CLINICAL PRACTICE

Panic Disorder

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 30-year-old woman, recently divorced, presents with daily episodes of chest pain, shortness of breath, sweating, and palpitations. She feels very anxious when these episodes occur and worries that she may be having a heart attack. She reports increasing avoidance of social activities, moodiness, poor sleep, and a low level of energy. She takes no medications and reports no drug or alcohol use. Her physical examination is normal. How should this case be managed?

THE CLINICAL PROBLEM

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Panic disorder occurred in approximately 1 to 3 percent of respondents to a community survey[1] and in 3 to 8 percent of patients seen by primary care physicians.[2-4] The disorder is twice as common among women as among men, and there appears to be a bimodal distribution in the age at onset, with one peak in late adolescence and a second peak in the mid-30s.[5,6] Patients who have panic disorder in adolescence frequently have depressive episodes or coexisting depression and anxiety in their early adult years.[7]

DIAGNOSIS

Table 1 lists the criteria for a diagnosis of panic disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.[6] These criteria require recurrent attacks of anxiety that build to a peak within seconds or minutes and a change in behavior such as avoidance of social activities, worry about having subsequent attacks, or concern about losing one's mind.[6] The worry in patients with panic disorder about recurrence of attacks or about the implication of attacks should be differentiated from the six months or more of worry about many other life issues required for the diagnosis of generalized anxiety disorder.

RISK FACTORS AND PRECIPITANTS

There are both biologic and environmental causes of panic disorder. Monozygotic twins have a significantly higher concordance rate for the disorder than do dizygotic twins.[8] The risk of panic disorder is increased by a factor of eight in first-degree relatives of patients with the disorder.[9] Panic disorder may result from an abnormally sensitive fear network, which includes the prefrontal cortex, insula, thalamus, amygdala and projections from the amygdala to the locus ceruleus, hypothalamus, periaqueductal gray substance, and parabrachial nucleus.[10]

Approximately 80 percent of patients with panic disorder report major life stressors during the previous 12 months.[11,12] Patients with a history of sexual or physical abuse in childhood have a higher risk of panic disorder as adults than those without this history,[13] as do teenagers who smoke, as compared with those who do not smoke.[14]

As many as 90 percent of patients with panic disorder will have at least one other psychiatric disorder during their lifetime.[1,5] Conditions reported more commonly among community-based–survey respondents with panic disorder than in the general population include major depression, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, bipolar disorder, and alcohol abuse.[1,5,15] In many patients, fears and avoidance of social situations develop after the development of panic disorder, along with a high associated risk of agoraphobia. Some,[16,17] but not all,[18] studies have shown an increased risk of suicidal ideation and suicide attempts in patients with panic disorder, even after adjustment for depression. The risk of suicidal behavior is likely to be increased among patients with panic disorder and coexisting major depression.[16-18]

The frightening physical symptoms of panic disorder often lead to extensive use of medical services.[19] Patients with medically unexplained syndromes such as irritable bowel syndrome,[20] chest pain with negative results on cardiac testing,[21] palpitations,[22] interstitial cystitis,[23] and chronic fatigue syndrome[24] have been shown to have higher rates of coexisting panic disorder than do control subjects with documented medical syndromes. The frequency of panic disorder is also higher among patients with asthma and other chronic respiratory disorders,[25] mitral-valve prolapse,[26] labile hypertension with negative results on testing for pheochromocytoma,[27] and migraine headache[28] than among those without these conditions.

Panic disorder is usually a relapsing–remitting disorder, although approximately 20 percent of patients have a chronic course.[29] Coexisting major depression, agoraphobia, and personality disorder, however, are predictive of more persistent panic attacks and symptoms of anxiety.[30]

Table 1. Criteria for a Diagnosis of Panic Disorder.*

Recurrent unexpected panic attack, defined as a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes:
- Palpitations, pounding heart
- Sweating
- Trembling or shaking
- Shortness of breath or choking
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, light-headed, or faint
- Derealization or depersonalization
- Fear of losing control or going crazy
- Fear of dying
- Chills or hot flushes
- Paresthesias

At least one of the attacks followed by one month (or more) of one (or more) of the following:
- Persistent concern about having additional attacks
- Worry about the implications of the attack or its consequences
- A clinically significant change in behavior related to the attacks

