despite the dearth of literature on the use of psychosocial interventions for women with panic disorder who are pregnant, nursing, or planning to become pregnant, these interventions should be considered in lieu of pharmacotherapy. Pharmacotherapy may also be indicated but requires consideration and discussion of the potential benefits and risks with the patient, her obstetrician, and, whenever possible, her partner. In making decisions about breast-feeding, discussions with the infant's pediatrician are also useful. Discussions should also consider the potential risks to the patient and the child of untreated psychiatric illness (475), including panic disorder and any co-occurring psychiatric conditions.

4. Ethnicity and cultural issues

Ethnicity and cultural factors are important to consider in assessing and treating individuals with panic disorder. As part of the assessment process, the DSM-IV-TR Outline on Cultural Formulation (490) can provide a systematic approach to determining the role of cultural factors in the clinical presentation. It also allows the psychiatrist to view the individual patient and the therapeutic relationship within the context of the patient's cultural background and support systems.

Relatively little research has been done pertaining to anxiety disorders in ethnic or cultural subgroups. In African Americans, data on the prevalence of anxiety disorders are somewhat conflicting. The National Institute of Mental Health Epidemiologic Catchment Area Study indicated that African Americans have a higher lifetime prevalence of agoraphobia but not panic disorder (491), the National Comorbidity Survey found no racial differences in the prevalence of any anxiety disorder (492), and the National Comorbidity Survey Replication found lower rates for panic disorder, generalized anxiety disorder, and social phobia (492–495). In Hispanic whites, the National Comorbidity Survey Replication showed lower risk of panic disorder relative to non-Hispanic whites in young (younger than age 43 years) cohorts (495).

There is some evidence that panic disorder may present differently in individuals of different cultural backgrounds. For example, panic disorder in African Americans has been specifically associated with isolated sleep paralysis (496), more intense fears of dying or "going crazy" (497), and hypertension (498, 499). Studies show that African American patients seen in primary care settings report more severe somatic symptoms and have a higher prevalence of panic disorder than whites (500). In addition, African Americans are more likely to seek help in medical than in mental health facilities (501, 502). The culture-bound syndrome *ataque de nervios* resembles panic disorder and may be relevant to understanding the symptom presentation of individuals from some Latino groups (e.g., those of Caribbean background). Although ataque de nervios is similar to a panic attack in that the patient experiences sudden and intense distress, loss of emotional control (e.g., crying, uncontrollable shouting) is a more prominent feature of ataque de nervios. Ataque de nervios also seems to be a more inclusive concept than panic disorder: only 36% of people with ataque de nervios met panic attack criteria, and only 17%–33% met panic disorder criteria (503). Finally, studies have examined the phenomenon of panic among Cambodian and Vietnamese refugees and highlighted several cultural syndromes that appear to be the equivalent of panic disorder. These include "sore neck," in which Cambodian patients fear that "wind" and blood pressure may burst the blood vessels in this area, and the syndrome of orthostatic dizziness, which is a frequent cue and concomitant of panic attacks in Vietnamese patients, who also report fears of a "wind overload" (504, 505).

In terms of treatment considerations, research findings indicate that African American (506), Latino (507), and Vietnamese (508) patients with panic attacks and panic disorder respond well to CBT treatments that are culturally adapted to fit these groups. When medications are a part of the treatment plan, the individual's cultural context may influence his or her beliefs about medication (509). Genetic polymorphisms (e.g., of cytochrome P450 isoenzymes) that vary in frequency among different ethnic groups may influence the patient's biological response to medication (e.g., metabolism, sensitivity to side effects) (510–512); as our understanding of genetic polymorphisms expand, these variations may become useful in individualizing treatment selection (509, 513).

Part B

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV. DISEASE DEFINITION, NATURAL HISTORY, AND EPIDEMIOLOGY

A. DIAGNOSIS OF PANIC DISORDER

The essential features of panic disorder identified in DSM-IV-TR are "recurrent unexpected panic attacks" (Criterion A1) that are followed by 1 month or more of "persistent concern about having additional attacks," "worry about the implications of the attack or its consequences," or "a significant change in behavior related to the attacks" (Criterion A2) (Tables 1 and 2).

A panic attack that counts toward a diagnosis of panic disorder is defined as a "discrete period of intense fear or discomfort" in which at least four of the following symptoms are present: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feelings of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, light-headed, or faint; derealization or depersonalization; fear of losing control or "going crazy"; fear of dying; numbness or tingling sensations; and chills or hot flushes (Table 3). The panic attacks that characterize panic disorder are not attributable to the direct physiological effects of a substance or to a general medical condition (Criterion C). It also must be established that the attacks are not better accounted for by another mental disorder (Criterion D).

Several types of panic attacks may occur. Prototypical is the unexpected attack, defined as one not associated with a known situational trigger. However, individuals may also experience situationally predisposed panic attacks (which are more likely to occur in certain situations but do not necessarily occur there) or situationally bound attacks (which occur almost immediately on exposure to a situational trigger), especially in later stages of the illness. Other types of panic attacks include those that occur in particular emotional contexts, those involving limited symptoms, and nocturnal attacks. Although numerous studies have sought to validate symptom-specific subtypes of panic attacks (e.g., cardiorespiratory, dizziness-derealization, nonfearful panic) as associated with specific levels of functional impairment, illness severity, comorbidity, or outcome, no consistently replicable associations have emerged.

In choosing the appropriate DSM-IV-TR diagnosis, the psychiatrist must also determine if agoraphobia is present (Criterion B) (see Table 4). Agoraphobia is defined as "anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help might not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms" (Criterion A). These situations must be "avoided or else endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion" (Criterion B). Finally, it must be established that the anxiety or agoraphobic avoidance is not better accounted for by another mental disorder (Criterion C). Typical situations eliciting agoraphobia include traveling on buses, subways, or other public transportation, and being on bridges, in tunnels, or far from home. Many patients who develop agoraphobia find that situational attacks become more common than unexpected attacks. Panic disorder with agoraphobia is typically a more severe and chronic condition than panic disorder without agoraphobia (62, 220).

B. SPECIFIC FEATURES OF PANIC DISORDER

1. Cross-sectional issues

There are a number of important clinical and psychosocial features to consider in a cross-sectional evaluation. First, because there is such variance in the types and duration of attacks that may occur with panic disorder, the psychiatrist should consider other possible diagnoses. The psychiatrist should assess the patient for the presence of life-threatening behaviors, the degree to which the

panic disorder interferes with the patient's ability to conduct his or her daily routine or to care for self and others, and the presence of substance use disorders, mood disorders, and other conditions that commonly co-occur with panic disorder (see Section III.A).

2. Longitudinal issues

Because of the variable nature of panic disorder, it is necessary to consider a number of longitudinal issues when evaluating the patient. These include the fluctuations in chronic variants of this condition, the response to prior treatments, and the development of complications such as co-occurring psychiatric and medical disorders and medication side effects.

C. NATURAL HISTORY AND COURSE

Panic attacks vary in their frequency and intensity, often waxing and waning over time and in response to psychosocial stressors. It is not uncommon for an individual to experience numerous moderate attacks for months at a time or to experience frequent attacks daily for a short period (e.g., a week), with months separating subsequent periods of attacks. Individuals with panic disorder commonly have anxiety about the recurrence of panic attacks or symptoms or about the implications (e.g., "Am I having a heart attack? Am I going crazy?") or consequences (e.g., "Will I be able to drive my children to school?"). Panic disorder, especially with agoraphobia, may lead to the loss or disruption of interpersonal relationships, especially as individuals struggle with the impairment or loss of social role functioning and the issue of responsibility for symptoms. Examples of the disrupting nature of panic disorder include the fear that an attack is the indicator of a life-threatening illness despite medical evaluation indicating otherwise or the fear that an attack is a sign of emotional weakness. Some individuals experience the attacks as so severe that they take such actions as quitting a job to avoid a possible attack. Others may become so anxious that they avoid most activities outside their homes (i.e., severe agoraphobia).

Evidence from naturalistic follow-up studies of patients in a tertiary-care setting suggests that at 4–6 years posttreatment about 30% of individuals are well, 40%–50% are improved but symptomatic, and the remaining 20%–30% have symptoms that are the same or slightly worse (514, 515). Thus, the disorder can be seen as one in which there is much more often improvement with residual symptoms than remission and one in which relapse after remission is more common than sustained remission (61).

Panic attacks appear to worsen the prognosis and/or delay a beneficial treatment outcome in multiple other disorders that may co-occur with them, including major depression (16), bipolar disorder (516), psychotic disorders (517), alcohol dependence (518), and nicotine dependence (519), and may be a particularly important risk factor for relapse in both depressive disorders (520) and alcoholism (521).

Co-occurring disorders may also influence the course of panic disorder. Prospective follow-up studies have shown that patients with co-occurring depression have worse courses of illness (61, 420). Studies of the impact of personality disorders on the course of panic disorder have produced mixed results (420, 422).

D. EPIDEMIOLOGY AND ASSOCIATED FEATURES

1. Prevalence and onset

Epidemiologic data collected from multiple countries have documented similarities in lifetime prevalence (1.6%–2.2%), age at onset (age 20–29 years), higher risk in females (about twofold), and symptom patterns of panic disorder (522). Although the full-blown syndrome is usually not present until early adulthood, limited symptoms often occur much earlier. Studies of community samples suggest that panic disorder occurs in 0.5%–1% of the general pediatric population (523–525). Panic disorder can have its onset prior to puberty (526), although this is relatively uncommon. When panic disorder does occur prior to adulthood, it is more likely to occur in adolescence, and particularly in females (527). Panic symptoms in childhood and adolescence are frequently a predictor of later onset psychiatric disorders (379).

