



Diagnosis and treatment of panic disorder

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ANXIETY DISORDERS are the most prevalent form of psychiatric disorder in the community, with phobic disorders representing the bulk of anxiety disorders.¹ In the United States 1% to 2% of the population has suffered from panic disorder (PD), and when agoraphobia is combined with PD, the prevalence is closer to 3% to 5% or nearly one in every 20 individuals. This is an important statistic in view of the pervasive social, economic, and health consequences of PD. Data from the Environmental Catchment Area (ECA) study show that patients with PD exhibit subjective feelings of poor physical and emotional health, alcohol and drug abuse, an increased likelihood of suicide attempts, impaired social and marital functioning, financial dependency, and a high utilization of psychoactive medications, health services, and hospital emergency services.²

Among the more remarkable findings is that both panic attacks and PD are associated with an increase in the risk of suicidal ideation and attempted suicide.^{2,3} Of those surveyed in the ECA study, 20% of the patients with PD and 12% of those with panic attacks had attempted suicide. The risk of a suicide attempt was further increased by drug abuse and by an early age of onset of PD. Neither comorbid major depression nor agoraphobia contributed significantly to these findings. Among the patients with PD, 47% indicated that they "felt so low [they] thought about committing suicide" and 64% indicated that they "thought a lot about death."³ Other data have demonstrated an excess mortality rate in PD patients as a result of suicide and cardiovascular disorders, and panic attacks in depressed

patients have been associated with an increased risk of suicide within one year of the diagnosis of major affective disorder (references for these data are available in reference 2).

Given these findings, the timely and effective treatment of PD is important. Both pharmacologic and behavioral modalities used either individually or in combination have proven useful and result at times in a dramatic reversal of both psychic pain and a restricted lifestyle. The optimal duration of treatment, however, is controversial. Naturalistic and treatment discontinuation studies should help clarify this matter.

DIAGNOSIS

Panic attack

The hallmark of PD is the panic attack, that is, a discrete episode of intense anxiety that crescendos within minutes, is frequently characterized by an intense desire to flee, and is associated with one or more somatopsychic symptoms suggestive of autonomic nervous system arousal (*Table 1*).

There are four subtypes of panic attacks. A panic attack has four or more of the symptoms listed in *Table 1*; a limited symptom panic attack has fewer than four. Panic attacks that seem to have no precipitant are referred to as spontaneous, or unexpected. Panic anxiety quickly generalizes to or becomes associated with the circumstance in which it occurred. Therefore, subsequent exposure to these circumstances may precipitate situational panic attacks. Given the propensity of panic anxiety to generalize, most attacks that occur during the course of panic disorder are thought to be situational.

Although not listed in the *Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric*

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TABLE 1
DIAGNOSTIC CRITERIA FOR PANIC ATTACK*

At least four of the following symptoms have developed suddenly and have increased in intensity within minutes of the beginning of the first symptom noticed in the attack:

1. Shortness of breath (dyspnea) or smothering sensations
2. Dizziness, unsteady feelings, or faintness
3. Palpitations or tachycardia
4. Trembling or shaking
5. Sweating
6. Choking
7. Nausea or abdominal distress
8. Depersonalization or derealization
9. Numbness or tingling sensations (paresthesias)
10. Flashes (hot flashes) or chills
11. Chest pain or discomfort
12. Fear of dying
13. Fear of going crazy or of doing something uncontrolled

* From ref 4.

*Association, Third Edition, Revised (DSM III-R),*⁴ atypical panic attacks are characterized by irritability and angry outbursts (“anger attacks”), psychosensory disturbances such as distortion of sound and light intensity, body-image distortions, and shock like sensations in the head, neck, and back. There can also be a speeding up or slowing down of thoughts or a sensation of floating, turning, or moving. These atypical attacks may mimic or be a manifestation of complex partial seizures.

