

Panic Disorder (panic disorder with or without agoraphobia, DSM-IV-TR #300.01, 300.21)

Panic disorder is characterized by the repeated occurrence of discrete panic attacks. Between attacks these patients are often well, although most, after repeated attacks, develop some persistent apprehension, or anticipatory anxiety, regarding the possibility of another attack; in turn, about one half of these patients eventually develop agoraphobia.

This is a relatively common disorder and has a lifetime prevalence of from 1 to 2%. It is several times more common in women than in men. In the past these patients might have received many different diagnoses including the following: DaCosta's syndrome, "effort heart," neurocirculatory asthenia, neurasthenia, and acute anxiety neurosis. However, in reading old reports keep in mind that these are not actual synonyms for panic disorder but rather loosely defined terms that include not only patients who today would be diagnosed as having panic disorder but also many other patients suffering sometimes from quite disparate disorders.

ONSET

Although some patients, in retrospect, report feeling vaguely unwell in the weeks or months before their first panic attack, most experience no prodrome, and the onset of the illness is heralded by the occurrence of the first attack. This experience is often recalled in vivid detail, and patients may be able to describe precisely the circumstances in which the attack occurred. This first attack generally occurs in late adolescence or the early twenties; however, later onsets, up to the thirties, are not uncommon. Rarely, onset may occur in childhood or over the age of 40.

CLINICAL FEATURES

The panic attack itself usually comes on acutely, often within a minute, and crescendos rapidly. Symptoms generally last only 5 to 15 minutes, or sometimes less, and very rarely up to an hour, and then recede over minutes. After the attack most patients feel "shaken," and may feel drained and apprehensive for a long time, sometimes hours. During the attack itself, patients may experience any of the symptoms listed in the box (this page). These symptoms may appear in any combination, and a patient rarely experiences all of these symptoms during any one attack.

The anxiety may take any of several forms. Some patients experience the classic "sense of impending doom," as if something terrible were about to happen. Some fear they are having a heart attack or a stroke, and this may occasion multiple visits to the emergency room. Some fear they will "go crazy." For others the anxiety may be only a minor part of the symptomatology of the attack; rarely, patients do not have any anxiety at all during the attack, only a sense of discomfort. The existence of these cases, dubbed "panic attacks without panic," was initially controversial. However, in every other respect they are typical attacks, and as no other etiology than panic disorder can be established for them, one

must assume that in rare instances a patient may experience a panic attack without undue anxiety at all.

Tremor may or may not be a complaint; some patients complain more of a sense of internal shakiness.

The palpitations and chest discomfort often prove most alarming to patients. The discomfort itself may be quite severe and sometimes radiates to the left shoulder or the left side of the neck. Such complaints, of course, also cause discomfort in the emergency room physician. The palpitations are often described as "racing," and less often as "skipped beats."

The other symptoms require little discussion. Patients describe them in the most varied terms, and one may inquire specifically after each term to become familiar with the range of descriptions possible.

In most patients the attacks are without precipitating factors, and this is perhaps one of the most striking features of panic attacks. They seem to "come out of the blue" and strike without warning. Although patients may recall with vivid clarity the exact circumstances surrounding the first attack, they are generally unable to identify anything that could conceivably have caused the attack. Many patients, after repeated attacks, may come to fear being in situations where help might not be readily available should another attack occur. Thus they may have anxiety about driving on limited access freeways, or bridges, or in tunnels. Flying or boating may likewise be avoided. In describing their fear of these situations, patients may give the impression that they are afraid that the situation itself might cause a panic attack. However, on closer questioning one can see that what they are afraid of is not so much that the situation will cause the attack but that they might have an attack in that situation and be unable to get to help.

Panic Attack Symptoms

Anxiety	Hot and cold flushes
Tremor	Dyspnea
Palpitations	Dizziness or faintness
Chest discomfort	Nausea or abdominal distress
Diaphoresis	Acral paresthesias

immediately. In some patients, as noted below, agoraphobia may develop.

Nocturnal panic attacks are not uncommon; however, as patients may not report them, one should inquire after them specifically. Polysomnography has revealed that these nocturnal attacks tend to arise from non-REM sleep.