2. Co-occurring disorders

Roughly one-quarter to one-half of individuals diagnosed with panic disorder in community samples also have agoraphobia, although a much higher rate of agoraphobia is encountered in clinical samples (522). The National Comorbidity Survey Replication found that approximately 20% of patients with lifetime panic disorder have agoraphobia.

Among individuals with panic disorder alone, the lifetime prevalence of major depression is 34.7%; in patients with panic disorder with agoraphobia, the lifetime prevalence of major depression is 38.7% (33). Approximately one-third of patients with panic disorder are depressed when they present for treatment (528). For individuals presenting to clinical settings with both panic disorder and major depressive disorder, the onset of depression has been found to precede the onset of panic disorder in one-third of individuals, whereas the onset of depression coincides with or follows the onset of panic disorder in the remaining two-thirds (529).

Children and adolescents with panic disorder display high rates of other co-occurring psychiatric disorders, especially other anxiety and mood disorders, including bipolar disorder (530–532).

3. Morbidity

Epidemiologic studies have clearly documented the morbidity associated with panic disorder (40, 368, 533–538). Patients with panic disorder, especially with co-occurring depression, are at higher risk for suicide attempts (368), impaired social and marital functioning (539), work impairment (533), use of psychoactive medication (535), and substance abuse (539).

4. Medical utilization

In the Epidemiologic Catchment Area study, subjects with panic symptoms or disorder, as compared to other disorders, were the most frequent users of emergency medical services and were more likely to be hospitalized for physical problems (535). Similarly, patients with panic attacks or disorder, who frequently present to ambulatory primary care settings reporting the somatic manifestations of their panic attacks, are often not recognized as having panic attacks unless the syndrome is severe, may receive extensive and costly medical work-ups, and often receive poor quality of care and inadequate and inappropriate treatment (540, 541). This phenomenon has sparked interest in disseminating evidence-based panic treatments to primary care settings (157). There is preliminary evidence that treatment of panic disorder in these settings may result in a significant cost offset and overall medical-care savings (542–544).

5. Frequency and nature of treatment

Relative to patients with other psychiatric disorders, patients with panic disorder seek help relatively frequently (545–547). Individuals frequently present to nonpsychiatrists first and may make greater use of the emergency department (548) or other medical specialists (549). However, an extensive body of evidence has documented that panic disorder is undertreated, whether in primary care (541) or specialty mental health settings (220). In particular, despite the strong evidence supporting CBT for panic disorder, this treatment is offered at a low rate, even in specialty mental health settings. When treatment is finally offered it is frequently inadequate or inappropriate. Incorrect kinds or doses of medication are often prescribed for periods of insufficient length, and psychosocial treatments are frequently provided that have minimal evidence base (550).

6. Family and genetics studies

Family studies using direct interviews of relatives and family history studies have shown that panic disorder is highly familial. Results from studies conducted in different countries (United States, Belgium, Germany, Australia) have shown that the median risk of panic disorder is eight times as high in the first-degree relatives of probands with panic disorder as in the relatives of control subjects (551). A family data analysis showed that forms of the disorder with early onset (at age 20 years or younger) were the most familial, carrying a more than 17 times greater risk (552). Results from twin studies have suggested a genetic contribution to the disorder (553–555).

Genetic studies of panic disorder patients have identified genes linked to panic subtypes associated with bladder problems, bipolar illness, and possibly smoking and have identified some associated genes with functional importance for anxiety pathophysiology. However, few studies have as yet been replicated, and it is still unclear whether panic exists in many distinct genetic forms, each with a different set of genes, or in one form with an underlying set of genes that confer broad vulnerability to panic and anxiety (556).

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

A. INTERPRETING RESULTS FROM STUDIES OF TREATMENTS FOR PANIC DISORDER

1. Measurement of outcomes

In the following sections available data on the efficacy of treatments for panic disorder are reviewed. Short-term efficacy has usually been evaluated over the course of 6- to 12-week clinical trials by observing changes in the presence and severity of patient- and physician-rated panic and agoraphobic symptoms. Earlier studies have focused on the primary outcome of being free of DSM-defined panic attacks at the end of the study. However, patients labeled "panic free" are not necessarily free of all panic symptoms (i.e., symptom free). Some studies have shown that reductions in other dimensions (e.g., agoraphobic avoidance, functional impairment) are more important to overall improvement than reduction in panic frequency (74). Thus, the field has moved toward a broader definition of remission that includes substantial reductions in panic attacks, anticipatory anxiety, and agoraphobic avoidance, as well as

a return to full function and good quality of life. One scale commonly used to examine this is the PDSS (51). Some definitions of remission have included a Clinical Global Impression (CGI) improvement rating of 1 or 2 (much or very much improved) and zero panic attacks (88, 557) or a CGI severity rating of 1 or 2 (borderline or not at all ill) and zero panic attacks at study endpoint (89, 558).

The long-term efficacy of treatments has been measured in terms of relapse rates among panic-free or symptom-free patients receiving treatment over the course of several years. A variety of definitions of relapse have been used, based on the emergence of a certain number of symptoms or based on the percentage of change in scores on symptom rating scales. In some studies, requests for or use of additional treatment have been considered indicative of relapse; whereas such outcome measures may reflect an intervention's effect on patient functioning as well as symptoms, they may also be affected by other clinical and nonclinical factors. Many studies report only short-term outcome. More studies that include longer follow-up periods of several years are needed in order to assess the potential of different treatments to produce sustained remission.

2. Issues in study design and interpretation

When evaluating clinical trials of medications for panic disorder, it is important to consider the design of the study (e.g., whether a placebo-control group was used, the response rate in the placebo-control group) and the definitions of treatment response and remission (e.g., which outcome measures were selected). Response rates as high as 75% have been observed among patients receiving placebo in clinical trials of patients with panic disorder (106). Placebo response rates (often in the range of 40%–50%) could explain much of the observed treatment effect in uncontrolled trials or make significant treatment effects more difficult to detect in controlled trials. It is also important to consider the potential use of additional treatments that are not prescribed as part of the study protocol (e.g., psychotherapy, other medications that are not being directly studied) and whether these factors were rigorously assessed in the study.

Some randomized controlled studies of medications for panic disorder use an "active" comparator, which may be a medication or psychosocial intervention with prior evidence supporting its efficacy in panic disorder. Although these studies are useful for comparing the efficacies of interventions, the lack of a placebo group limits the ability to determine if either agent is more effective than placebo in particular study populations or with specific treatment characteristics (e.g., treatment length, clinical contacts). It is also important to consider the dose of medication(s) employed in pharmacological trials. Some studies are designed as "fixed-dose" studies, which require titration to a set dose regardless of patients' response or side effects. Such trials allow assessment of a specific dose but are theoretically more likely to result in study discontinuation for those who cannot tolerate the medication. "Flexible-dose" studies allow dose adjustment based on individual tolerability and response, as would be done in clinical practice, but do not permit comparison of the efficacy and tolerability of specific doses of medication.

When evaluating studies of psychosocial treatments, such as CBT, which consist of multiple components, it may be difficult to determine which components are responsible for producing beneficial outcomes. It is also important to consider the nature of the components that are used. For example, although the types of CBT used in some trials have been rigorously defined and have been similar, they have not been identical and have been usually derived from one of several related, but not identical, approaches (133, 136, 138). It is also important to note whether a specific treatment protocol has been used and whether efforts have been made to ensure that all study clinicians have demonstrated adherence to the protocol as well as competence in delivering the intervention. Finally, some trials of psychosocial treatments have employed waiting-list control groups, which only control for the passage of time and not for the "nonspecific" effects of treatment (e.g., the benefits of a therapeutic relationship, positive expectancies for change).

Another factor to consider is the use of medications that are not prescribed as part of the treatment protocol. For example, patients in studies of CBT may be using prescription medications that are not taken into consideration in the study design or statistical analysis. In addition, patients in medication studies may be taking additional doses of the tested medications or other antipanic medications (either explicitly, as doses taken as needed, or surreptitiously). Studies that monitor such occurrences have shown rates of surreptitious benzodiazepine use to be as high as 33% (278). Furthermore, there is growing interest in specifically examining the role of treatment for those who do not respond to initial treatments; these studies may add a second agent to an initial agent to which a patient has had minimal or partial response to examine the safety and potential additional benefit derived from the combination. These studies provide guidance only for the potential efficacy of the treatment as an adjunct to the specific prior type of treatment (e.g., as augmentation of CBT or SSRIs). There are few data examining "next step" interventions for individuals with panic disorder who do not respond or tolerate initial first-line treatment(s).

For all studies, it is important to understand the characteristics of the study participants. The demographic

features of the sample and the inclusion/exclusion criteria are important to consider. No clinical trial adequately represents all patients with panic disorder, and some studies have specifically excluded patients with features (e.g., agoraphobia, depression, substance use disorders) that are frequently encountered in clinical practice.

Another issue important to understand when interpreting results of any study is the use of statistical testing. The traditional determination of statistical significance has been the *p* value, which is typically set at no higher than $p<0.05$ (i.e., an alpha of 0.05, representing a 5% probability that the rejection of the null hypothesis—that there was no difference between the treatments—was in error). It is important to note that as sample sizes become large, smaller absolute differences between the effects of agents on outcome measures are more likely to be statistically significant (i.e., achieve a *p* value 0.05); these differences may be statistically—but not necessarily clinically—significant. Similarly, small studies that fail to find a difference between two agents may not have had sufficient statistical power to detect such a difference. Under such circumstances, small randomized controlled trials with negative results cannot provide definitive conclusions. Further, findings from small studies are less reliable (i.e., if the same study is repeated with a different small sample of patients, the results are more likely to differ from those of the original study than if a very large study is repeated).

Some studies will also report an "effect size," which is another way to measure the magnitude of a difference between treatments in a trial with somewhat less dependence on sample size (559). Effect sizes can provide a common metric for comparing the magnitude of effects across studies. Psychiatrists should also look at the clinical significance of the level of improvement reported in a study (e.g., Were patients free of symptoms at the end of the study? Did they all improve significantly more with one treatment, but only by a very small amount that would not be clinically meaningful?).