Panic disorder

PD is a familial disorder that occurs about twice as often in females as males. The diagnosis is made when an individual has had (1) one or more panic attacks that were unexpected (and not triggered by being the focus of others' attention, as in Social Phobia); (2) either four attacks within a four-week period or one or more attacks that have been followed by a period of at least a month of persistent anticipatory anxiety; (3) at least four of the symptoms listed in *Table 1* during at least one of the attacks; and (4) no identifiable organic factor initiating or maintaining the disturbance.⁴

Panic anxiety is often disabling. For example, an individual having a panic attack may find it necessary to pull over to the side of the road or to leave a meeting. As a result panic attacks are frequently followed by anticipatory anxiety, that is, a fear of the next attack or those circumstances or thoughts that precipitate attacks. Intense anticipatory anxiety following the first panic attack (i.e., herald attack) may actually increase the likelihood of having subsequent panic attacks and is presumably a factor in the genesis of phobic avoidance, or agoraphobia. This view is

challenged by the observation that some patients experience agoraphobia without ever having a panic attack and also by data indicating that agoraphobic avoidance often precedes the first panic attack.⁵

Agoraphobia

In Greek, agoraphobia means “fear of the market place,” and in DSM III-R is defined as “fear of 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 a panic attack.... As a result of this fear, the person either restricts travel or needs a companion when away from home or else endures agoraphobic situations despite intense anxiety.”⁴ Common agoraphobic situations described by patients include being outside the home alone, being in a crowd or standing in a line, being on a bridge, and traveling in a bus, train, or car. Patients who suffer from mild agoraphobia may lead a relatively normal life, avoiding only a few things or enduring anxiety-provoking circumstances with some distress. However, when agoraphobia is severe, the degree of avoidance may result in a patient's being nearly or completely housebound.

Panic disorder and depression

Several lines of evidence point to a relationship between anxiety and depressive disorders.⁶ Symptoms of panic and depression frequently overlap. PD is responsive to antidepressants, while depressive symptoms often improve after treatment with an anxiolytic, and the family histories of patients with PD are positive for both panic and affective disorders. Approximately one-third of patients with primary PD develop a secondary major depressive episode.⁷ Patients with so-called atypical depression manifest rejection sensitivity, extreme fatigue, and phobic anxiety.

CLINICAL EVALUATION

Typical and uncomplicated PD is easily diagnosed. However, when making the diagnosis, the clinician must adhere closely to the diagnostic criteria for PD, since panic attacks accompany many disorders and can also be confused with other phenomena (e.g., stress-induced fragmentation of identity in the patient with borderline personality disorder). This requires a careful and detailed clinical evaluation, and in atypical or complicated cases, the clinician must entertain a lengthy differential diagnosis encompassing a broad

range of both medical and psychiatric disorders that either mimic or accompany PD.

Medical disorders that commonly are both associated with and mimic PD include endocrine disturbances (e.g., hyperthyroidism, hypoglycemia), cardiac disturbances (e.g., mitral valve prolapse [MVP], angina, arrhythmias), audiovestibular dysfunction, and complex partial seizures. The symptoms of hyperthyroidism can easily be mistaken for those of PD, and hyperthyroidism has been reported to occur in nearly 10% of patients with PD.⁸ Similarly, it is generally held that MVP occurs more frequently in PD patients than in the general population; in one carefully controlled study, the incidence of MVP in PD patients was 34%.⁹ It has been suggested, however, that a substantial proportion of the cases of MVP are secondary to the hyperdynamic cardiovascular state associated with PD and that M-mode echocardiography (i.e., the technique used in most studies to detect prolapse) is unreliable and capable of generating false-positive interpretations that contribute to overdiagnosis of MVP in patients with PD.

In contrast, PD may be underdiagnosed in patients who present to medical settings. Katon et al. found that up to 13% of patients in a primary care practice had underlying PD.¹⁰ Pain appears to be a common presenting complaint in this group. Among patients who presented to a primary care clinic and were ultimately diagnosed as having PD, 88% had a chief complaint of pain.¹¹ In this and other investigations of the relationship between chest pain and PD, 30% to 40% of patients who present with chest pain and have normal coronaries turn out to have PD.^{11,12}

Psychiatric disorders that often are comorbid or confused with PD include major depression (particularly atypical depression), obsessive compulsive disorder, substance abuse disorder, borderline personality disorder, and somatization disorder.