Panic attacks not due to the direct physiological effects of an illicit substance (or a prescribed medication) or a general medical condition (e.g., hyperthyroidism)

Panic attacks not better accounted for by another mental disorder, such as social phobia (on exposure to a feared social situation), a specific phobia (during exposure to a specific situation that prompts a phobic response), post-traumatic stress disorder (in response to stimuli associated with a severe stressor), or separation anxiety disorder (in response to being away from home or from a close relative)

* The criteria are from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition.[6]

STRATEGIES AND EVIDENCE

SCREENING

Screening for panic disorder is not routinely recommended but may be helpful in groups at high risk, such as heavy users of medical services and those with unexplained symptoms.[19-24,31] A two-item screening questionnaire has been shown to have a high sensitivity (range, 94 to 100 percent) but low specificity (range, 25 to 59 percent) in three primary care populations.[32] The two questions are as follows: In the past six months, did you ever have a spell or attack when all of a sudden you felt frightened, anxious, or very uneasy? In the past six months, did you ever have a spell or attack when for no reason your heart suddenly began to race, you felt faint, or you couldn't catch your breath? Another screening tool, the Patient Health Questionnaire, also includes screening questions for panic disorder (provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org).[32] This instrument is reported to have a high sensitivity (81 percent; 95 percent confidence interval, 69 to 93 percent) and specificity (99 percent; 95 percent confidence interval, 98 to 100 percent) for a diagnosis of panic disorder (as confirmed on an interview by a mental health professional).[33]

EVALUATION

A careful history taking and physical examination are warranted for all patients to rule out medical causes of symptoms. Conditions and agents that

can mimic or cause panic attacks include hyperthyroidism and hypothyroidism, temporal-lobe epilepsy, asthma, cardiac arrhythmias, pheochromocytoma, excessive intake of caffeine or other stimulants, withdrawal from alcohol, and treatment with high doses of corticosteroids.[33] Chemistry panels, measurement of thyrotropin levels, and electrocardiography are often ordered to identify underlying medical causes, but these tests usually have negative results in the absence of other evidence suggesting medical causes. Screening for depression[33] is important, given the increased prevalence of depression among patients with panic disorder and the associated risk of suicidal behavior.

EDUCATION OF PATIENTS

An essential step after the clinical diagnosis is made is to review with the patient her or his fears of medical illness and expectations of medical testing and treatment. More than 80 percent of patients with panic disorder present with a medical symptom, and most are fearful of having a serious condition, such as a heart attack.[31] Clinical experience suggests that patients benefit from education about panic disorder as the cause of their symptoms and the mechanism by which a brain disorder may provoke physical symptoms. Educational materials for patients may be obtained from the Anxiety Disorders Association of America (www.adaa.org) and the National Institute of Mental Health (www.nimh.nih.gov/healthinformation/anxietymenu.cfm).

PHARMACOLOGIC MANAGEMENT

Five classes of medication have been shown in randomized trials to be more effective than placebo in patients with panic disorder: selective serotonin-reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), high-potency benzodiazepines, tricyclic antidepressants, and monoamine oxidase inhibitors.[34-40] A recent meta-analysis compared the efficacy of three pharmacologic classes of medications with placebo in patients with panic disorder as measured by levels of global anxiety (frequency of panic attacks, and agoraphobia) and depression: SSRIs (in 17 trials), tricyclic antidepressants (in 23 trials), and benzodiazepines (in 25 trials).[34] The three classes of medication were equally effective in treating anxiety, but the effect of benzodiazepines in treating depression was marginally less that that of either tricyclic antidepressants or SSRIs.[34] Large studies have shown a clinically significant response (defined by a 50 percent decrease in the frequency of panic attacks or global anxiety) in 50 to 80 percent of patients treated with SSRIs, tricyclic antidepressants, or benzodiazepines.[34]

An earlier meta-analysis compared the effects of SSRIs or placebo in 12 randomized, controlled trials.[36] SSRIs were significantly more effective than placebo in reducing global anxiety and the frequency of panic attacks; more than 50 percent of patients treated with SSRIs became panic-free in seven of nine studies reporting this outcome. Another earlier meta-analysis found that tricyclic antidepressants were more effective than placebo in nine studies in reducing global anxiety and the mean frequency of panic attacks and that benzodiazepines were more effective than placebo in treating global anxiety (in 13 studies) and the frequency of panic attacks (in 7 studies).[37] In the seven studies that reported whether patients were panic-free at study completion, the rate of freedom from panic attacks was 61 percent for benzodiazepines and 58 percent for tricyclic agents.[37]