Two final measures of effect that may be used in studies are the odds ratio and the "number needed to treat." The odds ratio provides a measure of the odds of one binary event occurring versus another (e.g., the ratio of the odds of achieving remission with treatment A, compared to the odds of achieving remission with treatment B). For example, an odds ratio of 2 in a study of the proportion of patients achieving remission with two different interventions would suggest that one intervention resulted in twice the odds of remission as the other. In general, an odds ratio of 1 implies the odds of the outcome are equal for the interventions, an odds ratio of less than 1 suggests the odds are less for the comparator treatment, and an odds ratio greater than 1 suggests the odds are higher for the comparator treatment. When interpreting odds ratios, it is also important to realize that this is not a measure of absolute difference. Thus, the odds may be represented as the proportion achieving remission divided by the proportion who do not (e.g., if 20% achieve remission with treatment A, the odds are 0.2/0.8 = 0.25, or 1 in 4 for treatment A; if treatment B has a 40% remission rate then the odds of achieving remission with treatment B are 0.4/0.6 = 0.67, or 2 in 3. The odds ratio for treatment B versus A would then be 0.67/0.25 = 2.7).

The number needed to treat is another measure of effect designed to give a sense of how many patients would need to be treated with the new intervention to achieve the desired outcome for one additional patient. For example, if 20% of the study population achieved remission with one intervention and 40% with the alternate intervention, the absolute difference would be 20%, or one of five additional patients achieving remission. Thus, from a public health point of view, to have one additional patient achieve remission with the novel intervention than would with the standard intervention, five patients would need to be treated. When using these measures to assess the benefit of a novel intervention clinically, the risks associated with the intervention (side effects, higher costs, etc.) should also be considered in a risk/benefit assessment. More information about odds ratios and number needed to treat can be found in standard epidemiological textbooks (for example, see reference 560).

B. SPECIFIC PSYCHOSOCIAL INTERVENTIONS

1. Cognitive-behavioral therapy

There are numerous controlled trials demonstrating the efficacy of CBT for panic disorder (67, 111, 133–144), although specific CBT protocols used in clinical trials vary in their emphasis on different treatment components. Meta-analyses of clinical trials have concluded the effects of CBT for panic disorder are robust and durable (172, 561–564).

To date, the largest controlled efficacy trial of CBT for panic disorder included 312 panic disorder patients who were randomly assigned to five groups: imipramine, CBT, CBT and imipramine, CBT and placebo, and placebo (111). CBT consisted of 11 individual 50-minute sessions over 12 weeks. The imipramine treatment was slowly titrated up to a maximum of 300 mg/day. Response was defined as a 40% or greater reduction in symptoms on the PDSS (50). In this study, CBT (49% response) was superior to placebo (22%) at the end of the 12-week acute treatment phase. The response rate in the CBT group was statistically equivalent to that of the imipramine (46%), CBT plus placebo (57%), and CBT plus imipramine (60%) groups. At the end of the 6-

month maintenance phase (in which responders were continued on their medication or on monthly CBT), CBT (40%) was again superior to placebo (13%) and equivalent to imipramine (38%). However, the combination of CBT and imipramine (57%) was significantly superior to all other treatment conditions, including CBT alone. Finally, at the end of the 6-month follow-up phase (during which patients were receiving no treatment), CBT (32%) and CBT plus placebo (41%) were the only two treatment conditions that were superior to placebo (9.1%). This study provided evidence for the short- and long-term efficacy of CBT. It further showed that CBT is largely equivalent in short-term efficacy to imipramine and combination treatments, and that it may produce more durable effects than imipramine or the combination of CBT and imipramine. See Section V.B.6 for further discussion of this study.

Several studies have examined the use of one component of CBT, situational exposure, specifically for patients with panic disorder who also have substantial agoraphobia (149, 184, 218, 565–568). These studies support the efficacy of exposure treatment in reducing panic and agoraphobic symptoms. Given the efficacy of exposure treatment, some investigators have questioned whether more elaborate protocols that include cognitive restructuring are necessary for treatment of panic disorder (especially when agoraphobic symptoms are the main problem). One comparative study showed similar rates of response for patients treated with exposure therapy alone and for those who received a CBT package that included both cognitive and exposure techniques (140).

Some CBT protocols teach breathing retraining as an anxiety management skill; however, the incremental benefit of this treatment component has been questioned in the literature (142, 175). In one study, 77 patients with panic disorder were randomly assigned to receive CBT with breathing retraining, CBT without breathing retraining, or a delayed-treatment control (175). Both forms of CBT were superior to the waiting-list condition on most outcome measures; however, CBT with breathing retraining was no better than the version of CBT without breathing retraining, despite the fact that patients learned an additional anxiety management skill. Moreover, at posttreatment the group that received CBT without breathing retraining was superior to the control group on 11 of 12 outcome measures, whereas the group that received CBT with breathing retraining was superior to the control group on only 8 of 12 outcome measures. Thus, breathing retraining did not contribute any incremental benefit over other CBT components, and there was some evidence that it was associated with poorer response (175).

Many patients who respond to short-term CBT (i.e., 10–15 sessions) experience long-lasting beneficial effects (111, 135, 569, 570). In the longest follow-up study to date, reported by Fava and colleagues (571), 200 consecutive patients with panic disorder were treated with 12 sessions of exposure therapy. Patients with co-occurring major depressive disorder, social phobia, and/or obsessive-compulsive disorder were excluded. Of the 200 patients, 165 were panic free after treatment, and 132 patients were available for follow-up between 2 and 14 years (median of 8 years). Twenty-three percent of the 132 patients had a relapse at some time during follow-up. These findings suggested that the majority of patients who responded acutely to exposure therapy experienced long-lasting maintenance of response. However, the conclusion may not be generalizable to patients with co-occurring conditions (e.g., depression), who were not represented in the study. Another limitation is that some patients (30%) were unable to fully taper benzodiazepines during the treatment period. Remission of symptoms therefore may not be completely attributable to the exposure therapy. However, use of benzodiazepines during exposure treatment predicted worse outcome in this sample, making it unlikely that medication effects explain the sustained remission in the majority of patients who responded well to exposure therapy.

Given the efficacy of 12 weekly sessions of CBT, there have been attempts to modify the treatment such that it can be delivered to a wider population of patients with panic disorder. Initial open-label and small randomized controlled trials have found that modified forms of CBT are efficacious. Studies have examined the impact of CBT delivered by telephone (184), assisted by a computer (186), using virtual reality (572), or given in a high-density format (i.e., several hours of therapy within a few days) (182, 183). There has been interest in reducing clinician time by having a computer assist in some of the routine components of CBT (139, 188, 189). Although some studies have reported similar efficacy between computer-assisted psychotherapy and therapist-conducted psychotherapy (186), other studies have not replicated these findings (139). Larger controlled trials are required.

2. Psychodynamic psychotherapy

Support for psychodynamic psychotherapy targeting panic disorder includes observations of experts in psychodynamic therapy (145, 204, 205, 573), as well as uncontrolled studies and case reports (201, 204, 574–579) published over its long history of use. Published literature also discusses the theoretical rationale for applying psychodynamic principles in panic disorder treatment (205, 580–582).

More recently, manual-guided PFPP (145, 583, 584) has been shown to be efficacious in a randomized controlled trial (146). This controlled trial supported the efficacy of PFPP in

reducing the severity of panic symptoms and improving psychosocial functioning and showed that these treatment gains were maintained at a 6-month follow-up. Forty-nine adult patients with panic disorder were randomly assigned to either PFPP (26 patients) or applied relaxation therapy (23 patients). Both groups received individual sessions twice weekly for 12 weeks. Panic-focused psychodynamic psychotherapy showed significantly superior reduction in panic symptoms measured by the PDSS (76% vs. 39%) and a greater reduction in functional impairment as measured by the Sheehan Disability Scale. These findings provide initial support for the use of PFPP as a treatment for panic disorder and suggest a need for further research in this area. It is unknown whether the positive results obtained with PFPP generalize to other forms of psychodynamic psychotherapy that are more commonly offered in the community (e.g., psychodynamic psychotherapy that has a broader focus).

3. Eye movement desensitization and reprocessing

Originally developed as a treatment for posttraumatic stress disorder (206), EMDR involves reprocessing distressing memories while engaging in guided eye movement. It has been studied as a possible treatment for panic disorder in two trials. In the first study, 40 patients with panic disorder were randomly assigned to EMDR, a version of EMDR that excluded the definitive eye movement component (eye fixation exposure and reprocessing [EFER]), or a waiting-list control condition (207). At posttreatment, the EMDR group was superior to the waiting-list control group on all outcome measures but superior to EFER on only two of five outcome measures. By 3-month follow-up, with 28 patients remaining in the sample, EMDR and EFER were equivalent. Because subjects in the waiting-list control group were crossed over to an active form of treatment, no comparison with a waiting-list control condition was possible. Although EMDR was statistically superior to the control conditions at post-test, the researchers questioned the clinical significance of its effect because very few patients who received EMDR showed substantial functional recovery at follow-up (207). The second trial included 46 patients with panic disorder who were assigned to EMDR, a credible attention-placebo control, or a waiting-list control (208). In this study, EMDR was superior to the waiting-list control on only two of four outcome measures and was equivalent to the attention-placebo control. Investigators concluded that the results did not support the use of EMDR as a treatment for panic disorder.