Laboratory investigation

There is no laboratory finding that confirms the diagnosis of PD. Therefore, laboratory testing helps either to verify or to exclude underlying medical disorders.

Blood and urine tests may be used in the evaluation of substance abuse, metabolic and endocrine (e.g., hyperthyroidism and hypoglycemia), or fluid and electrolyte disturbances (e.g., hyponatremia). The electrocardiogram and Holtor monitor will assist in the evaluation of cardiac arrhythmias and chest pain, and the two-dimensional Doppler echocardiogram will help in

the resolution of questions about MVP. An electroencephalogram (EEG) performed during sleep may be indicated for the patient who presents with atypical panic attacks. Since complex partial seizures are difficult to detect with a routine surface EEG (presumably because the seizure focus is in deep limbic structures), repeated sleep EEGs performed with nasopharyngeal or sphenoidal leads may increase the yield of positive findings. All-night polysomnography or a telemetered EEG is useful in diagnostically ambiguous cases, in the evaluation of nocturnal panic, and when episodic seizure activity might not be detected by one or more transient EEG recordings. A computerized tomographic (CT) scan and/or magnetic resonance imaging (MRI) are indicated if a structural lesion is suspected in the central nervous system (CNS). Positron emission tomographic (PET) scanning has demonstrated abnormal asymmetry of blood flow in the area of the parahippocampal gyrus in patients who develop panic attacks during lactate infusion; however, this remains an unconfirmed research finding.

Panic disorder in the emergency room

Patients with PD utilize the services of both general medical and psychiatric professionals more frequently than do patients with major depression, and the emergency room (ER) seems to be an important site of these services.² Among those in the ECA population who had active PD within the past year, 42% went to an ER for emotional problems. Little has been reported about this ER subpopulation. Presumably, many of these patients present with physical complaints (e.g., chest pain) and are discharged with reassurances that they are in good physical health and that their complaints are due to "nerves." Also, on the basis of the ECA study data, it is possible that PD patients, particularly those who abuse alcohol and other drugs, present to the ER as victims of attempted suicide.

TREATMENT

General principles

Anxious patients generally respond favorably to discussion, education, and reassurance. Patients with PD, in particular, are relieved to know that their suffering is not unique, that their fear of death or insanity is groundless, and that their symptoms may have a biological rather than a purely psychological basis.

All anxious patients should discontinue or at least minimize use of products that augment anxiety. Caf-

feine-containing foods (e.g., colas, tea, coffee, and chocolate) should be eliminated from the diet. Medications such as theophylline, diet pills containing phenylpropanolamine or other amphetamine-like substances, and decongestants (e.g., pseudoephedrine) should be reduced or discontinued if possible.

Since substance abuse is prevalent and also a common cause of secondary anxiety, patients should be advised to eliminate recreational substances that may cause anxiety (e.g. cocaine, marijuana, phencyclidine [PCP], and amphetamines) and to limit or avoid altogether the use of alcohol. This last point cannot be overstated since patients frequently use alcohol and other sedative-hypnotic agents both indiscriminately and surreptitiously to control anxiety and tension. Anxiety and panic attacks are likely to occur as blood levels of sedative-hypnotics and alcohol fall, resulting in an ongoing cycle of substance abuse, anxiety, and further abuse in response to the secondary anxiety. Finally, the clinician should advise the patient to get adequate rest, since fatigue can be a precipitant of anxiety.

Following these preliminary measures, and assuming that other causes of anxiety have been treated or ruled out, a course of anxiolytic therapy is indicated. Successful treatment of PD and phobic avoidance often requires a multimodal strategy involving one or more behavioral, cognitive, and drug therapies.

Behavioral and cognitive therapies

Some will argue that all patients with PD should be given an initial trial of behavioral therapy since it has been shown to reduce both panic attacks and phobic avoidance and avoids the potential risks of pharmacologic management.¹³ Some behaviorists maintain that medication can interfere with a successful response to behavioral therapy. Most techniques focus on increasing patient exposure to phobic circumstances with a goal of gradual desensitization and recovery of normal involvement.