COURSE

The frequency with which panic attacks occur varies widely, and it appears that the long-term course falls more or less into one of two patterns. In one pattern, the frequency gradually waxes and wanes (anywhere from once daily to once every few months), over many years or decades, without the patient ever experiencing any prolonged attack-free intervals. In the other pattern one does see prolonged attack-free intervals, and in this pattern it may be appropriate to speak of an "episodic" course, wherein episodes, characterized by panic attacks occurring with varying frequency, are separated by intervals free of attacks.

COMPLICATIONS

The most common complication of panic disorder is agoraphobia, and this is seen in anywhere from one-third to one-half of all patients, generally within the first year. Here the anticipatory anxiety becomes so severe and attached to so many different situations that patients begin to more or less severely restrict their travels. Truck drivers may give up their long-distance routes and restrict themselves to local deliveries; traveling salespersons may quit their routes altogether. At its worst these patients may become housebound.

Abuse of alcohol, benzodiazepines, or other tranquilizers or sedatives is a serious risk. Patients may use these to quell anticipatory anxiety; others may take them during the panic attack itself in the mistaken belief that blood levels sufficient to have an effect will occur before the attack remits spontaneously. This complication may compound itself if tolerance and withdrawal occur. During withdrawal, panic attacks are more likely to occur, which in turn could spur further use of a tranquilizer, thus setting up a vicious cycle.

Patients who suffer from both panic disorder and major depression may be at higher risk for suicide than those with major depression alone. However, contrary to earlier reports, those with panic disorder alone do not appear to be at higher risk for a suicide attempt.

ETIOLOGY

Panic disorder appears to run in families. As the degree of consanguinity increases from general population to first-degree relatives, or from dizygotic to monozygotic twins, so too does the risk of having panic disorder. Although this is consistent with a hereditary basis, the effects of a shared environment cannot be ruled out, and until adoption studies are done, the basis for the familial occurrence of panic disorder remains uncertain. Genetic and linkage studies, to date, have not yielded robust findings.

The discovery of panicogens has been one of the major fruits of research in panic disorder. These are substances that, though innocuous to normal controls, reliably produce panic attacks in patients with panic disorder. These induced panic attacks are essentially identical to the naturally occurring ones. Furthermore, these induced attacks may be prevented by the same medications that are effective in preventing the naturally occurring attacks.

Several substances have been shown to be panicogenic. They include sodium lactate, inhalation of 5% or 35% carbon dioxide, cholecystokinin tetrapeptide, caffeine, yohimbine, isoproterenol, and the benzodiazepine antagonist, flumazenil. Of these the best studied is sodium lactate infusion. In light of the family studies noted above, it is of interest that the inhalation of 35% carbon dioxide by the asymptomatic and not-ill relatives of probands induces panic attacks, an effect not seen in normal controls.

Various neurotransmitters have also been investigated. The noradrenergic system is strongly implicated by the panicogenic efficacy of adrenergic agents such as yohimbine and isoproterenol, and this is further supported by studies demonstrating a blunted GH response to clonidine administration. The serotonergic system is implicated not only by the undoubted efficacy of serotonergic antidepressants in the treatment of panic disorder, but also by studies involving manipulation of brain serotonin levels. For example, depletion of tryptophan, the dietary precursor of serotonin, increases the effectiveness of a panicogen such as flumazenil, whereas the administration of 5-hydroxytryptophan, which increases serotonin levels, will blunt the effectiveness of CO₂ inhalation as a panicogen. The GABA-ergic system is strongly implicated by the effectiveness of flumazenil as a panicogen and by the effectiveness of benzodiazepines in the treatment of panic disorder, and is supported by a recent finding of reduced GABA levels in the occipital cortex of panic disorder patients.

Functional MRI studies, although not entirely in agreement, suggest strongly that the hippocampus and parahippocampal gyrus are abnormally activated in panic disorder.

Integrating these findings into a coherent etiologic theory is problematic and requires some speculation. However, it appears plausible to say that panic disorder represents an inherited disturbance in the overall function of noradrenergic, serotonergic or GABAergic systems in one or more of those central nervous system structures responsible for anxiety. Candidate structures include the locus ceruleus, dorsal raphe nucleus, parahippocampus, hippocampus and amygdala. The locus ceruleus is noradrenergic, the dorsal raphe nucleus serotonergic, and both send fibers to a large number of structures, including the parahippocampus, hippocampus and amygdala, structures rich in GABA receptors. Stimulation of these limbic structures, in turn, is well known to produce fear and anxiety. If one assumes that overactivity of the amygdala is the "final common pathway," then disturbance in any one of the other structures, or the amygdala itself, could cause a panic attack.