4. Group therapy

Reports in the literature of group therapy in the treatment of panic disorder have consisted primarily of cognitive-behavioral approaches. Evidence suggests that group CBT and individually administered CBT may be equally effective (137, 176–179). In one study, 67 patients with panic disorder were randomly assigned to group CBT or a delayed treatment control (137). At posttreatment, 64% of the group CBT participants met the criteria for remission (defined as attainment of normal functioning on measures of panic attacks, anxiety, and avoidance). Only 9% of the control group met the remission criteria at posttreatment. The remission rate reported in this study compares favorably to remission rates reported in trials of individually administered CBT and pharmacotherapy.

Mindfulness-based stress reduction, which includes training in meditation and relaxation strategies, is another group-based treatment that has a limited research base in relation to panic disorder. The effectiveness of this treatment was evaluated in one uncontrolled trial that included 22 patients with either panic disorder or generalized anxiety disorder (209). The 8-week program was associated with significant reductions in ratings of anxiety symptoms and panic attacks (209), and a 3-year follow-up study suggested that these benefits were maintained (210).

Other types of groups that are sometimes recommended to patients with panic disorder (e.g., medication support groups, consumer-run self-help groups) have not been evaluated empirically.

5. Marital and family therapy

There are very few studies on the use of marital or family therapy alone for the treatment of panic disorder or agoraphobia. Findings from one very small comparative efficacy study that included 11 patients suggested that systems-oriented marital therapy was inferior to partner-assisted exposure therapy in reducing panic symptoms (211). In contrast, partner-assisted exposure therapy for panic disorder has been shown to reduce symptoms of panic disorder in several studies, at levels roughly comparable to individually administered exposure therapy (180). Some studies of group CBT have shown an advantage when partners were included in the treatment group, compared to when patients attended the group alone (177, 212, 213). Another study showed more benefits of adding couples-based communication training to exposure treatment compared to adding couples-based relaxation training to exposure treatment (214). Thus, some evidence exists that couples-based interventions can enhance response to exposure treatment and CBT (180). No empirical studies of the involvement of partners or family members in other types of treatment (e.g., pharmacotherapy) have been published.

6. Combined treatments

Investigators have examined use of the combination of antidepressants and CBT for patients with panic disorder

and agoraphobia. Some older studies that evaluated short-term efficacy showed that the combination of the TCA imipramine with one component of CBT, behavioral exposure, was superior to imipramine alone (152, 153) or exposure plus placebo (91, 150, 153). In studies using SSRIs, paroxetine plus CBT was statistically superior to CBT plus placebo on two of three outcome measures after acute treatment (69), and, in the short-term, fluvoxamine plus placebo was superior to exposure alone in the treatment of panic disorder with severe agoraphobia (68).

The largest randomized controlled trial to date that evaluated combination treatment included 312 panic disorder patients who were randomly assigned to five groups: imipramine, CBT, CBT and imipramine, CBT and placebo, and placebo (111) (also described in Section V.B.1). A 12-week acute-phase assessment demonstrated that the response rate for the combination of CBT and imipramine (60%) was superior to the response rate for placebo (22%) but statistically equivalent to the response rate for CBT alone (49%), imipramine alone (46%), and CBT plus placebo (57%). The combination of CBT and imipramine (57%) demonstrated a statistically significant advantage over CBT alone (40%), imipramine alone (38%), CBT plus placebo (47%), and placebo (13%) at the end of the 6-month maintenance phase. However, at the end of an additional 6-month follow-up phase (during which patients were receiving no treatment), the combination of CBT plus imipramine (25%) was equivalent to placebo (9%). Only CBT (32%) and CBT plus placebo (41%) were superior to placebo after treatment withdrawal. This study suggested a relatively modest benefit of combination treatment, which was apparent at the assessment point conducted after 6 months of maintenance treatment. This modest benefit must be considered alongside the evidence that simultaneously initiating medication and CBT may have negatively influenced the durability of the effects of CBT after all treatments were withdrawn. Of those who responded to acute treatment and were carried into the follow-up phase, CBT and CBT plus placebo were shown to have higher response rates than CBT plus imipramine (111).

Another randomized controlled trial, which included 154 patients, compared alprazolam plus exposure, alprazolam plus relaxation (psychosocial placebo), placebo plus exposure, and placebo plus relaxation (double placebo) (149). Among patients who received alprazolam, doses were titrated up to 5 mg/day. In the acute term, all four groups improved significantly on panic measures and were not statistically different. After treatment withdrawal, participants who received exposure plus alprazolam were less likely to maintain their response, compared to those who received exposure plus placebo (149).

A study of treatment for panic disorder in primary care that included 232 patients found that a collaborative-care intervention that included CBT plus pharmacotherapy was more effective than the usual care (i.e., pharmacotherapy alone) (157). Collaborative care included six sessions of CBT adapted for primary care (159) and algorithm-based pharmacotherapy. At 12-month follow-up, 68% of the patients in the collaborative-care group and 38% in the treatment-as-usual group met the criteria for response. The addition of CBT to medications led to statistically and clinically significant improvements, compared to medications alone (158).

A follow-up study looking at remission from panic disorder with agoraphobia after drug treatment in patients who received concurrent CBT appeared to show a long-term therapeutic advantage of integrated treatment over medication alone. Among 32 patients who received medication alone, 25 (65%) relapsed during the first year, whereas among 21 patients who received integrated treatment, only three (14.3%) relapsed (585).

The discontinuation of benzodiazepines, such as alprazolam or clonazepam, for patients with panic disorder is often accompanied by withdrawal symptoms and relapse into panic disorder. Several studies have shown that using adjunctive CBT in this clinical situation results in successful discontinuation of the benzodiazepine for significantly more patients (354–357).

There has been one study of the combination of psychodynamic psychotherapy with medication (156). Patients with panic disorder (with and without agoraphobia) were randomly assigned to receive clomipramine alone or clomipramine plus 15 sessions of psychodynamic psychotherapy. The combination treatment resulted in a significantly reduced relapse rate over 18 months, relative to the clomipramine monotherapy (156).

C. PHARMACOLOGICAL INTERVENTIONS

Medications have been known to be useful in the treatment of panic disorder for more than 40 years. Most studies have focused on their ability to stop or reduce the frequency of panic attacks, but many have also addressed the effect of medication on anticipatory anxiety, agoraphobic avoidance, limited symptom attacks, associated depression, and global function. Medications from several classes have been shown to be effective. When interpreting results from trials of pharmacological interventions, it is important to consider the study design and methods for measuring treatment outcome (see Section V.A) and the funding source of the study.

1. Selective serotonin reuptake inhibitors

a. Efficacy

Numerous clinical trials indicate that the SSRIs are effective for the acute and long-term treatment of panic disorder, although there is no clear evidence of differential efficacy among agents in this class. Whereas an early meta-analysis (586) suggested that the effect size for improvement with SSRIs in panic disorder was significantly greater than for alprazolam or imipramine, subsequent meta-analyses incorporating a larger number of SSRI studies demonstrated comparable efficacy for the SSRIs and TCAs, with mixed results regarding the question of whether dropout rates were lower in studies in which patients received SSRIs, compared to those for TCAs (587, 588).

Data from a number of large randomized controlled trials demonstrate the acute and long-term efficacy of fluoxetine for panic disorder (74, 80, 83). Results from one multicenter, double-blind, placebo-controlled study demonstrated that doses of both 10 mg/day and 20 mg/day were effective, although the 20 mg/day dose was more consistently effective across a variety of measures (74).

Results for a number of large randomized controlled trials demonstrate the efficacy of sertraline for the acute and long-term treatment of panic disorder (76–78, 82, 85). Results from a fixed-dose randomized controlled trial of 50 mg/day, 100 mg/day, or 200 mg/day of sertraline showed significantly greater reduction for the SSRI, compared to placebo, on measures of panic and anxiety, without evidence of a dose-response relationship (76).

Paroxetine, both in its immediate-release and controlled-release formulation, has demonstrated efficacy for the acute and long-term (immediate-release formulation) treatment of panic disorder in several large randomized controlled trials (69, 70, 72, 73, 79, 87). Ballenger and associates (73) compared placebo to three doses of paroxetine; the percentages of patients given paroxetine at daily doses of 40 mg, 20 mg, and 10 mg and patients given placebo who were subsequently panic free were 86%, 65%, 67%, and 50%, respectively. Only the difference between 40 mg/day of paroxetine and placebo was statistically significant.

Several randomized controlled trials of fluvoxamine for panic disorder have also been published, with most (66–68, 84), although not all (256, 589), demonstrating efficacy of this agent for panic disorder. In one study (66), a greater proportion of patients who had been given fluvoxamine became panic free, compared with those who received placebo (61% vs. 36%). Fluvoxamine has been shown to be effective in doses from 100 mg/day to 300 mg/day (84).

Citalopram has also demonstrated acute and long-term efficacy for panic disorder in large randomized controlled trials (71, 75, 81, 86). In one double-blind trial in which 475 patients were randomly assigned to receive citalopram (10–15 mg/day, 20–30 mg/day, or 40–60 mg/day), clomipramine (60–90 mg/day), or placebo, citalopram at 20–30 mg/day or 40–60 mg/day was significantly superior to placebo; citalopram at 20–30 mg/day was more effective than 40–60 mg/day and comparable to clomipramine (71). In one 10-week, double-blind, randomized controlled trial of escitalopram and citalopram, administration of escitalopram led to a significantly greater reduction in panic frequency, compared to placebo, and had comparable overall efficacy to citalopram (86).

b. Implementation issues

1. Side effects

The concerns and debate regarding the relationship between antidepressants and increased suicidality have already been reviewed (see Section II.H).

There is accruing evidence for a discontinuation syndrome caused by the abrupt discontinuation of SSRIs (85, 258, 259). Although most evidence comes from studies of patients who are being treated with SSRIs for depression, Black and colleagues (67) studied the effect of abrupt withdrawal of fluvoxamine from patients with panic disorder after 8 months of treatment. A discontinuation syndrome characterized by dizziness, incoordination, headache, irritability, and nausea began within 24 hours, peaked at day 5 after withdrawal, and was generally resolved by day 14.

