CME CREDIT

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Panic disorder in primary care: A cause of unexplained symptoms

ABSTRACT:

Patients with panic disorder often believe they are suffering a myocardial infarction or another life-threatening illness. The history and physical examination and a few tests usually suffice to diagnose this disorder, which is treatable with behavioral therapy, antidepressants, and benzodiazepines.

KEY POINTS:

Many symptoms of panic attacks are physical, making diagnosis difficult and often suggesting another physical illness.

The etiology of panic likely represents a neurochemical imbalance of serotonin, norepinephrine, and other neurotransmitters.

Treatment consists of a combination of cognitive behavioral therapy, selective serotonin reuptake inhibitors, benzodiazepines, and tricyclic antidepressants. Other agents can be used in refractory cases, but usually require psychiatric referral and evaluation.

PANIC DISORDER IS COMMON, chronic, and, if unrecognized and untreated, costly. As many as 3.5% of the general population suffers from it at some point in their lives,[1] and the prevalence has been reported to be as high as 11% in general medical patients.[2,3]

The cost to the patient of unrecognized panic disorder may include other anxiety disorders, depression, drug and alcohol abuse, impaired social and physical functioning, lost workdays and productivity, occupational disability,[4,5] and even suicide attempts.[6–9] The cost to the health care system: increased use of general medical services, frequent clinic and emergency department visits, and excessive testing for organic causes. Fortunately, panic disorder is treatable, and early diagnosis and psychiatric care can significantly reduce the use of nonpsychiatric services.[5]

Many patients with panic disorder present to primary care physicians, but specialists such as emergency room physicians, cardiologists, gastroenterologists, and neurologists should also keep this disorder in mind as a cause of unexplained or persistent physical symptoms in their patients. This review presents the diagnosis and treatment of panic disorder; we also delve into its pathophysiology.

DIAGNOSING PANIC DISORDER

Many of the symptoms of panic attacks are physical (TABLE 1), making its diagnosis difficult. Further, many patients minimize or deny psychological symptoms. Because of these factors, panic disorder often becomes a diagnosis of exclusion with an extensive differential diag-

TABLE 1

SYMPTOMS OF PANIC ATTACKS

Four of these symptoms are required for the diagnosis of panic attack:

- Chest pain or discomfort
- Chills or hot flushes
- Depersonalization (feeling detached from oneself)
- Derealization (feelings of unreality)
- Fear of losing control or going crazy
- Fear of dying
- Feeling dizzy, unsteady, lightheaded, or faint
- Feeling of choking
- Nausea or abdominal distress
- Palpitations, pounding heart, or accelerated heart rate
- Paresthesias
- Sensations of shortness of breath or smothering
- Sweating
- Trembling or shaking

SOURCE: ADAPTED FROM THE AMERICAN PSYCHIATRIC ASSOCIATION, REFERENCE 10

TABLE 2

DIFFERENTIAL DIAGNOSIS OF PANIC DISORDER

- Atypical migraines
- Carcinoid syndrome
- Cardiac arrhythmia
- Chronic fatigue syndrome
- Coronary artery disease
- Diabetes mellitus
- Drug withdrawal
- Hypertension
- Hyperthyroidism
- Hypoglycemia
- Meniere's disease
- Partial complex seizures
- Pheochromocytoma
- Recurrent pulmonary emboli
- Substance abuse

SOURCE: ADAPTED FROM WEINSTEIN, REFERENCE 38

nosis (TABLE 2); yet it should be a diagnosis of inclusion, as its symptoms are quite consistent from patient to patient.

Criteria for diagnosing panic disorder

Many patients with panic disorder develop agoraphobia

According to criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV),[10] panic disorder consists of:

Recurrent panic attacks—acute episodes of severe anxiety accompanied by a variety of somatic symptoms: cardiac, neurologic, gastrointestinal, respiratory, and psychologic (TABLE 1). An attack must include at least four of the symptoms listed in TABLE 1, develop abruptly, and reach a peak intensity within 10 minutes. Panic attacks may be unexpected or occur in response to upsetting circumstances, such as exposure to heights or the sight of blood. Patients usually clearly recall the initial or "herald" attack even years later. Many patients report episodes of panic starting during sleep.