Maladaptive behavioral patterns are also maintained by erroneous or irrational thoughts, such as "I am going to die," "I will fall or faint and no one will help me," or "I am going to end up in a psychiatric ward." Cognitive therapy can assist the patient in eradicating such negative, anxiety-provoking thinking by replacing it with positive thoughts such as "This anxiety will pass as it always does," and "This is only a panic attack, which means that I am not going to die." These simple cognitive maneuvers are based on the principle that negative, pessimistic, or unwarranted thoughts are

TABLE 2
STANDARD PHARMACOLOGICAL ALTERNATIVES FOR
TREATMENT OF PANIC DISORDER

Generic name	Brand name	Starting dose (mg/day)	Dosage range (mg/day)	Usual dosing interval
Tricyclic antidepressants				
Imipramine	Tofranil	10–25	150–300	hs
Desipramine	Norpramin, Pertofrane	10	150–300	hs
Nortriptyline	Aventyl, Pamelor	10	75–150	hs
Monoamine oxidase inhibitors				
Phenelzine	Nardil	15–30	45–90	tid-qid
Tranylcypromine	Parnate	10–20	20–40	bid-tid
Benzodiazepines				
Alprazolam	Xanax	0.25 tid	3–6	tid-5id
Clonazepam	Klonopin	0.25–0.5	1–3	bid-tid

often the source of anxiety and depression.

Although many anxious patients prefer and benefit significantly from behavioral and cognitive therapies, persistent panic and anticipatory anxiety often interfere with successful performance of the prescribed tasks. Some patients will resist exposure techniques until panic attacks have been controlled. This group requires primary pharmacotherapy. Once panic attacks have been brought under control, the behavioral management of remaining avoidance can proceed more smoothly.

Pharmacologic treatments

Traditionally, the tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) have been regarded as first-line agents for the treatment of panic disorder.¹ Clinical investigation in the early 1960s demonstrated that imipramine successfully treated certain types of anxiety neurosis, later known as panic disorder. Not only did this finding challenge notions about the etiology and classification of anxiety and depressive disorders, it also relegated benzodiazepines to a position of secondary importance for the treatment of PD. However, in the past 10 years, high-potency benzodiazepines have achieved recognition as effective antipanic medications.^{1,14} Table 2 summarizes the use of standard antipanic agents.

Antidepressants. Imipramine is the prototype antipanic agent, but theoretically any TCA can effectively treat PD.¹ The mechanism of action is uncertain.

Despite occasional advice to use less than the recommended doses of antidepressant medication, controlled trials and clinical experience suggest that PD responds only to full antidepressant doses of TCA (e.g.,

150 to 300 mg of imipramine or desipramine per day). However, the starting dose may need to be lower than is customary for routine antidepressant therapy. Initiation of treatment with 25 to 50 mg of TCA often causes jitteriness, insomnia, and tremulousness in PD patients, who as a group are more susceptible to TCA-induced symptoms of CNS stimulation. Consequently, it is preferable to initiate treatment with TCA (e.g., imipramine, desipramine, or nortriptyline) at 10 mg/day and to increase gradually to a therapeutic dose. The rate of escalation depends on the intensity of therapeutic and adverse effects and on the patient's degree of comfort with adjustments of his or her medication. In addition, PD patients are either more likely than depressed patients to develop other TCA-associated side effects (e.g., anticholinergic and sexual) or are perhaps more sensitive to the development of these effects. Side effects may prevent an optimal anxiolytic response to TCA in a significant number of patients.

MAOIs are as effective or possibly more so than TCA for control of panic anxiety, but their use is often limited by intolerable side effects (e.g., orthostatic hypotension, weight gain, and sexual dysfunction). In addition, MAOIs pose the risk of hypertensive crisis unless a restricted (tyramine-free) diet is carefully followed. Anxious patients are often frightened by a discussion of these risks and potential side effects and refuse treatment that might otherwise be beneficial.

The management of dosage is much the same as it is for the treatment of major depression. The physician should advise the patient to avoid both the medications and tyramine-containing food substances that can cause a rise in blood pressure. Also, concurrent antihypertensive medication may need to be adjusted or discontinued if postural hypotension develops during MAOI therapy.