2. Length of treatment

There are few data on the optimum length of treatment following response. Gergel and associates (342) selected patients who had responded to paroxetine in an acute-phase trial and randomly assigned them to receive placebo or 10 mg/day, 20 mg/day, or 40 mg/day of paroxetine for a 12-week maintenance period. After the maintenance phase, the rate of relapse was significantly higher among the responders who had crossed over to placebo than among those whose paroxetine treatment had been maintained (30% vs. 5%).

LeCrubier and associates (70) evaluated the efficacy of paroxetine, clomipramine, and placebo for patients who completed a 12-week double-blind trial and then chose to continue receiving the randomly assigned treatment for an additional 36 weeks. Compared with the placebo-treated patients, the patients who received paroxetine experienced significantly greater reductions in panic symptoms, and a larger proportion remained free of panic attacks throughout the long-term study. There were no significant differences in efficacy between paroxetine and clomipramine.

Rapaport and associates (85) examined the long-term efficacy of sertraline in the treatment of panic disorder. Pa-

tients received 52 weeks of open-label sertraline treatment followed by a 28-week, double-blind, placebo-controlled discontinuation trial. Compared to those blindly tapered and switched to placebo, patients who continued to receive sertraline were less likely to have an exacerbation of panic symptoms (13% vs. 33%) or discontinue the study because of insufficient clinical response (12% vs. 24%).

2. Serotonin-norepinephrine reuptake inhibitors

Three large, international, randomized controlled trials have been performed that together provide support for the efficacy and safety of venlafaxine ER for panic disorder. In a multicenter study of 361 individuals with panic disorder without co-occurring depression, the intent-to-treat population consisted of 160 participants who were randomly assigned to receive a 10-week course of venlafaxine ER flexibly dosed from 75 mg/day to 225 mg/day (initiated at 37.5 mg/day for 4 days) and 168 participants who were randomly assigned to receive matched placebo (88). Although this study failed to find a statistically significant difference between venlafaxine ER and placebo on the a priori primary endpoints (CGI severity rating and proportion of participants free of panic attacks at study endpoint), there was a significantly greater reduction in panic attacks, with overall improvement as rated by the CGI improvement rating and remission at endpoint (defined as a CGI improvement rating of 1 or 2 and no panic attacks) for the venlafaxine ER group. In a second multicenter randomized controlled trial, which included 664 individuals with panic disorder without co-occurring depression, participants were randomly assigned to receive venlafaxine ER at fixed doses of 75 mg/day or 150 mg/day, paroxetine at 40 mg/day, or placebo for 12 weeks after a 2-week placebo lead-in period (89). All active treatments were found to be significantly more effective than placebo, with no significant difference between the venlafaxine ER doses or paroxetine and somewhat less sedation with the venlafaxine ER doses (3% and 4%) than with paroxetine (13%). In a third multicenter randomized controlled trial, which included 653 individuals with non-co-occurring panic disorder, participants were randomly assigned to receive 225 mg/day of venlafaxine ER, 75 mg/day of venlafaxine ER, 40 mg/day of paroxetine, or placebo for 12 weeks after a single-blind placebo lead-in (590). In this study, a significantly greater proportion of patients receiving the active medications were panic free and in remission (defined as a CGI severity score of 1 or 2 or zero panic attacks) at endpoint and had greater response from weeks 2 or 3 onward as measured by the CGI improvement rating. All active treatments were generally well tolerated.

An additional study examined the ability of venlafaxine ER to prevent relapse in individuals whose panic disorder symptoms had responded to a 12-week course of flexibly dosed (75–225 mg/day) venlafaxine ER (344). Of the 89 individuals who had been randomly assigned to receive venlafaxine ER, time to relapse was significantly longer than in the 80 individuals assigned to receive placebo. During the 26-week follow-up period, secondary measures of therapeutic efficacy, including quality of life and disability, also showed a significant benefit for venlafaxine ER treatment, relative to placebo.

There are currently no systematic data available on the use of duloxetine in panic disorder, although its similar mechanism of action to venlafaxine suggests it could be a potentially effective agent.

3. Tricyclic antidepressants

a. Efficacy

The first controlled study documenting the efficacy of the TCA imipramine in blocking panic attacks was conducted by Klein and published in 1964 (90). In this study, imipramine was superior to placebo for antipanic effect and for change in the CGI. Since then, numerous controlled trials have shown that imipramine is effective in reducing panic attacks (91, 92, 94–102, 104, 105, 107, 108, 111). After treatment with imipramine, 45%–70% of patients were found to be panic free, compared to 15%–50% of those receiving placebo. In addition, patients with panic disorder who were treated with imipramine had less agoraphobic avoidance and anticipatory anxiety than those receiving placebo.

A number of placebo-controlled randomized trials have documented the acute and long-term efficacy of clomipramine for panic disorder (70, 72, 79, 103, 109, 110). Clomipramine appears at least as effective as imipramine for panic disorder (93); in the one double-blind, placebo-controlled study addressing this issue, clomipramine (mean dose of 109 mg/day) was superior to both imipramine (mean dose of 124 mg/day) and placebo in panic reduction and decrease in score on the Hamilton anxiety scale (102). Most placebo-controlled studies comparing clomipramine to an SSRI demonstrate equivalent efficacy, although with a less favorable side effect profile for the TCA.

The few studies that have evaluated other TCAs for panic disorder support the efficacy of desipramine (106) and nortriptyline (112). However, randomized trials comparing desipramine with clomipramine (591) and maprotiline with fluvoxamine (272) both found the more noradrenergic TCA to be less effective than the serotonergic comparator.

b. Implementation issues

1. Side effects

Several research studies have shown that some patients with panic disorder are sensitive to both the beneficial and adverse effects of TCAs (91, 106). For example, Zitrin and associates (91) found that 20% of the patients in their study could not tolerate doses of imipramine higher than 10 mg/day but still experienced panic blockade. Higher doses of TCAs are associated with a higher dropout rate in research studies. For example, Mavissakalian and Perel (108) reported that among subjects treated with an average of 35 mg/day, 99 mg/day, and 200 mg/day of imipramine, the dropout rates because of drug side effects were 6%, 15%, and 36%, respectively.

2. Dose

Few studies have rigorously addressed the optimum dose of TCAs for panic disorder. In most research studies, the mean final dose is approximately 150 mg/day of imipramine and the maximum final dose is up to 300 mg/day. Mavissakalian and Perel (108) randomly assigned patients with panic disorder to low-dose (mean, 35 mg/day), medium-dose (mean, 99 mg/day), and high-dose (mean, 200 mg/day) imipramine. They found that both the medium and high doses were superior to placebo in reducing panic and not significantly different from each other; the low dose was no more effective than placebo.

There is a suggestion in the literature that clomipramine may be effective in somewhat lower doses than imipramine. Clomipramine can generally be used effectively with doses less than 150 mg/day. Given the results of the studies by Modigh and associates (102) and Cassano and colleagues (93), it may be reasonable to administer clomipramine in a dose range of 25–150 mg/day.

3. Length of treatment

Most controlled trials of TCAs for the treatment of panic disorder were for a minimum of 8 weeks, and time to patients' response has not always been reported. There are few long-term studies of TCA treatment for panic disorder in the literature. Cassano and colleagues (99) continued to treat patients with imipramine or placebo for 6 months after an acute-phase 8-week study and found that imipramine remained superior to placebo for panic reduction. Curtis and associates (104) also maintained patients on a regimen of placebo or imipramine for up to 8 months after acute 8-week treatment and found that the placebo-treated patients had more panic attacks and agoraphobic avoidance and were more likely to drop out of treatment during the maintenance phase. The limited available data are mixed about whether patients who remit during treatment benefit more from over a year of subsequent treatment, compared with 6 months of continued pharmacotherapy prior to discontinuation (343, 592, 593). In one study that examined the impact of longer-term treatment with imipramine on relapse, relapse rates for a combined group of patients who were randomly assigned to receive placebo discontinuation or open discontinuation after 12–30 months of remission were compared with relapse rates for patients randomly assigned to placebo discontinuation after 6 months of remission (592). The rates of reported relapse were nearly identical for the two groups (37%) during the follow-up period after discontinuation, suggesting that the achievement of remission prior to treatment discontinuation may be a more critical determinant in preventing relapse than the subsequent duration of maintenance therapy.

4. Benzodiazepines

a. Efficacy

Alprazolam has been studied more extensively than any other benzodiazepine for the treatment of panic disorder and is approved by the FDA for the treatment of panic disorder. Eleven trials of alprazolam IR for treatment of panic disorder have been published, including the Cross-National Collaborative Panic Study, which involved more than 1,000 patients randomly assigned to receive imipramine, alprazolam, or placebo (594). Nine of the trials were double-blind, and seven were placebo-controlled. Two meta-analyses of studies on alprazolam treatment for panic disorder are also available (402, 586).

In six of the seven double-blind, placebo-controlled trials, alprazolam was found to be superior to placebo in the treatment of panic attacks (104, 116, 118, 122, 123, 126), although the remaining trial did not assess panic attacks as an outcome measure (276). The percentage ranges of patients who were panic free (generally assessed over a 1-week period) at endpoint were 55%–75% for alprazolam (at doses of 5–6 mg/day) and 15%–50% for placebo. These percentages represent the intent-to-treat proportions (i.e., the panic-free proportion of patients who were originally assigned to receive active treatment or placebo at the start of the trial); the differences between the completers were less striking or nonsignificant because of higher dropout rates for the nonresponders in the placebo groups. Alprazolam was superior to placebo in reducing agoraphobic avoidance in five of the six studies in which it was assessed, disability in five of five studies, anticipatory anxiety in three of three studies, and Hamilton anxiety scale scores in six of seven studies. In most of the studies, patients with primary current major depression were excluded and the level of agoraphobic avoidance was moderate.

