Panic Disorder

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Panic disorder is a subtype of anxiety manifested by discrete periods of apprehension or fear and at least four of the following somatic symptoms: dyspnea, palpitations, chest pain, choking, dizziness, depersonalization or derealization experience, paresthesias, hot and cold flashes, sweating, faintness, trembling, and fear of dying, going crazy, or doing something uncontrolled during an attack. Because the patient with panic disorder often selectively focuses on one of these somatic symptoms and may minimize or deny psychosocial distress, panic disorder is frequently misdiagnosed. As a result of the frightening nature of the symptoms, a pattern of overutilization of medical care systems frequently ensues. Panic disorder is usually precipitated by stressful life events, most commonly separation or loss, in a patient with a genetic or acquired vulnerability. As with other psychophysiologic illness (depression, duodenal ulcer) resolution of the acute stressful life event may not lead to resolutions of the physiologic changes. Two specific tricyclic antidepressants, imipramine and desipramine, have been shown to be effective therapeutic agents in treating panic disorder.

Primary care physicians currently treat an estimated 60 percent of the patients with mental illness in the United States.[1] Patients with psychiatric illness obtain two to four times as much nonpsychiatric medical care as patients without such diagnoses.[2] Anxiety and depression constituted 86.8 percent of the psychiatric problems seen in a large computer-based study in Virginia of 526,196 patient visits to 118 family physicians.[3] Anxiety alone was the fifth most common diagnosis in this study. Antianxiety medications in general and benzodiazepines in particular have consistently been the most frequently prescribed medications in the United States over the last 10 years, and primary care physicians wrote the majority of these prescriptions.[4] In 1971, a National Institute of Mental Health study determined that 15 percent of the United States population had taken at least a single dose of an antianxiety medication in the last year.[5]

This paper will focus attention on a particular subtype of anxiety, panic disorder, which is uniquely treatable by a combination of medication

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attack. During this second phase, events and circumstances associated with the attacks may be selectively avoided, leading to specific phobic behaviors. For example, a person who developed an attack during public speaking may avoid such an activity. The third stage of panic disorder is the most disabling, the development of agoraphobia. In agoraphobia the patient develops a fear of going outside his home and becomes incapacitated as a result of the association of panic attacks with many different stimuli. Also, agoraphobic patients often avoid being alone and desperately cling to others for comfort.

Diagnostic Problems

Patients with panic disorder often choose to seek help in a setting consistent with their own explanatory model of what is happening to them. Those who perceive the symptoms as a threat primarily to their mental health might focus on the affective and cognitive symptoms of fear and worry. These individuals may consequently consult many of the large variety of psychotherapists, including psychiatrists, psychologists, or social workers operating within the recognized mental health system. Many other patients focus selectively on their physical symptoms because they are unable to justify within their personal or cultural belief systems seeking help for "mental illness." These individuals are more likely to consult the primary care physician when faced with the symptoms of panic disorder. There are many reasons for this phenomenon: the health care profession as a whole is biologically oriented, paying more heed to disorders felt to be physiologically based.[23] This orientation reflects a similar cultural bias whereby people learn early in life that they are more likely to be taken seriously and considered legitimately ill if they are physically suffering. Also, the most frightening aspects of the syndrome, such as chest tightness, tachycardia, dyspnea, diaphoresis, tremulousness, and dizziness, are somatic manifestations probably caused by a burst of catecholamines into the blood stream. In fact, isoproterenol infusion has been found to induce panic attacks that can be reversed with propranolol infusion.[24] Typically such patients visit multiple medical specialists. In one large study of panic disorder patients, 70 percent had visited more than 10 physicians.[13]

An association between mitral valve prolapse (MVP) and panic attacks has been observed. Several studies have confirmed an incidence of mitral valve prolapse in 32 to 47 percent of patients diagnosed as having panic disorder.[25-27] It is unclear whether mitral valve prolapse predisposes a patient to panic disorder or whether panic disorder causes MVP. The recent finding that patients with hyperthyroidism have an increased rate of MVP that does not disappear with treatment and return to the euthyroid state is suggestive evidence that a hyperdynamic β-adrenergic state may have an etiologic role in MVP.[28] However, patients with mitral valve prolapse and panic disorder respond to treatment with imipramine as well as patients with panic attacks alone.[29]