In a recent large, placebo-controlled trial in patients with panic disorder, the SNRI venlafaxine (Effexor, Wyeth-Ayerst), at a dose of 75 to 225 mg per day, reduced the global severity of panic, anticipatory anxiety, and fear and avoidance of social activities on the basis of validated anxiety scales. However, the drug did not increase the likelihood of becoming free of panic.[35]

Because of their safety profile, as compared with the safety profiles of tricyclic agents and monoamine oxidase inhibitors, SSRIs are recommended as the first drug option in the treatment of panic disorder.[36,38] The side effects of SSRIs (Table 2) tend to occur early in treatment, before the therapeutic effects. Because clinical experience suggests that many patients with panic disorder are hypervigilant regarding side effects, SSRIs should be started at low doses, with dose titration every five to seven days, as tolerated. The goal of treatment should be to eliminate panic attacks, if possible, because a partial response often results in continued avoidance of frightening situations and impairment in social functioning. After the patient is free of panic,

Table 2. Pharmacologic Treatment for Panic Disorder.*

Medication	Starting Dose	Therapeutic Dose	Half-Life	Side Effects
	mg/day			
Selective SSRIs				Class effects include nausea, anorexia, tremors, anxiety, sexual dysfunction, jitteriness, insomnia
Fluoxetine (Prozac, Eli Lilly)†	10	20–60	Long	Class effects
Sertraline (Zoloft, Pfizer)†	25	50–200	Short	Class effects and loose stools
Citalopram (Celexa, Forest)	10	20–60	Short	Class effects
Escitalopram (Lexipro, Forest)	10	10–30	Short	Class effects
Paroxetine (Paxil, GlaxoSmithKline)†	10	20–60	Short	Class effects and drowsiness, fatigue, weight gain
Paroxetine (controlled release) (Paxil CR, GlaxoSmithKline)†	12.5	12.5–25	Short	Class effects
Fluvoxamine (Luvox, Solvay)	50	150–300	Short	Class effects
Tricyclic antidepressants‡				Class effects include sedation, weight gain, dry mouth, urinary hesitancy, constipation, orthostatic hypotension, and slow conduction time through the His bundle
Imipramine (Tofranil, Mallinckrodt)	10–25	100–300	Short	Class effects
Nortriptyline (Pamelor, Mallinckrodt)	10–25	75–125	Short	Class effects
Desipramine (Norpramin, Sanofi Aventis)	10–25	100–300	Short	Class effects
Benzodiazepines§				Class effects include sedation, cognitive slowing, physical dependence
Clonazepam (Klonopin, Roche)†	0.25, 3 times daily	0.5–1.5, 3 times daily	Moderate	Class effects
Alprazolam (Xanax, Pharmacia and Upjohn)†	0.25, 3 times daily	0.5–1.5, 3 times daily	Short	Class effects
Alprazolam (extended-release) (Xanax XR, Pharmacia and Upjohn)†	0.50–1.0, 3 times daily	1–5, once daily	Long	Class effects
Lorazepam (Ativan, Wyeth)	0.25, 3 times daily	0.5–1.5, three times daily	Short	Class effects
SNRI				
Venlafaxine (extended-release) (Effexor XR, Wyeth)†	37.5	75–300	Short	Class effects include nausea, sweating, dry mouth, dizziness, insomnia, somnolence, sexual dysfunction, and hypertension at doses >300 mg

* Clonazepam and all SSRIs, except paroxetine, are in Food and Drug Administration (FDA) pregnancy category C. Paroxetine is in category D, as are all tricyclic antidepressants, lorazepam, and alprazolam. Category C drugs include those for which "either studies in animals revealed adverse effects on the fetus and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus." Category D drugs include those for which "there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)."

† This drug was approved by the FDA for the treatment of panic disorder.

‡ Baseline electrocardiography is recommended (tricyclic antidepressants are contraindicated for patients with conduction abnormalities).