In addition, the criteria stipulate that patients must have at least one of the following, lasting at least 1 month:

Persistent concern about having additional attacks.

Worry about the implications of the attack or its consequences (eg, losing control, having a heart attack, "going crazy").

A significant change in behavior related to the attacks.

Repeated panic attacks may lead sufferers to avoid situations that may precipitate attacks or from which getting help or escaping may be difficult. Patients may completely avoid anxiety-provoking situations, endure them with great distress, or require the presence of a companion. Agoraphobia may develop in almost 40% of persons with panic disorder; some patients never leave home, or leave home only with a spouse or family member.[1]

Differential diagnosis

A complete history and physical examination can rule out most of the disorders in the differential diagnosis (TABLE 2); other disorders can be ruled out by routine screening tests such as a complete blood count, thyroid function tests, a fasting glucose level, serum electrolyte levels, and an electrocardiogram.

PANIC DISORDER CAN MIMIC OTHER CONDITIONS

Cardiac conditions

Unexplained chest pain, palpitations, or hypertension may precipitate a consultation with a cardiologist. A variety of "functional" cardiac syndromes such as soldier's heart, neurocirculatory asthenia, hyperdynamic beta-adrenergic circulatory state, and hyperventilation syndrome are likely panic disorder or closely related to it.[11] Many patients with these symptoms initially present to the emergency department.

Chest pain. One study found that roughly one in four patients presenting to the emergency department because of chest pain suffered from panic disorder, although chart reviews indicated that 98% of the cases of panic disorder were not recognized as such at the time.[12] Between 20% and 30% of patients who undergo coronary arteriography for chest pain have normal coronary arteries, and in one study, 43% of patients with negative arteriograms were found to have panic disorder.[13,14]

Labile hypertension. In patients with labile hypertension screened for pheochromocytoma with negative results, psychiatric interviews determined that nearly half had either panic disorder or agoraphobia or both.[15]

A link with mitral valve prolapse. Echocardiographic studies have revealed that as many as 40% of patients with panic disorder may also have mitral valve prolapse, but this relationship is of unclear significance.[16]

Neurologic conditions

A variety of the symptoms listed in TABLE 1 may prompt a neurologic consultation.

Headache frequently occurs during panic attacks, although it is not included in the DSM-IV diagnostic criteria. In one study, nearly 28% of people ages 24 to 29 who visited a physician for headache had a history of panic disorder.[17]

Epilepsy. Although some features of panic disorder (paroxysmal onset, short duration, psychosensory symptoms, dissociative states) may resemble epilepsy, the relationship between the two is not clear.

Irritable bowel syndrome

Patients with irritable bowel syndrome are frequently referred to gastroenterologists and tend to use a disproportionate amount of medical services.[18] Panic disorder was diagnosed in 28% of irritable bowel syndrome patients, and 41% met the criteria for agoraphobia.[19] Therefore, close screening for anxiety disorders such as panic disorder is warranted as part of any evaluation of a patient with irritable bowel symptoms.

The onset of panic attacks after age 60 should increase suspicion of an organic cause

EPIDEMIOLOGY

Panic attacks may first appear after a significant life event or stressor, such as the death of a close family member, divorce, or loss of a job. However, they most often afflict people who have no past or recent history of emotional turbulence or traumatic life events. Panic disorder affects 2.5 times more women than men.[1] More than 7% of all people experience a panic attack in their lifetime, and the estimated lifetime prevalence of panic disorder is 3.5%.[1] The prevalence of panic disorder and panic attacks is greatest in persons aged 15 to 24 years; however there is another peak between the ages of 45 and 54.[1] Although panic disorder may develop later in life, the onset of panic attacks after age 60 should increase one's suspicion of an organic cause (TABLE 2).

Genetics

Panic disorder tends to be familial. One study reported that first-degree relatives of patients with panic disorder had a prevalence of panic disorder of 41%.[20] The concordance rate for panic disorder in monozygotic twins has been reported to be five times greater than in dizygotic twins.[21] In addition, children of patients

What causes panic disorder?

RESEARCHERS HAVE UNCOVERED certain biological alterations in panic disorder, as in many other psychiatric disorders.

NEUROTRANSMITTER IMBALANCES

This disease probably does not result from simple underactivity or overactivity of any one neurotransmitter; rather, there is most likely an imbalance in several neurotransmitter systems that interact in an intricate neural circuit.