Differential Diagnosis

The patient, because of the possibility of a coexisting physical disorder, warrants a complete history and physical examination. In a patient with a known medical ailment, that illness (including the symptoms, complications, and pharmacologic treatment) should always be suspected.[30] For instance an asthmatic patient with a toxic aminophylline serum level, a diabetic patient with hypoglycemic episodes, and a patient with the cardiac illness paroxysmal atrial tachycardia may all suffer from symptoms that are very similar to the panic attack patient. Panic attacks have also been associated with endocrinologic changes including oophorectomy, hysterectomy, the postpartum period, and initiation of thyroid replacement for hypothyroidism. Other physical disorders that may cause symptoms resembling a panic attack include hypoglycemia, pheochromocytoma, hyperthyroidism, cardiovascular disease, caffeinism, and drug intoxication and withdrawal. Initial panic attacks are also often precipitated by recreational use of marijuana, amphetamines, or cocaine.

One of the most difficult differential diagnoses occurs when panic attacks develop concomitantly with a known physical illness such as asthma or

Table 3. DSM III Criteria for Generalized Anxiety Disorder

Generalized, persistent anxiety is manifested by symptoms from three of the following categories:

1. Motor tension: Shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle
2. Autonomic hyperactivity: Sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, light-headedness, paresthesias (tingling in hands and feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiratory rate
3. Apprehensive expectation: Anxiety, worry, fear, rumination, and anticipation of misfortune to self or others
4. Vigilance and scanning: Hyperattentiveness resulting in distractibility; difficulty in concentrating, insomnia, feeling "on edge," irritability, impatience

The anxious mood has been continuous for at least one month

Not due to another mental disorder, such as depressive disorder or schizophrenia

At least 18 years of age

Source: Diagnostic and Statistical Manual of Mental Disorders[18]

angina pectoris. Both of these illnesses normally cause anxiety in the patient, which is a signal of physical distress, but they also are occasionally exacerbated by the development of pathological anxiety, ie, panic attacks.

Psychiatrically, care should be exercised to differentiate among the symptoms of panic disorder and those of generalized anxiety, simple phobia, and depression. The symptoms of generalized anxiety disorder are persistent anxiety with three of the four following symptoms: motor tension, autonomic hyperactivity, apprehensive expectation, vigilance, and scanning (Table 3).[18] These symptoms must be present for at least one month, and the patient with generalized anxiety does not have acute panic attacks or specific phobias. Simple phobia involves a persistent irrational fear of and compelling desire to avoid an object or specific situation other than being alone. Simple phobias are sometimes referred to as "specific" phobias, the most common ones in the general population involving animals, particularly dogs, snakes, and mice. Other simple phobias are claustrophobia (fear of closed spaces) and acrophobia (fear of heights). Psychosocial trauma can almost always be identified as the original precipitant (eg, being bitten by a dog as a child may cause a phobia to all dogs). When exposed to a phobic stimulus, the patient may experience symptoms identical to those of a panic attack, but patients with simple phobia do not have panic attacks when not exposed to their specific phobic stimulus.

Major depression may be diagnosed by the prolonged presence of depressed mood and at least four of the following vegetative and cognitive symptoms: appetite disturbance, sleep disturbance, psychomotor agitation or retardation, anhedonia, decreased libido, loss of energy, thoughts of worthlessness or guilt, decreased ability to think or concentrate, or suicidal thoughts (Table 4). Many patients have major depression and panic disorder concurrently, and the panic attacks will resolve with successful treatment with a tricyclic antidepressant that acts on the noradrenergic system.

Patients with panic attacks often self-medicate with alcohol and sedative hypnotics, resulting at times in abuse of these general central nervous system depressants.[31] Several studies have demonstrated a very high incidence of panic disorder in the alcoholic population, and thus this population should be carefully screened for the presence of panic attacks.[32] Symptoms of generalized anxiety as well as acute panic often are integral symptoms of drug withdrawal or alcohol withdrawal syndromes, and the patient must always be questioned about past drug use.