§ These agents could be used as needed to help patients confront feared situations. A 0.5-mg dose of oral clonazepam, alprazolam, or lorazepam or a 0.5-mg dose of sublingual lorazepam is recommended.

the clinician should encourage her or him to reencounter feared situations to increase confidence in abilities and participation in social activities.

Although rigorous data are lacking to guide the care of patients who do not have a response to initial SSRI therapy, clinical experience suggests that it is reasonable to try an alternative SSRI. If there is still no response, switching to another class of drug — tricyclic antidepressant, benzodiazepine, or SNRI — is recommended.[38]

Although the benzodiazepines continue to have an important role in the treatment of panic disorder, concern with respect to dependence, medication abuse, side effects, and the rapid reemergence of symptoms after discontinuation have led to the recommendation that these agents should not be the first choice for treatment.[39] When benzodiazepines are used in combination with antidepressants, there is a more rapid treatment response than with antidepressants alone.[40] In a trial comparing sertraline (Zoloft, Pfizer) and placebo with sertraline and clonazepam (Klonopin, Roche) (at a dose of 0.5 mg three times a day), the clonazepam group had a significantly higher rate of response (defined by a decrease in symptoms of 50 percent or more) than the group receiving sertraline and placebo at week 1 (41 percent vs. 4 percent) and week 3 (63 percent vs. 32 percent), but not at later points of assessment.[40] Benzodiazepines can also be added to antidepressants to counteract patients' early jitteriness and agitation or to augment antidepressants in those who have a partial response to treatment.[39] Benzodiazepines with longer half-lives (such as extended-release alprazolam [Xanax XR, Pharmacia and Upjohn] and clonazepam) are often preferred in order to reduce breakthrough anxiety. Benzodiazepines are frequently used "as needed," to permit confrontation with feared stimuli (e.g., air travel). Infrequent as-needed use, such as three times a month, is not a matter of concern, but more frequent use may lead to fluctuating serum levels and withdrawal symptoms.[39]

A disadvantage of the benzodiazepines is that as many as 40 to 80 percent of patients treated with them for longer than four months may have a discontinuation syndrome, characterized by anxiety, irritability, headache, muscle tension, perceptual abnormalities, insomnia, decreased concentration, and cardiorespiratory symptoms upon stopping the medication.[41] A slow tapering over four to eight weeks is recommended. Switching to a benzodiazepine with a longer half-life may facilitate tapering of the dose.[39] Generally, patients who have a history of substance abuse, personality disorder, or chronic pain should not be treated with benzodiazepines because of the high risk of overuse of these medications. Those with moderate-to-severe major depression and panic should initially be treated with antidepressants (either alone or in combination with other medications).[38]

NONPHARMACOLOGIC MANAGEMENT

Cognitive behavioral treatment is provided in 12 to 16 sessions over a period of three to four months and is focused on recreating the feared symptoms and then modifying the patient's usual responses to the symptoms.[42] If a feared symptom is rapid heart rate, for example, the mental health professional or physician may have the patient jog in place until the symptoms are provoked. The mental health professional or physician helps the patient correct cognitive distortions such as exaggerating the threat to health (e.g., having thoughts such as "I am going to die") that precipitate more anxiety. Finally, the mental health professional or physician helps the patient modify the associated behaviors, such as seeking escape and avoidance.

A recent meta-analysis of 11 randomized clinical trials comparing the use of cognitive behavioral treatment and antidepressants (SSRIs or tricyclic antidepressants) showed that these treatments had similar effects on global anxiety, clinical response (defined by a decrease in symptoms of 50 percent or more), and depression.[34] The largest of these trials compared cognitive behavioral treatment (initially weekly) alone, an antidepressant (imipramine [Tofranil, Mallinckrodt]) alone, cognitive behavioral treatment plus imipramine, and cognitive behavioral treatment plus placebo with placebo alone in a study of 312 patients with panic disorder uncomplicated by depression or agoraphobia.[43] After three months, response rates (defined by a decrease in symptoms of 40 percent or more, according to a global panic measure) were significantly greater for all active treatments than for placebo: 49 percent with cognitive behavioral treatment alone, 46 percent with imipramine alone, 60 percent with cognitive behavioral treatment and imipramine, and 57 percent with

cognitive behavioral treatment and placebo (vs. 22 percent with placebo). There were no significant differences between the group receiving imipramine alone and the group receiving cognitive behavioral treatment alone.