Four of the 11 trials compared alprazolam to imipramine (104, 126, 221, 594). Three of these trials were double-blind. Alprazolam and imipramine were comparable in efficacy as measured by reduction of panic attacks and phobias, Hamilton anxiety scores, disability ratings, and CGI ratings. More dropouts occurred in the imipramine group in three of the four studies.

These data support the efficacy of alprazolam (especially in the 5–6 mg/day range) in treating multiple dimensions of illness in patients with panic disorder who do not have primary current major depression. A sustained-release form of alprazolam is FDA-approved for once-daily dosing based on two placebo-controlled studies (125, 129).

Fourteen studies regarding other benzodiazepines have also been published (113–117, 119–122, 124, 127, 128, 130–132). These studies support the short-term efficacy of other benzodiazepines for panic disorder. The agents studied include clonazepam (effective in the three double-blind, placebo-controlled trials and the only other FDA-approved benzodiazepine besides alprazolam), diazepam (effective in two of two trials, both double-blind and one placebo-controlled), and lorazepam (equivalent to alprazolam in three of three double-blind trials). One study showed superiority of imipramine over chlordiazepoxide.

Three controlled trials have established that the short-term (4–6 week) addition of benzodiazepines (alprazolam and clonazepam) to antidepressants produces a more rapid therapeutic response (100, 222, 223). Whereas no discontinuation problems were reported in the two studies using the longer half-life clonazepam added to an SSRI and a 3-week taper (222, 223), 10 of 17 patients in the alprazolam study were unable to taper from 1.5 mg/day to discontinuation in 2 weeks after 4–6 weeks of treatment added to imipramine (100).

b. Implementation issues

1. Side effects

The adverse effects of benzodiazepines in patients with panic disorder appear similar to those reported when benzodiazepines are used for other indications. They include primarily sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness. Some sedation or drowsiness occurred in 38%–75% of alprazolam-treated subjects and 11%–21% of those taking placebo. In addition, an increased risk of motor vehicle accidents in association with benzodiazepine use has been reported (288). In geriatric patients, the risk of falls and fractures appears to be greater in individuals taking a benzodiazepine, regardless of the medication half-life or duration of use (283–287, 295, 458, 595, 596).

Memory problems were reported by up to 15% of patients taking alprazolam and 8.5% of patients taking placebo in the Cross-National Collaborative Panic Study (101). However, patients may not recognize their own cognitive impairment, which limits spontaneous reporting of this side effect and has prompted several controlled studies to more systematically investigate the cognitive effects of these agents in people with panic disorder. Two placebo-controlled studies have examined the effects of alprazolam on short-term memory at baseline and in the acute (8–12 week) treatment phase in small samples of patients with panic disorder (about 20 patients per group). In one study using alprazolam IR at a mean dose of 5.5 mg/day, some evidence of memory impairment was found (292), whereas no evidence of memory impairment was found in another study using alprazolam extended release at a mean dose of 4 mg/day (293). A follow-up of the positive study found that, 3.5 years after discontinuation, there were no long-term memory deficits, suggesting that there is no carryover effect after medication has been discontinued (597). Two other reports, one meta-analysis (598) and one review (296), do not provide convincing evidence of long-term cognitive effects of benzodiazepines in mixed groups of patients because of the spotty nature of the findings and because many studies have serious methodologic flaws.

Major concerns about benzodiazepine tolerance and withdrawal have been raised. However, according to the report of the APA Task Force on Benzodiazepine Dependence, Toxicity, and Abuse, "There are no data to suggest that long-term therapeutic use of benzodiazepines by patients commonly leads to dose escalation or to recreational abuse" (294). The studies of long-term alprazolam treatment for panic disorder show that the doses patients use at 32 weeks of treatment are similar to those used at 8 weeks, indicating that, as a group, patients with panic disorder do not escalate alprazolam doses or display tolerance to alprazolam's therapeutic effects, at least in the first 8 months of treatment. Furthermore, data in the more severely ill Medicaid population with a mix of mostly mood and anxiety disorder diagnoses show that long-term use of benzodiazepines (at least 2 years) does not typically result in dose escalation, with the incidence of escalation to a high dose being 1.6% (346). Nevertheless, studies of dose escalation following longer periods of benzodiazepine use, especially in specific cohorts of patients with panic disorder, are lacking, making it difficult to draw definitive conclusions about the potential for benzodiazepine tolerance in the clinical treatment of panic disorder.

In terms of the occurrence of benzodiazepine withdrawal symptoms, studies of alprazolam discontinuation in patients with panic disorder demonstrated that significant numbers (ranging from 33% to 100%) are unable to complete a taper of the medication after 6 weeks to 22 months

of treatment. Another study showed that, compared with imipramine, alprazolam causes significantly more withdrawal symptoms, recurrent panic attacks, and inability to discontinue the medication (351). An additional study suggested that patients with panic disorder have more difficulty during tapering of alprazolam than do those with generalized anxiety disorder, even when the patients in both groups are treated with similar doses (599). Difficulties during alprazolam tapering seem most severe during the last half of the taper period and the first week after the medication is discontinued. In many instances, it is difficult to determine the extent to which symptoms are occurring because of withdrawal, rebound, or relapse.

The one study comparing diazepam to alprazolam for panic disorder indicated that both are no different from placebo during gradual tapering of the first half of the dose (600). With abrupt discontinuation of the remaining dose, however, alprazolam caused significantly more anxiety, relapse, and rebound. This finding is consistent with reports of the APA Task Force on Benzodiazepine Dependence, Toxicity, and Abuse (294), which suggest that there are more difficulties with short half-life, high-potency compounds. However, apart from this one study, the issue of discontinuation of benzodiazepines with short versus long half-lives or high versus low potency has not been adequately addressed in relation to panic disorder. In addition, studies by Schweizer, Rickels, and associates (126, 351) of benzodiazepine-treated patients with other psychiatric disorders show no significant effect of half-life on the results of a gradual taper, but greater withdrawal severity after abrupt discontinuation with compounds that have shorter half-lives and with higher daily doses. Taken together, these studies suggest that half-life is less of a factor, or in fact may not be important, given a gradual taper schedule.

Other data suggest that certain personality traits may increase the likelihood of discontinuation effects in panic disorder patients. In one study of 123 patients with panic disorder, after accounting for the effects of dose and duration of alprazolam use, as well as pretreatment anxiety and panic frequency, measures of anxiety symptom sensitivity and avoidance predicted difficulty discontinuing alprazolam during a tapered, gradual withdrawal process (353).

2. Dose

Very few studies have empirically evaluated dosing of benzodiazepines for panic disorder. Two studies compared alprazolam doses of 6 mg/day and 2 mg/day (95, 278). One of the studies showed a significant advantage for the higher dose in reducing frequency of panic attacks (95). The other study showed very little difference between the higher and lower doses; absence of panic attacks at study end was found for 65% of patients taking the higher dose, 50% of those taking the lower dose, but only 15% of those taking placebo (278). However, the rates of surreptitious benzodiazepine use for the lower-dose (23%) and placebo (35%) patients were considerably greater than the rate for the patients taking the higher alprazolam dose (4%) (278), perhaps suggesting that the patients did not find the lower dose or placebo clinically effective. In addition, adverse side effects were more pronounced at the higher dose than at the lower dose of alprazolam in that study.

In one multicenter dose-ranging trial, patients with panic disorder were randomly assigned to placebo or one of five fixed doses (0.5 mg/day, 1 mg/day, 2 mg/day, 3 mg/day, or 4 mg/day) of clonazepam (601). During 6 weeks of treatment, the minimum effective dose was 1 mg/day, and daily doses of 1 mg/day and higher were equally effective in reducing the number of panic attacks.

The dosing of other benzodiazepines in the treatment of panic disorder is less well established. In controlled studies, lorazepam has been given at doses of about 7 mg/day, usually two or three times daily (119, 128). Diazepam doses ranged from 5 mg/day to 40 mg/day in two published trials (115, 116).

3. Length of treatment

Very few data indicate the optimum length of maintenance therapy for responders to benzodiazepines. Two published trials have compared maintenance imipramine, alprazolam, and placebo treatment, and both suggested that imipramine may be superior. In the study by Cassano and colleagues (99), patients who received imipramine and those who received alprazolam fared equally well in terms of panic reduction during a 6-month maintenance phase, but the imipramine-treated patients had less agoraphobic avoidance. There were more dropouts in the alprazolam group during the maintenance phase than during the 8-week acute treatment phase, whereas the number of dropouts in the imipramine group did not differ between the two phases. Curtis and associates (104) found that from month 4 through the end of an 8-month maintenance phase patients taking imipramine had virtually no panic attacks, whereas alprazolam-treated patients continued to experience infrequent panic attacks. On all other measures, however, the two medications performed equally well. In a third investigation by Lepola and colleagues (602), 27 patients who had been treated with alprazolam and 28 patients who had been treated with imipramine in a 9-week trial were then followed for 3 years in a naturalistic study. Significantly more alprazolam users than imipramine users were found to still be using their original medication after 3 years (74% vs. 32%). The authors pointed out that it is difficult to know whether this difference is attributable to a

better long-term response among the imipramine users than among the alprazolam users, a greater degree of intolerable side effects for the imipramine users, or greater difficulty in discontinuing treatment among the alprazolam users because of physiologic dependence.

5. Other antidepressants

a. Monoamine oxidase inhibitors

No studies of the nonselective MAOIs phenelzine and tranylcypromine have been performed since the diagnosis of panic disorder was introduced in DSM-III. The most modern and rigorous study (603) involved the use of phenelzine for the treatment of "phobic neurosis" (604). This study included patients with what would now be called panic disorder and found phenelzine to be effective (297).