Treatment

Upon concluding that the patient does meet the criteria for panic disorder, as well as excluding co-

Table 4. Diagnostic Criteria for Major Depressive Disorder

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by terms such as depressed, sad, blue, hopeless, down in the dumps, irritable
B. At least four of the following symptoms have each been present nearly every day for a period of at least 2 weeks:
   1. Poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain
   2. Insomnia or hypersomnia
   3. Psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down)
   4. Loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating
   5. Loss of energy; fatigue
   6. Feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional)
   7. Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with marked loosening of association or incoherence
   8. Recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt
C. Neither of the following dominates the clinical picture when an affective syndrome is absent (ie, symptoms in criteria A and B above):
   1. Preoccupation with a mood-incongruent delusion or hallucination
   2. Bizarre behavior
D. Not superimposed on schizophrenia, schizophreniform disorder, or a paranoid disorder
E. Not due to any organic mental disorder or uncomplicated bereavement

existing medical or psychiatric disorders, treatment may be undertaken. Choice of treatment depends upon the stage in which the disorder is encountered. In all three stages, support and medication may be useful. However, when the symptoms have progressed to include anticipatory anxiety or agoraphobia, supportive or behavioral psychotherapy directed toward these symptoms may be needed.

As is common in patients presenting with an illness, there is a feeling of fear with apprehension of bad, or even terminal, outcome and a sense of loss of control. By its very name, panic disorder signifies an overwhelming sense of helplessness in the face of frightening and foreboding symptoms. The physician, who is satisfied that a life-threatening emergency is not present, should reassure the patient that his illness is extremely uncomfortable but one that is treatable with proper medication. This effort, combined with a statement that the symptoms will subside and that treatment is available and effective, will provide great comfort and hope to many patients. A subgroup of patients who are extremely somatically oriented will reject the physician diagnosis of panic disorder because of the cultural stigma to mental illness and the profound physiologic changes the panic syndrome causes.

A useful tool in both confirming diagnosis and negotiating treatment is to have the patient hyperventilate for two to five minutes, which will usually precipitate all of the symptoms of a panic anxiety attack, and then have the patient breathe into a paper bag with a calming suggestion by the physician that the symptoms will quickly abate. Hyperventilation is a core part of panic disorder, and this clinical trial not only confirms diagnosis but is a powerful, convincing tool demonstrating to the patient and his family that the overwhelming frightening symptoms are not dangerous and can be controlled and treated.[33]

Reassurance and demonstration of the onset of symptoms with hyperventilation, while important, may have minimal effect without a demonstrated ability to pharmacologically treat the patient. By the time the patient has sought counsel, he or she is aware that something is quite wrong and that previously normal activities such as taking a test, going for a walk, or attempting to sleep invoke new-found terror. Specific medications have been found to support the clinician's reassurances. Effective medications include specific tricyclic antidepressants (imipramine and desipramine) and the monamine oxidase inhibitors (MAOIs) phenelzine and tranylcypromine. There is also recent re-

search that suggests that alprazolam, a new benzodiazepine, is an effective medication in the treatment of panic disorders.[34]

Imipramine has a recognized effectiveness in the treatment of panic attacks. While commonly used as an antidepressant in standard maintenance doses of 100 to 300 mg, the dosage effective in treatment of panic disorder is much lower, 25 to 200 mg. An appropriate initial dose of imipramine or desipramine in this disorder is 25 mg daily. Some patients are exquisitely sensitive to this medication and may develop jitteriness, irritability, or inability to fall asleep. For these individuals the dosage should be dropped to as low as 5 mg. Patients who do not respond to 25 mg should have weekly increases in their dosage of 25 mg. In some cases patients respond only at a higher antidepressant level of 150 to 300 mg.

For patients with major depression and panic attacks, the noradrenergic antidepressants (imipramine, desipramine) are the medications of choice but should be prescribed in antidepressant dosages.