It has been proposed that one possible "trigger" for the activation of this neuronal circuit is an abnormal sensitivity to disturbances of acid-base balance in the brainstem. Such a sensitivity, if it did exist, could explain the efficacy of panicogens such as lactate infusion and CO₂ inhalation,

maneuvers which both induce changes in acid-base balance. This “false suffocation alarm” could then lead to overactivation of either the locus ceruleus or dorsal raphe nucleus.

Before leaving this discussion of the etiology of panic disorder a word is in order regarding the association of panic disorder with mitral valve prolapse. Although this association has not been consistently replicated, most studies do support it. It appears unlikely, however, that mitral valve prolapse causes panic or that, vice versa, panic causes prolapse; rather the association is probably secondary to some commonly shared abnormality, the nature of which is unclear.

DIFFERENTIAL DIAGNOSIS

Panic attacks may be seen in simple phobia, social phobia, posttraumatic stress disorder, and obsessive-compulsive disorder. In these disorders, however, the panic attacks are precipitated. For example, if the simple phobic has to approach a snake, the social phobic public speaking, the posttraumatic patient a situation reminiscent of the original trauma, or the obsessive-compulsive patient a contaminated object, a severe panic attack may indeed occur. If, however, these patients can avoid the stimuli, there are no panic attacks. In such cases a separate diagnosis of panic disorder is not made.

Occasionally an otherwise normal individual experiences a spontaneous panic attack; to qualify, however, for a diagnosis of panic disorder, the attacks must be either severe enough to cause marked distress or be frequent, occurring generally once a month or more.

Panic attacks are also seen with some frequency in patients suffering from a depressive episode either as part of major depression or bipolar disorder. In some cases the panic attacks may actually predate the onset of the depressive symptoms, and when they are concurrent with depressive symptoms, no relationship between them and the severity of the depressive symptoms is evident. In such cases a separate panic disorder is occurring in addition to the depressive disorder, and consequently, two diagnoses are given.

A number of conditions may produce symptomatic episodes that may very closely resemble panic attacks, thus engendering some diagnostic confusion (see the box on this page). Usually, however, certain differential points allow a correct diagnosis.

Parkinson’s disease is associated with panic attacks when patients are treated with levodopa and have a prominent “on-off” effect. Here, as the preceding dose of levodopa wears off and the parkinsonism worsens, patients may have a panic attack very similar to those seen in panic disorder.

Patients suffering a myocardial infarction or an attack of angina pectoris may complain of chest pain, dyspnea, nausea, diaphoresis, and often a sense of impending doom. Radiation of pain to the neck or arm is not an infallibly reliable diagnostic point, since this may also occur during a panic attack. The general medical setting of the illness is often diagnostically helpful. Clearly, if the patient is elderly, with known cardiac disease or multiple coronary risk factors, one might lean toward a diagnosis of myocardial insufficiency. Conversely, if the patient is young, with no risk factors, one

might be inclined toward a diagnosis of panic disorder, especially with a history of numerous prior identical attacks.

At the moment of lodgment of a relatively large pulmonary embolus, patients may have a sudden onset of chest discomfort, dyspnea, nausea, diaphoresis, and significant anxiety, thus presenting a clinical picture quite similar to a panic attack. The disproportionate emphasis on dyspnea relative to other symptoms is a helpful diagnostic point for pulmonary embolus. Likewise, hemoptysis or wheezing point immediately to the correct diagnosis; however, these latter two symptoms are often not present. As is the case with myocardial ischemia, the setting of the illness may be a helpful point. Prolonged immobilization, thrombophlebitis or cardiac failure would make one’s index of suspicion higher for pulmonary embolus, especially if this were a first episode.

Paroxysmal supraventricular tachycardia (SVT), also known as paroxysmal atrial tachycardia, occasionally may cause diagnostic problems because the patient may become quite anxious during an attack of tachycardia. Two diagnostic points strongly suggest SVT: first, a hyperacute onset (often less than a second) and, second, the ability of the patient to terminate the attack by a Valsalva maneuver. Holter monitoring will help establish the diagnosis; however, it is important to utilize “event monitoring” so that the episode is not missed.