Four studies have examined the effectiveness of moclobemide, a reversible inhibitor of monoamine oxidase A, in panic disorder, and the results are only modestly encouraging. Although two studies with active comparators, but no placebo, showed comparable efficacy to both fluoxetine (298) and clomipramine (299), respectively, the only two published placebo-controlled studies of this medication failed to show an effect greater than placebo (300, 301). Although the MAO-B inhibitor selegiline is available in the United States, there are no data to support its efficacy for the treatment of panic disorder.

b. Trazodone

There is minimal support for the use of trazodone in panic disorder. Although a single-blind study of 11 patients with panic disorder treated with trazodone found significant improvement in panic symptoms compared to a baseline period of placebo treatment (307), a double-blind study in which 74 patients with panic disorder were assigned to trazodone, imipramine, or alprazolam showed trazodone to be less effective than either imipramine or alprazolam (221). Further, a study of trazodone flexibly dosed from 50 mg/day to 300 mg/day (mean, 178 mg/day) alone and as augmentation to CBT failed to show greater efficacy with trazodone or combination therapy than with CBT alone, and patients who took trazodone had greater rates of side effects and study discontinuation (308).

c. Bupropion and bupropion sustained release

Bupropion has been found to be effective in the treatment of depression, but there is little systematic study of its efficacy in panic disorder, and the available data are contradictory. Two small uncontrolled trials have been published, one positive and one negative. In the positive trial, which included 20 patients, bupropion sustained release flexibly dosed at 200 mg b.i.d. was effective and well tolerated (313). In the negative trial, which included 12 patients, bupropion immediate release at high doses of 300–700 mg/day was associated with significant side effects, including myoclonus and one seizure (314).

d. Nefazodone

Although there are a few small, positive open-label reports examining nefazodone in panic disorder, large randomized controlled trials are lacking (605), and there are concerns about liver toxicity (309–311).

e. Mirtazapine

Although there are a few open short-term studies supporting the potential efficacy of mirtazapine for panic disorder (315–319) and a very small randomized controlled trial (involving 27 patients) of mirtazapine compared with paroxetine suggesting similar efficacy (320), substantial side effects have been noted, and no data from large randomized controlled trials are available.

f. Reboxetine

Reboxetine, a norepinephrine reuptake inhibitor, is currently not available for use in the United States or Canada. Reboxetine has been studied with preliminary support for its efficacy and safety in a small randomized controlled trial involving 42 patients in Europe and Brazil (606) and an open-label trial for resistant patients (607), with mixed support in single-blind comparison with SSRIs (608, 609).

6. Other agents

a. Anticonvulsants

There are limited data concerning the use of anticonvulsant medications in the treatment of panic disorder. One randomized controlled trial of gabapentin in 103 patients with panic disorder provided partial support for its efficacy and safety (321). The only other randomized study, a small placebo-controlled trial, suggested that carbamazepine was not effective for panic disorder (328). Data from small open-label studies support the efficacy of valproic acid (322–324) and levetiracetam (326), and very preliminary case report data support the efficacy of tiagabine (327) and vigabatrin (327), but more rigorous studies of these medications are needed.

b. Antipsychotic agents

There is minimal evidence that first-generation antipsychotic medications are effective for panic disorder. In small open-label trials, significant reductions in symptoms were observed in patients with treatment-resistant panic disorder treated with olanzapine (329) and adjunctive risperidone (330). Double-blind, randomized controlled trials are needed.

c. Antihypertensives

A limited number of trials of antihypertensive medications have been conducted in panic disorder. Results with beta-adrenergic blocking agents are mixed but suggest that propranolol offers peripheral blockade but is ineffective and/or less effective than benzodiazepines (115, 332, 333). A single small, 4-week, randomized controlled trial that included 25 patients supported the potential efficacy of pindolol, dosed 2.5 mg t.i.d., as augmentation for patients with panic disorder resistant to 8 weeks of treatment with an SSRI (334). Data are even more limited for calcium channel blockers (335) and clonidine (336, 337) and suggest only mild and/or transient effects, if any, for panic disorder.

d. Inositol

Although inositol is rarely used clinically for panic disorder, two small studies have supported its potential efficacy in treatment of panic disorder (216, 217).

e. Buspirone

Minimal data are available on the use of buspirone in panic disorder, and no systematic controlled trials support its efficacy. Two reports suggest that buspirone monotherapy is not effective for panic disorder (338, 339), and a randomized controlled trial examining augmentation of CBT does not suggest additional efficacy with buspirone (340).

Part C

FUTURE RESEARCH NEEDS

Although existing psychosocial and pharmacological interventions are effective for many patients with panic disorder, more research is needed to optimize these treatments and to develop novel approaches that will expand the array of treatment options. Research on optimizing effective treatments could evaluate methods for improving the quality, rapidity, and durability of response to standard treatments for panic disorder. Additional research is also needed to provide clinicians with guidance in treating patients whose panic symptoms are resistant to initial treatments. For example, studies of specific augmentation or switching strategies (within and across modalities) would make valuable contributions to the literature on treatment of panic disorder.

Basic and translational research is essential for informing the optimization of existing treatments as well as developing novel therapeutics. More studies of the basic pathophysiology of panic disorder are needed in order to identify potential mechanisms to target with drug development. Basic and translational research also informs development and refinement of psychosocial treatments. For example, animal studies showing that D-cycloserine facilitates extinction of conditioned fear have led to research on whether this agent could optimize response to exposure therapy. Recently D-cycloserine was shown to enhance response to exposure therapy in patients with social phobia, and initial work suggests it may demonstrate similar effects in treatment of panic disorder, but this possibility remains to be further studied. This is a potentially fruitful avenue for research on enhancing the effects of psychosocial treatments with specific pharmacological agents in panic disorder.

Genetic studies are needed to identify genes that increase susceptibility to panic disorder. Advancing knowledge in this area would help to identify individuals at high risk for the disorder. Delineation of susceptibility genes for panic disorder (and, potentially, their interaction with known environmental risk factors for panic disorder such as smoking or childhood maltreatment) could help identify new potential pathways and mechanisms to target for therapeutic development. Other biomarkers (e.g., neuroimaging findings) may also be useful in understanding the neurobiological bases of panic disorder and in identifying effects of medications or psychosocial treatments that predict treatment outcome.

Across all effective treatment modalities, more research is needed to evaluate long-term effectiveness and relapse prevention strategies. In addition, little is known about characteristics of individuals with panic disorder that predict response to any specific treatment. As such, there is a minimal evidence base to aid psychiatrists and patients in choosing among standard treatments for panic disorder based on patient characteristics. Researchers should continue to search for factors that predict positive response and resis-

tance to standard psychosocial and pharmacological treatments. In this regard, studies are particularly needed to identify genes that are associated with response to particular therapies. Such studies could aid in the development of more tailored and effective interventions, bringing the treatment of panic disorder into an era of personalized medicine.

With regard to standard pharmacological treatments (e.g., SSRIs and SNRIs), more studies are needed to strengthen the empirical basis of recommendations regarding next-step treatments (e.g., switch vs. augment), optimum length of treatment, and optimal up- and down-titration schedules. Other medications (e.g., mirtazapine, gabapentin) have shown promise in uncontrolled trials and/or small controlled trials and require more systematic investigation to better establish their appropriate place in the treatment of panic disorder. In addition, the efficacy of venlafaxine ER for panic disorder suggests that evaluating the efficacy of duloxetine (another SNRI) would be a worthwhile research endeavor. Benzodiazepines are clearly effective for panic disorder, but concerns about their side effects and propensity for producing physiological dependence constrain their use. Although benzodiazepines have been marketed for more than 30 years, more research that clarifies the effects of chronic benzodiazepine use (e.g., long-term cognitive effects) is needed in order to clarify the cost-benefit profile of this medication class for patients with panic disorder.

With regard to CBT, dismantling studies that aid in determining which elements of CBT are essential for treatment response are needed. Research focusing on identifying mechanisms of action of CBT would also be valuable. These lines of research could aid in developing more targeted, streamlined interventions that lead to faster and more complete symptom resolution. Continuing research on the efficacy of self-directed CBT treatments (e.g., Internet-based CBT) is also encouraged, to increase accessibility of this intervention.

Panic-focused psychodynamic psychotherapy is a promising psychosocial treatment, with efficacy supported by a randomized controlled trial. Additional controlled investigation of PFPP is needed to confirm its efficacy and to compare it to other standard treatments such as SSRIs and CBT. More controlled research supporting the efficacy of PFPP would strengthen the recommendation of PFPP as a first-line treatment for panic disorder. Given that some preliminary work suggested greater potency of PFPP in patients with comorbid personality disorders, continued research that explores the effectiveness of PFPP in patients with these and other co-occurring disorders would be especially worthwhile. Randomized controlled study of other psychodynamic psychotherapies would also be of interest.

This guideline concluded that there is presently insufficient evidence to recommend combined pharmacological and psychosocial treatment as superior to either treatment modality alone. However, only a limited number of combined treatments have been rigorously investigated. More studies of combination treatments are needed to clarify the potential benefits (e.g., more rapid or durable treatment effects) or disadvantages (e.g., reduced durability of psychosocial treatment effects) of interventions that combine psychosocial and pharmacological approaches.

More research is needed to evaluate the efficacy of standard treatments for panic disorder across the life span. For example, research is needed to understand the reasons for the decline in incidence and prevalence of panic disorder in later life. Developing an evidence base for treating panic disorder in pediatric and geriatric patients is critical. At present, recommendations for children and older adults are primarily based on extrapolating from data collected with general adult samples. Some uncontrolled studies are also available, but controlled trials of standard treatments for panic disorder in pediatric and geriatric patients are clearly needed. Additional research is also required to evaluate the efficacy of standard treatments for members of ethnic minority groups. Most participants in clinical trials for panic disorder are Caucasian, and investigations are needed to delineate any adaptations that are needed to improve acceptability, adherence, and overall effectiveness in individuals from ethnic minority groups.