Benzodiazepines. Alprazolam was among the first benzodiazepines (BZDs) to demonstrate clear-cut efficacy in the treatment of PD.^{1,14} Given the previous doubts about the antipanic efficacy of BZDs, the success of alprazolam was attributed to its unique triazolo ring structure, which was believed to account for its putative antidepressant properties as well. In short, alprazolam was thought to be effective for PD principally because of its antidepressant characteristics.

The importance of BZD potency was brought into focus by the finding that other high-potency BZDs, such as clonazepam, also have antipanic properties.¹⁴⁻¹⁶ Both uncontrolled¹⁵ and controlled^{16,17} clinical trials have shown that clonazepam and alprazolam have at least comparable efficacy in the treatment of

PD. Endpoint analysis of the results in 72 patients randomized to receive clonazepam (N = 26), alprazolam (N = 24), and placebo (N = 22) demonstrated a significant effect of both active treatments on measures of panic anxiety.¹⁷ Clinical experience with these agents also suggests that clonazepam may circumvent the interdose rebound and symptom recurrence that can occur with alprazolam.¹⁵ These characteristics have been attributed to the longer elimination half-life of clonazepam (approximately 35 hours *v* 12 hours for alprazolam).

As a result, clonazepam has recently been advocated as the BZD of choice for treatment of PD. Like alprazolam, it is effective in around 70% to 80% of individuals with panic anxiety but has proven superior for patients who develop interdose rebound or symptom recurrence with alprazolam.¹⁸

When these agents are ineffective, another BZD, an antidepressant, or both may be tried. Although the use of BZDs has been criticized because of their potential for abuse, this complication appears to be unusual in individuals who do not otherwise abuse drugs or alcohol.¹⁹ Patients often develop a psychological and physiological dependence on BZDs, and because the risk of a withdrawal syndrome is significant, it is imperative that BZDs not be discontinued suddenly. Many individuals with panic anxiety remain on BZDs, antidepressants, or the combination of the two chronically and indefinitely because symptoms recur when medication is reduced or discontinued. It is not clear to what extent the persistence of symptoms is a drug-induced phenomenon and to what extent it reflects the chronic, relapsing nature of anxiety.

The starting dose of alprazolam is generally 0.5 mg orally, two to three times per day. Initial drowsiness usually passes after several days of continued use, but if it does not, the dose should be lowered. The average maintenance dose is 3 to 6 mg per day. Patients may report that the anxiolytic effect of alprazolam begins to wane 4 to 6 hours after the last dose, particularly if the duration of alprazolam use has been 6 months or longer. Interdose recurrence of anxiety is believed to be due to the relatively short elimination half-life of alprazolam (i.e., 10 to 14 hours) and may contribute to the need for up to five or six doses of medication per day. Patients have been known to awaken regularly in the early hours of each morning to take a scheduled dose of alprazolam. Such circumstances foster intense psychological and physiological dependence. When interdose symptom recurrence and signs of dependence develop, it may prove helpful to switch the patient to clonaze-

pam or to add an antidepressant.¹⁸ Sudden discontinuation of alprazolam can precipitate a serious withdrawal syndrome characterized by seizures and/or delirium that is difficult to treat with other BZDs, presumably because of the unique triazolo-ring structure and receptor-binding characteristics of alprazolam.

Clonazepam, which is approximately twice as potent as alprazolam, is started at a dosage of 0.5 mg once a day with a goal of reaching 1 to 2 mg daily in two divided doses. Its relatively long half-life permits less frequent dosing and also results in more continuous control of anxiety. The risks of dependence and withdrawal should be reported to the patient, but unsubstantiated clinical experience suggests that they are comparatively less intense than those seen with alprazolam. The prolonged elimination half-life of clonazepam probably accounts for the findings of less interdose recurrence of symptoms, less drug craving, and less severe withdrawal, as well as its reported success in helping patients withdraw from alprazolam.²⁰ Patients should be warned about the risks of additive toxicity when clonazepam (or any BZD) is taken in combination with alcohol or other CNS depressant. Furthermore, patients should be dissuaded from using alcohol because it can exacerbate or trigger panic anxiety.