Monamine oxidase inhibitors may be considered a second-line drug in the treatment of panic disorder. Though effective, the necessity of avoiding foods high in tyramine, because of the potential of inducing a hypertensive crisis, makes them less likely to be chosen for use by many patients. On the other hand, MAOIs are at least as effective as tricyclic antidepressants in the treatment of panic disorder and generally have fewer side effects.

The minor tranquilizers (benzodiazepines) are felt to be ineffective or inferior to imipramine, desipramine, and MAOIs in the treatment of panic disorder with associated generalized anxiety state. However, these drugs, if employed, should be used on a time-limited basis as an adjunct to psychotherapy.

Both supportive and behavioral psychotherapy are useful and effective in treating the interpersonal problems, anticipatory anxiety, and avoidance behaviors developed by patients with panic disorder. Once medication stops the panic attacks, supportive and behavioral psychotherapy aimed at re-exposure to phobic stimuli the patient has been avoiding because of the association of the stimuli with panic attacks should be undertaken. Thus, the patient is encouraged to re-enter feared situations so that he can then experience them without the adverse consequences of panic and gradually expand a life that has been constricted by the panic attacks.

Most patients will respond within weeks to treatment of simple panic disorder but not necessarily to reduction of their anticipatory anxiety and agoraphobic pattern. The clinician may wish to consider psychiatric consultation in refractory patients and in patients whose diagnosis remains less clear. In addition, the clinician must be prepared for family repercussions in the treatment of any behavioral disturbance, as the symptoms may have begun to fulfill a role in the family environment, and their resolution will affect other members. Many patients who have been chronically ill with panic attacks may unconsciously sabotage treatment because of secondary gains that have developed in the family such as increased nurturance by a formerly distant spouse, avoidance of conflict secondary to the patient symptoms, and increased fulfillment of dependency needs. Patients who wish to examine more closely the precipitating factors and possible meanings of their symptoms may want to embark upon a longer term insight-oriented psychotherapy.

Conclusions

As a result of the severe autonomic nervous system manifestations, panic disorder has often been misdiagnosed as primarily a physical disorder. Patients who focused on cardiac symptomatology have been described in the literature as suffering from irritable heart or effort syndrome, hyperdynamic β-adrenergic state, pseudoangina, or most recently, mitral valve prolapse. If dyspnea or other respiratory symptoms predominate, the term *hyperventilation syndrome* was often used. With gastrointestinal symptoms of diarrhea, constipation, bloating, and nausea, *irritable colon* or *spastic colitis* were the diagnostic terms used. Certainly the increased specialization of medicine has been partially responsible for the lack of recognition of panic disorder as a syndrome that, like depression, can be diagnosed from clinical history but is often masked by physical symptomatology.

Panic disorder is a classic psychophysiologic illness with stressful life events precipitating

measurable physiological changes that become autonomous from the original stressful life events. An apt analogy can be made to peptic ulcer disease. As in peptic ulcer disease, there is a multimodal etiology with both genetic susceptibility and stressful life events influencing initial incidence. Once either panic attacks or peptic ulcer develops, these pathological physiologic changes may not be alleviated with resolution of life stress. In fact, these illnesses, because of their frightening and discomforting symptomatology, cause significant distress to the patient, often affecting key biological systems such as sleep, appetite, and sexual drive, as well as adversely affecting the patient's social, vocational, and family functioning. Stressful life events, easily coped with in the past, may now precipitate abdominal pain in the peptic ulcer patient or a flurry of panic attacks in the patient with panic disorder.

Thus it is important to treat the patient with peptic ulcer and panic attacks pharmacologically to decrease the physiologic symptoms that are themselves a cause of significant psychological distress. In addition, counseling by the primary care physician may decrease symptoms as a result of the social support provided as well as lead to improved coping mechanisms that enable the patient to decrease his or her own stress. Adjunctive treatment with relaxation exercises, self-hypnosis, or biofeedback may also decrease anxiety and dampen physiological arousal. As does peptic ulcer disease, panic disorder tends to be a relapsing, remitting illness. Thus, the physician needs to monitor further symptomatology, especially at times of stressful life changes.

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