Research on treatment for panic disorder in the presence of specific co-occurring conditions (e.g., depression, substance use disorders) is another valuable direction for future research. In addition, given evidence that subthreshold panic disorder can be an impairing condition requiring treatment, research focused on treatment of this variant of panic disorder should be pursued.

Research on the relationship of certain lifestyle patterns to panic disorder might also contribute to optimizing treatment of this condition. Investigations of the relationship of sleep, exercise, and nutrition to panic disorder symptoms could be illuminating in this regard, as would trials of interventions that incorporate specific instructions for lifestyle changes (e.g., improving sleep hygiene, exercising regularly).

Finally, more effectiveness studies of treatments for panic disorder administered in "real world" clinical practice settings (e.g., primary care, community mental health) are needed to supplement the results of stringently controlled efficacy trials. Initial research suggests that standard treatments for panic disorder (e.g., CBT, antidepressants) are both effective and cost-effective for patients who receive services in the community. More research is needed to determine the optimal pathways and methods for providing care to as diverse a patient population as possible across a variety of settings.

APPENDIX: EDUCATIONAL RESOURCES FOR PATIENTS AND FAMILIES

The American Psychiatric Association does not endorse the accuracy of the information contained in any of the publications or web sites listed in this Appendix at the time of writing or in the future, although they are believed to be generally trustworthy at the time of writing. The psychiatrist should review a particular book or visit the particular web site before recommending it to a patient.

RESOURCES FOR PANIC DISORDER AND AGORAPHOBIA

1. Antony MM, McCabe RE: 10 Simple Solutions to Panic: How to Overcome Panic Attacks, Calm Physical Symptoms, and Reclaim Your Life. Oakland, Calif, New Harbinger Publications, 2004
2. Barlow DH, Craske MG: Mastery of Your Anxiety and Panic (MAP-3): Client Workbook for Anxiety and Panic, 3rd ed. New York, Oxford University Press, 2005
3. Barlow DH, Craske MG: Mastery of Your Anxiety and Panic (MAP-3): Client Workbook for Agoraphobia, 3rd ed. New York, Oxford University Press, 2005
4. Bassett L: From Panic to Power: Proven Techniques to Calm Your Anxieties, Conquer Your Fears, and Put You in Control of Your Life. New York, HarperCollins, 1997
5. Beckfield DF: Master Your Panic and Take Back Your Life: Twelve Treatment Sessions to Conquer Panic, Anxiety, and Agoraphobia, 3rd ed. Atascadero, Calif, Impact Publishers, 2003
6. Otto MW, Jones JC, Craske MG, Barlow DH, Pollack MH: Stopping Anxiety Medication: Panic Control Therapy for Benzodiazepine Discontinuation (Patient Workbook). San Antonio, Tex, Psychological Corporation, 2000
7. Pollard CA, Zuercher-White E: The Agoraphobia Workbook: A Comprehensive Program to End Your Fear of Symptom Attacks. Oakland, Calif, New Harbinger, 2003
8. Rachman S, De Silva P: Panic Disorder: The Facts, 2nd ed. New York, Oxford University Press, 2004
9. Ross J: Triumph Over Fear: A Book of Help and Hope for People with Anxiety, Panic Attacks, and Phobias. New York, Bantam, 1995
10. Wilson RR: Don't Panic: Taking Control of Anxiety Attacks, revised ed. New York, HarperCollins, 1996
11. Wilson RR: Facing Panic: Self Help for People with Panic Attacks. Silver Spring, Md, Anxiety Disorders Association of America, 2003
12. Zuercher-White E: Overcoming Panic Disorder and Agoraphobia: Client Manual. Oakland, Calif, New Harbinger Publications, 1999
13. Zuercher-White E: An End to Panic, 2nd ed. Oakland, Calif, New Harbinger Publications, 1998

RESOURCES FOR ANXIETY DISORDERS IN GENERAL (NOT DISORDER-SPECIFIC)

1. Bourne EJ: The Anxiety and Phobia Workbook, 4th ed. Oakland, Calif, New Harbinger Publications, 2005
2. Bourne EJ: Coping with Anxiety: 10 Simple Ways to Relieve Anxiety, Fear, and Worry. Oakland, Calif, New Harbinger Publications, 2003
3. Brantley J, Kabat-Zinn J: Calming Your Anxious Mind. Oakland, Calif, New Harbinger, 2003
4. Burns DD: The Feeling Good Handbook. New York, Plume, 1999
5. Burns DD: When Panic Attacks: The New, Drug-Free Anxiety Therapy That Can Change Your Life. New York, Morgan Road Books, 2006
6. Foa EB, Andrews LW: If Your Adolescent Has an Anxiety Disorder: An Essential Resource for Parents. New York, Oxford University Press, 2006
7. Greenberger D, Padesky C: Mind Over Mood. New York, Guilford, 1995
8. Mackay M, Fanning P, Davis M: Thoughts and Feelings: Taking Control of Your Moods and Your Life: A Workbook of Cognitive-Behavioral Techniques, 2nd ed. Oakland, Calif, New Harbinger, 1998
9. Marks IM: Living With Fear: Understanding and Coping With Anxiety, 2nd ed. New York, McGraw-Hill, 2002

ORGANIZATIONS THAT PROVIDE INFORMATION ABOUT ANXIETY DISORDERS AND OTHER MENTAL HEALTH ISSUES

Anxiety Disorders Association of America
8730 Georgia Avenue
Suite 600
Silver Spring, MD 20910
Tel: 240-485-1001
http://www.adaa.org

The ADAA web site provides facts about anxiety disorders, self-administered tests, a guide to treatments, information for families, a listing of clinical trials, and other

resources. Visitors to the web site can search for therapists and support groups in their geographic area.

Anxiety Disorders Association of Canada
P.O. Box 117
Station Cote St-Luc
Montreal, Quebec
H4V 2Y3
Tel: 888-223-2252
http://www.anxietycanada.ca

The ADAC web site provides information for patients and families.

American Psychiatric Association
1000 Wilson Boulevard, Suite 1825
Arlington, VA 22209-3901
Tel: 703-907-7300
http://www.healthyminds.org

The Healthy Minds web site of the American Psychiatric Association provides brochures about panic disorder and other mental health problems, instructions for how to find a psychiatrist, hotline numbers, and other information.

American Psychological Association
750 First Street, NE
Washington, DC 20002-4242
Tel: 800-374-2721
http://www.apahelpcenter.org

The Help Center web site of the American Psychological Association provides facts and statistics about panic disorder and other mental health problems, instructions for how to find a psychologist, and other resources.

American Academy of Child and Adolescent Psychiatry
3615 Wisconsin Avenue, NW
Washington, DC 20016-3007
Tel: 202-966-7300
http://www.aacap.org

Facts for Families database: http://www.aacap.org/page.ww?section=Facts+for+Families&name=Facts+for+Families

AACAP provides fact sheets for families about panic disorder in children and adolescents and other anxiety disorders, as well as information about locating treating clinicians.

Association for Behavioral and Cognitive Therapies
305 7th Avenue, 16th Floor
New York, NY 10001
Tel: 212-647-1890
http://www.abct.org

The ABCT web site provides information about cognitive-behavioral therapy, fact sheets about panic disorder and other mental health problems, a "find a therapist" database, and other resources.

National Alliance on Mental Illness (NAMI)
Colonial Place Three
2107 Wilson Boulevard, Suite 300
Arlington, VA 22201
Tel: 1-800-950-6264
http://www.nami.org

The NAMI web site provides facts about mental health problems, information about medication treatment, information about research studies, helpline numbers, online discussion groups about anxiety disorders, and other resources.

National Institute of Mental Health (NIMH)
Public Information and Communications Branch
6001 Executive Boulevard
Room 8184, MSC 9663
Bethesda, MD 20892
Tel: 866-615-6464
http://www.nimh.nih.gov

The NIMH web site includes facts about anxiety disorders and other mental health problems, information about treatments, instructions about how to locate mental health services, and other information.

National Library of Medicine
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

The NLM is the U.S. government online repository of articles published in peer-reviewed medical journals.

National Mental Health Association
1021 Prince Street
Alexandria, VA 22314-2971
Tel: 800-969-6642 or 703-684-7722
http://www.nmha.org

The NMHA web site provides information about anxiety disorders and other mental health problems, information about treatments, resources for finding mental health services, a crisis number, and other resources.

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Academy of Psychosomatic Medicine
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American Academy of Pediatrics
American Academy of Psychoanalysis and Dynamic Psychiatry
American Association for Geriatric Psychiatry
American Association for Marriage and Family Therapy
American Association of Acupuncture and Oriental Medicine
American College of Neuropsychopharmacology

American Group Psychotherapy Association
American Nurses Association
American Psychiatric Nurses Association
American Psychological Association
Anxiety Disorders Association of America
Association for Academic Psychiatry
Association for Behavioral and Cognitive Therapies
Association for Behavioral Health and Wellness
Association of Family Psychiatrists
Bangladesh Association of Psychiatrists
Canadian Psychiatric Association
German Academy for Psychoanalysis
Indian Psychiatric Society
Kenya Psychiatric Association
Malaysian Psychiatric Association
Netherlands Psychiatric Association
Royal Australian and New Zealand College of Psychiatrists
Russian Society of Psychiatrists
Society for Adolescent Medicine
The American Academy of Psychoanalysis and Dynamic Psychiatry
World Federation for Mental Health

REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the summary recommendations and references:

[A] *Randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
[A–] *Same as above*, but not double-blind.
[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.
[D] *Case-control study.* A study in which a group of patients is identified in the present and information about them is pursued retrospectively or backward in time.
[E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.
[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
[G] *Other.* Textbooks, expert opinions, case reports, and other reports not included above.

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