Finally, since clonazepam has not yet been approved by the Food and Drug Administration (FDA) for use in the treatment of PD, it is advisable that patients be so informed. Lack of FDA approval should not dissuade one from prescribing a drug approved for other purposes; however, it is recommended that the physician document and provide information about the indications, risks, and benefits of treatment with the drug.

SUMMARY

Patients who suffer from anxiety disorders such as PD have been referred to colloquially as the "worried well." Recently published data and clinical experience indicate that they are indeed "worried" but not necessarily so "well." Acute treatment is effective in reducing if not eliminating troublesome symptoms and is associated with dramatic improvements in the lifestyle of some patients. However, further experience is neces-

sary to determine the impact of treatment on the long-range morbidity and mortality associated with PD.

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REFERENCES

1. Barlow DH, Shear MD, ed. Panic disorder. [In] Frances AJ, Hales RE, eds. *Review of Psychiatry*. Washington, DC, American Psychiatric Press, 1988, Vol 7, pp 5-138.
2. Markowitz JS, Weissman MM, Oullette R, Lish JD, Klerman GL. Quality of life in panic disorder. *Arch Gen Psychiatry* 1989; **46**:984-992.
3. Weissman MM, Klerman GL, Markowitz JS, Oullette R. Suicidal ideation and suicide attempts in panic disorder and attacks. *N Engl J Med* 1989; **321**:1209-1213.
4. *Diagnostic and Statistical Manual of Mental Disorders*, ed 3, revised. Washington, DC, American Psychiatric Press, 1987.
5. Lelliott P, Marks I, McNamee G, Tobena A. Onset of panic disorder with agoraphobia. *Arch Gen Psychiatry* 1989; **46**:1000-1005.
6. Breier A, Charney DS, Heninger GR. The diagnostic validity of anxiety disorders and their relationship to depressive illness. *Am J Psychiatry* 1985; **142**:787-797.
7. Lesser IM, Rubin RT, Pecknold PC, et al. Secondary depression in panic disorder and agoraphobia. *Arch Gen Psychiatry* 1988; **45**:437-443.
8. Lindemann CG, Zitron CM, Klein DF. Thyroid dysfunction in phobic patients. *Psychosomatics* 1984; **25**:603-606.
9. Libberthson R, Sheehan DV, King ME, et al. The prevalence of mitral valve prolapse in patients with panic disorder. *Am J Psychiatry* 1986; **143**:511-515.
10. Katon W, Vitaliano PP, Russo J, et al. Panic disorder: Epidemiology in primary care. *J Fam Practice* 1986; **3**:233-239.
11. Katon W. Panic disorder and somatization. *Am J Medicine* 1984; **77**:101-106.
12. Beitman BD, Lamberti JW, Mukerji V, et al. Panic disorder in patients with angiographically normal coronary arteries. *Psychosomatics* 1987; **28**:480-484.
13. Marks IM. Behavioral aspects of panic disorder. *Am J Psychiatry* 1987; **144**:1160-1165.
14. Tesar GE. High-potency benzodiazepines for the short-term management of panic disorder: The U.S. experience. *J Clin Psychiatry* 1990; **51**(suppl 5):4-10.
15. Pollack MH. Clonazepam: A review of open clinical trials. *J Clin Psychiatry* 1987; **48**(suppl 10):12-15.
16. Tesar GE, Rosenbaum JF, Pollack MH, Sachs G, Herman JB, Cohen L. Clonazepam versus alprazolam in the treatment of panic disorder: Interim analysis. *J Clin Psychiatry* 1987; **48**(suppl 10):16-19.
17. Tesar GE, Rosenbaum JF, Pollack MH, et al. Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder: Final results. *J Clin Psychiatry* (submitted).
18. Herman JB, Rosenbaum JF, Brotman AW. The alprazolam to clonazepam switch for the treatment of panic disorder. *J Clin Psychopharmacol* 1987; **7**:175-178.
19. Woods JH, Katz JL, Winger G. Use and abuse of benzodiazepines. *JAMA* 1988; **260**:3476-3480.
20. Patterson JF. Alprazolam dependency: use of clonazepam for withdrawal. *Southern Med J* 1988; **81**:830-831.