Neurotransmitters linked to panic disorder include norepinephrine, serotonin, gamma-aminobutyric acid (GABA), dopamine, and cholecystokinin.[1] Current treatments mostly target norepinephrine and serotonin.

Norepinephrine. Central noradrenergic mechanisms have been identified as a possible pathophysiologic pathway for the development of anxiety and panic. The locus caeruleus, located in the pons, has diffuse ascending projections for noradrenergic transmission to the limbic system and the paralimbic prefrontal and temporal cortex. This system helps process sensory information and, notably, enhances environmental stimuli crucial to survival.[2] Heightened reactivity of this system may be responsible for anxiety and panic, as suggested by experiments in monkeys in which electrical stimulation of the locus caeruleus produced fear behaviors.[3] Further, drugs that produce anxiolysis, such as tricyclic antidepressants, decrease the activity of the locus caeruleus neurons.[4]

Serotonin. A serotonergic pathway originates in the dorsal and median raphe nuclei and ascends to the frontal cortex and limbic system; this pathway, like the noradrenergic system described above, may also heighten sensory perception, participate in interpreting emotionally significant events, and produce fear, anxiety, and panic reactions under dysfunctional states.

The best evidence for serotonin dysfunction in panic disorder comes from studies in which patients were given direct serotonin agonists or agents that affect serotonin reuptake. One study reported heightened anxiety responses and abnormally elevated cortisol and prolactin responses to fenfluramine, an indirect serotonin agonist.[5] In addition, selective serotonin reuptake inhibitors are effective in treating anxiety and panic disorder, lending support to the hypothesis of serotonergic dysfunction.

GABA is hypothesized to have a role in the pathophysiology of panic disorder, primarily because benzodiazepines, which act as agonists at the GABA/benzodiazepine receptors, are effective for treating panic attacks.

HYPERSENSITIVITY TO CARBON DIOXIDE

Inhalation of 35% CO_2 produces acute anxiety in patients with panic disorder but not in normal controls or patients with other anxiety disorders.[6] According to a "false suffocation alarm" theory, patients with panic disorder have a genetic impairment of the respiratory control system that makes them hypersensitive to CO_2—ie, "normal" respiratory stimulations produce abnormal responses of a suffocation alarm system, experienced as acute anxiety attacks.[7]

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with panic disorder appear to be at increased risk for anxiety disorders and certain temperamental characteristics.[22] Separation anxiety in childhood may also lead to panic disorder in adulthood.[23]

TREATING PANIC DISORDER

From the outset, patients should receive information about panic disorder; many are relieved to find that their symptoms are not life-threatening or "crazy" and that the disorder may have more of a biological than psychological cause.

Patients should reduce their intake or stop using potentially anxiety-provoking substances such as:

- Caffeine.
- Pseudoephedrine and other decongestants.
- Diet pills.
- Theophylline (if possible).
- Alcohol (although it initially reduces anxiety, its effects wear off quickly, resulting in rebound anxiety and panic symptoms).
- Recreational drugs.

Behavioral therapy

Many mental health professionals favor an initial trial of behavioral therapy before resorting to medications, because this approach is effective and free of side effects. In cognitive-behavioral therapy, patients learn how to reduce panic symptoms through relaxation, diaphragmatic breathing, and other methods. Therapists address the patients' catastrophic misinterpretation of panic symptoms, such as their beliefs that they may die or that the attacks produce physical harm, and teach them appropriate cognitive interventions.

Some studies have shown behavioral therapy to have both long-term and short-term benefits, particularly in patients who have had a poor response to pharmacotherapy.[24] When patients need medications, they tend to need lower doses if they are also undergoing behavioral therapy. They are also more likely to be able to stop taking medications and less likely to have a relapse.[25,26]

TABLE 3

MEDICATIONS FOR PANIC DISORDER

Drug	Dosage range (mg/day)	
	Initial	Therapeutic
Selective serotonin reuptake inhibitors		
Fluoxetine	5–10	10–60
Sertraline	25–50	50–200
Paroxetine	10–20	20–50
Fluvoxamine	25–50	25–300
Benzodiazepines		
Alprazolam	1–2*	1–8*
Clonazepam	1–2†	1–8†
Lorazepam	1–2†	1–8†
Diazepam	2–10‡	2–40‡