Simple partial seizures may occasionally be characterized by a panic attack. Clues to this diagnosis include not only the occurrence, at other times, of other seizure types (e.g., grand mal or complex partial) but also the exquisitely paroxysmal nature of the ictal panic attack: whereas panic attacks in panic disorder take minutes to crescendo, the ictal anxiety peaks within seconds. An EEG may or may not be helpful in such cases, as it may be normal even while the patient is having the seizure.

Episodic hypoglycemia may be very difficult to distinguish from a panic attack. Symptomatic episodes of hypoglycemia, however, tend to have a slower onset than a panic attack and tend to last longer. Relief of symptoms with orange juice or some other sugar is a helpful diagnostic point. The setting is also helpful; the suspicion for hypoglycemia is higher in a patient taking insulin or an oral hypoglycemic and in those in whom the attacks tend to occur postprandially.

A minority of patients with pheochromocytoma have paroxysmal attacks that very closely resemble panic attacks. Typically, though, in contrast to patients with panic attacks, these patients have a prominent headache. Furthermore, hypertension is always present during the attack and is often also present between the attacks. Furthermore, although paroxysms in pheochromocytoma may occur spontaneously, at times they are precipitated by abdominal compression or micturition, factors that clearly distinguish them from panic attacks.

Mastocytosis may present with episodes of light-headedness, palpitations, headaches, dyspnea, chest pain, and nausea. Though these episodes, in these respects, are similar to panic attacks, certain points suggest the correct diagnosis. Patients with mastocytosis almost always experience intense flushing during the episode. Interestingly, though this can be profound, they rarely complain of it and must be questioned directly about the presence or absence of flushing. Furthermore, after the attack most patients experience

profound lethargy to the point of prostration, which may last for days or longer. Such post-attack prostration is not seen after a panic attack. Finally, physical examination generally reveals

Conditions that may Produce Symptomatic Episodes that Resemble Panic Attacks	
Parkinson's disease	Simple partial seizures
Myocardial infarction	Hypoglycemia
Angina pectoris	Pheochromocytoma
Supraventricular tachycardia	Mastocytosis
Pulmonary embolus	Carcinoid syndrome

urticaria pigmentosa, although not all patients with mastocytosis have this.

Carcinoid syndrome is often included in the differential diagnosis of panic attacks, but it would appear difficult to confuse the two. The flushing and diarrhea that are hallmarks of the carcinoid syndrome are relatively minor in a panic attack.

Certain other disorders are often included on the differential diagnosis for panic disorder, including hyperthyroidism, certain drug intoxications, and certain drug withdrawals; however, the anxiety seen in these disorders is generally not paroxysmal. The anxiety of hyperthyroidism may wax and wane, but is not episodic. Drugs such as caffeine, cocaine, amphetamines and various over-the-counter sympathomimetics may produce an episode of anxiety, but, unless the drug is injected intravenously or taken by inhalation, the onset is usually gradual. Withdrawal from alcohol, benzodiazepines or other sedative-hypnotics is often accompanied by anxiety which may at times undergo an episodic surge similar to a panic attack. In such cases, these "attacks" subside with abstinence.

As may be gathered from the foregoing discussion, the differential diagnosis in patients suspected of panic disorder is rather extensive. The task of differential diagnosis here, however, is not as formidable as it may seem. A careful history generally points in the right direction. If one is lucky enough to have the patient under observation during an attack, one should, in addition to a careful description of symptoms and cutaneous signs, note blood pressure, pulse, and if possible obtain an ECG, blood for a glucose level, and, if suspicious of mastocytosis, a histamine level. Determination of CBC and cardiac enzymes depends on the level of suspicion of cardiac or pulmonary disease. Other tests (such as a pulmonary scan, arteriography, Holter monitor, electroencephalogram, glucose tolerance test, plasma norepinephrine and epinephrine, and 24-hour urine for 5-hydroxyindoleacetic acid or histamine and its

metabolites) should be used only as indicated by one's diagnostic suspicions.

TREATMENT

The goal of treatment in panic disorder is twofold: to prevent future attacks and to relieve anticipatory anxiety and enable patients to overcome any avoidance behavior they may have developed. Both cognitive-behavioral treatment and medication have a role; medications are discussed first.