Patients with a response at three months entered a six-month maintenance phase of monthly appointments; at nine months, response rates for all groups receiving active treatment remained better than for placebo: 40 percent in the group receiving cognitive behavioral treatment alone, 38 percent in the group receiving imipramine alone, 57 percent in the group receiving cognitive behavioral treatment and imipramine, and 47 percent in the group receiving cognitive behavioral treatment and placebo, as compared with 13 percent in the placebo group. Response rates for cognitive behavioral treatment at nine months were similar to that (54 percent) reported in a meta-analysis of 14 studies.[44] The combination of cognitive behavioral treatment and imipramine was more effective than cognitive behavioral treatment alone or imipramine alone but not significantly more effective than cognitive behavioral treatment and placebo.[43]

A meta-analysis of 20 studies comparing cognitive behavioral treatment and antidepressant medication with cognitive behavioral treatment alone likewise suggested that the combination was more effective in reducing global anxiety and depression than either therapy alone.[34] However, this meta-analysis found that both approaches were similarly effective during long-term follow-up after treatment had ended.

Some improvement is expected within 2 to 4 weeks with medication and within 4 to 8 weeks with cognitive behavioral therapy, although a full response to either therapy may take 8 to 12 weeks. If there is no improvement within six to eight weeks, reconsideration of the diagnosis is warranted. The clinician should also consider the need for a different treatment or for combined cognitive behavioral treatment and medication. When treatment with medication is effective, discontinuation should be considered after 12 months, although data are lacking to guide the optimal duration of therapy. Close follow-up is warranted, because as many as one third of patients will have a relapse within two years after treatment has ended.[45] If the patient has a relapse, it is reasonable to start another course of the treatment that was previously successful. For patients who have two or more relapses, long-term use of medication may be necessary.[38]

GUIDELINES

The clinical practice guidelines for the treatment of panic disorder of both the American Psychiatric Association[38] and the Royal Australian College of Psychiatrists[46] recommend that the severity of symptoms, patients' preferences, the response to treatment during prior episodes, and the availability of a clinician with experience with cognitive behavioral treatment should influence the treatment recommendations, since medications and cognitive behavioral treatment are equally effective. When medications are used, both of the guidelines recommend initiating SSRIs as the first line of treatment on the basis of their better side-effect profile and safety than tricyclic antidepressants and benzodiazepines and given the more limited data on the efficacy of SNRIs.

AREAS OF UNCERTAINTY

The optimal length of prophylactic pharmacotherapy after a response to short-term treatment is unclear. There are limited data regarding the role of cognitive behavioral treatment in patients with a partial response or no response to pharmacotherapy, and vice versa. There are also limited data on the optimal choice of a next medication if the first one proves to be ineffective. More studies are needed to confirm whether cognitive behavioral treatment, as compared with pharmacotherapy, may be associated with a lower risk of relapse.[34,43]

Strategies are needed to enhance the provision of effective care to people in the general population who have panic disorder, since only a minority of those with this disorder receive any mental health treatment. In two trials, the integration of mental health professionals into primary care to help in the provision of pharmacotherapy, cognitive behavioral treatment, or both in patients with panic disorder was associated with a reduction in the levels of anxiety and total health care costs, as compared with usual primary care.[47,48] In the first trial, psychiatrists consulted with patients for approximately two visits to assist the primary care physician with pharmacologic man-

agement of the disorder. In the second trial, mental health professionals were integrated into the primary care to provide cognitive behavioral treatment and aid pharmacologic management on the basis of recommendations of the supervising psychiatrists.[47,48]

SUMMARY AND RECOMMENDATIONS

The patient in the vignette has symptoms typical of panic disorder associated with increasing avoidance of social activities and associated depressive symptoms. Either pharmacologic therapy or cognitive behavioral treatment is a reasonable initial approach, because the two therapies are equally effective in controlling symptoms. The choice between them should be based on the patient's preference and the availability of competent cognitive behavioral therapists. SSRIs should be the first line of pharmacologic treatment for patients with panic disorder. If side effects such as jitteriness arise, adjunctive short-term treatment with a benzodiazepine may be helpful. One year of treatment is generally recommended after an initial response. If bothersome side effects persist, tricyclic antidepressants, an SNRI, or benzodiazepines may be used, since all have also been proven to be effective in the treatment of panic disorder in randomized clinical trials.

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