*In divided doses, three to four times a day
†In divided doses, two to three times a day
‡In divided doses, twice a day

Selective serotonin reuptake inhibitors as first-line drugs

Most clinicians favor selective serotonin reuptake inhibitors (SSRIs) as first-line drugs because these agents have a favorable side-effect profile and minimal risk of overdose. Fluoxetine, sertraline, paroxetine, and fluvoxamine have all proved effective in treating panic disorder.[26–29]

Dosage. SSRIs should be started at very low doses and gradually titrated upwards (TABLE 3). This approach may decrease side effects such as the abnormal stimulation ("activation") sometimes seen in patients with panic disorder treated with these drugs, and thus increase patient compliance. SSRIs often take at least 2 to 6 weeks to produce an antipanic response, a delay in onset of action similar to that seen in treating depression with these agents.

Start SSRIs at very low doses and gradually titrate upward

Benzodiazepines as adjunctive treatment

Some patients with severe panic attacks may also need benzodiazepines, especially patients presenting to the emergency department.

Benzodiazepines have the benefit of relieving distressful symptoms faster than do SSRIs. They are also better for treating phobic avoidance. These agents are often effective as monotherapy as well.

Most of the benzodiazepines are effective in treating panic. Highly potent agents such as alprazolam and clonazepam may be better tolerated than less potent agents such as diazepam because they cause less sedation and incoordination.[30] Nevertheless, diazepam and alprazolam have been shown to be equally effective.[31]

Cautions. All benzodiazepines can produce physiologic and psychologic dependence, and patients need to be told about this possibility, as well as the danger of a withdrawal syndrome if these drugs are suddenly stopped. Tolerance to benzodiazepines may develop, necessitating an increase in dosage for the drug to remain effective. Long-term use of benzodiazepines may lead to depression, particularly in patients with panic disorder.[32] Stopping benzodiazepines may be difficult and requires gradual reduction of dosages to avoid the increase in panic symptoms commonly seen with rapid tapering after long-term use.

Benzodiazepines can provide fast relief before the SSRI "kicks in"

Dosage. TABLE 3 lists the dosages of some of the benzodiazepines typically used for managing panic disorder. Although alprazolam, with its rapid onset and short duration of action, can be used "as needed" to stop panic attacks, long-term treatment of panic disorder with benzodiazepines is best managed with regular daily doses. Treatment with shorter-acting benzodiazepines may lead to panic symptoms at night or just before the next scheduled dose of the medication, likely due to a trough concentration effect.

Tricyclic antidepressants

Although no longer used as frequently as SSRIs or benzodiazepines, tricyclic antidepressants are also effective against panic attacks and panic disorder. Imipramine is the prototypical tricyclic antidepressant for panic; its effects are dose-dependent, and plasma levels may assist in individual dosing strategies.[33]

Dosage. Treatment with imipramine should start with a low dose (10 mg) at bedtime and increase to a full antidepressant dose of 150 to 300 mg daily. Adverse effects may limit treatment and include typical anticholinergic side effects such as dryness of mucous membranes, constipation, blurry vision, and urinary retention. Weight gain and sedation can also be troublesome.

Combined treatment

A common approach is to begin treatment with both an antidepressant and a benzodiazepine, particularly for patients with severe panic symptoms. This approach provides the rapid anxiolysis of the benzodiazepine, while waiting for the antidepressant to "kick in." When symptoms are adequately controlled, the benzodiazepine can be gradually tapered and discontinued, and most patients can continue taking an antidepressant as monotherapy. Occasionally, patients may need benzodiazepines on an "as needed" basis for breakthrough panic symptoms.

Other agents

Many other agents have also been reported effective against panic disorder, including venlafaxine, nefazodone, monoamine oxidase (MAO) inhibitors, and carbamazepine.[34–37] At present these medications are not first- or second-line agents and may be more suitable for use by a psychiatrist or other physician who is familiar with their use in panic disorder. Oftentimes these medications, particularly the MAO inhibitors, are reserved for treatment-resistant panic or for patients who cannot take SSRIs, tricyclic antidepressants, or benzodiazepines for whatever reason.

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