When initiating pharmacologic treatment one must impress on the patient the fact that, short of intravenous medication, probably nothing is available that reliably aborts an attack once it has begun, and that therefore the thrust of drug treatment is to prevent future attacks.

Once the patient has decided on prophylactic treatment, the next step is to select the prophylactic agent best suited for the patient. Two groups of medicines provide effective prophylaxis: certain benzodiazepines and most of the currently available antidepressants. Which group to choose has been the subject of intense debate. Buspirone is not effective.

Four benzodiazepines are clearly effective: alprazolam, clonazepam, lorazepam and diazepam. The benzodiazepines offer certain advantages. They have a rapid onset of action, generally few side effects, and often serve to reduce the anticipatory anxiety that most patients with panic disorder experience. The total daily dose is gradually titrated up until symptoms are controlled: alprazolam may be started at from 0.75 to 1.5 mg, with most patients responding to doses of from 1.5 to 6 mg; comparable figures for clonazepam are 0.5 to 1.5 mg to start, titrating to from 1.0 to 4.0 mg, for lorazepam 1 to 2 mg to start, titrating to from 2 to 6 mg, and for diazepam 4 to 10 mg to start, titrating to from 10 to 60 mg. Alprazolam, if given in the extended-release formulation, may be given once daily; otherwise the total daily dose must be divided into three or more administrations; clonazepam and diazepam are generally given in two divided doses.

Given the risk of neuroadaptation with benzodiazepines, many clinicians prefer to start with an antidepressant, choosing an SSRI, tricyclic or MAOI. The SSRIs are generally better tolerated than the tricyclics, and the MAOIs, though undoubtedly effective, are generally held in reserve given their side-effect profile and dietary requirements. Regardless of which antidepressant is chosen it is generally prudent to start with a low dose: although in most cases a full "antidepressant" dose is required, starting at or near such a dose often precipitates either agitation or a "flurry" of panic attacks, and consequently one should begin with a dose from one-tenth to one-third of the "full" dose, followed by an upward titration, in similar increments, every week or so. Importantly, although most patients do indeed both tolerate and require a titration to a "full dose" there is a small minority of patients who do not tolerate more than a small amount but yet do get a good anti-panic effect from it. Unfortunately, one cannot as yet tell prospectively which patients will have this sort of response. Once an optimum dose has been reached, a response may not be seen for weeks, and a full response may be delayed for up to 3 months. Given this potentially long delayed response, many clinicians will begin treatment with a combination of a benzodiazepine and an SSRI (e.g., clonazepam and sertraline) and then taper off

the benzodiazepine once the SSRI has had a chance to become effective.

Among the SSRIs, the following (with their average doses) have been shown to be effective in double-blinded studies: paroxetine (40 mg), fluoxetine (20 mg), fluvoxamine (150 mg), citalopram (20 mg), escitalopram (10 mg) and sertraline. In the case of sertraline, it appears that any dose between 50 and 200 mg is effective.

Of the tricyclics, imipramine, in doses of 150 to 200 mg, although effective, and indeed the “gold standard,” is generally poorly tolerated over the long haul. Nortriptyline, in doses of from 50 to 150 mg, desipramine, in doses of from 150 to 200 mg, and clomipramine, in doses of from 50 to 150 mg, are alternatives.

Of the MAOIs, phenelzine, in doses of 30 to 90 mg, is effective. Two other reversible MAOIs, not yet available in the United States, are also effective, namely brofaromine and moclobemide.

Other medications that may be considered include propranolol and inositol. Propranolol, in total daily doses of roughly 180 mg, may be effective, but the clinical impression is that it is less reliably so than a benzodiazepine or an antidepressant. Inositol is an isomer of glucose which serves as a precursor for inositol, an intracellular “second messenger”: remarkably, in a double-blinded comparison, with doses of roughly 6000 mg bid, it was more effective than fluvoxamine. Clearly, this is very promising, and bears watching for replication.

Response to medical treatment is usually quite good. Many patients become completely free of panic attacks. However, a large percentage continue to have attacks, albeit much less frequently and of much less severity.

Cognitive-behavior therapy, used either independently or in conjunction with medical treatment, should also be considered, especially in light of the fact that in addition to reducing the frequency of panic attacks, it is also an effective treatment for agoraphobia.

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