

Panic Disorder and Agoraphobia: Hypothesis Hothouse

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Panic disorder and agoraphobia have been postulated to occur when (1) fear is elicited by some automatic mechanism that requires catastrophic cognition, (2) there is a flaw in the physiology of fear, with special reference to the noradrenergic system, or (3) a putative suffocation alarm mechanism sends out false alarms. The presence of a suffocation alarm system has been supported by studies of children who lack this protective mechanism because they suffer from congenital central hypoventilation syndrome. Antidepressants with serotonin activity seem to control panic disorder by down-regulating the suffocation alarm system. Serotonin selective reuptake inhibitors (SSRIs) are among the most effective drugs for panic disorder, emphasizing the role of serotonin in respiratory regulation. Dyspnea and hyperventilation are the cardinal signs of a panic attack. Because carbon monoxide (CO) does not cause panic, it may sabotage the suffocation alarm system by acting as an inhibitory neurotransmitter within the carotid body.

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Various theories have been developed over the years to account for the causes and diverse manifestations of anxiety disorders, notably panic attacks. To place these theories in perspective, it is important to examine them in the light of relevant clinical observations and available laboratory data.

HISTORICAL PERSPECTIVE: SYMPTOMATOLOGY

The earliest reference to a panic attack is found in Plato's *The Timaeus*.¹ Although Plato has been commonly thought to believe that hysteria was due to a "wandering womb," the original passage in his dramatic dialogue actually reads as follows:

The womb is an animal which longs to generate children. When it remains barren too long after puberty, it is distressed and sorely disturbed, and straying about in the body and cutting off the passages of breath, it impedes respiration and brings the sufferer into the extremest anguish and provokes all manner of diseases besides. [Italics added for emphasis]

As Plato noted, the matter of respiration and dyspnea is central to panic attacks. Further, Plato astutely noted that

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the illness occurred most often in women of childbearing age and implied that pregnancy would alleviate the illness. We have recently indicated this is the case.²

Furthermore, shortness of breath is not a manifestation of fear. The results of several well-controlled studies involving people in mortal danger—being shot at on the battlefield or jumping out of airplanes—have been similar. When asked to describe their autonomic responses in these situations, the subjects invariably reported palpitations, sweating, and trembling, but not dyspnea. Sometimes, subjects reported rapid respiration but not the sensation of shortness of breath.^{3,4}

These observations are interesting and distinct from those of panic attacks. Indeed, the theoretician and physician Sigmund Freud noted this difference in his practice. As reported by one of his hysterical patients⁵:

I woke up at 2:30 am with hot flashes. My whole body felt like it was burning up, my neck and hair were wet with sweat. My skin felt prickly; if I had hair on my back, it would have been standing up. I felt like I couldn't breathe . . . like I was being burned alive. It was the worst terror I had ever experienced.

In his *Introductory Lectures on Psychoanalysis*,⁶ Freud described a panic attack as follows:

The immense increase of stimulation owing to the interruption of the renovation of the blood (internal respiration) was . . . the cause of the experience of anxiety; the first anxiety was thus a toxic one. The name "Angst"—"angustiae," "Enge" [Latin and German for "narrow place" and "straits"]—emphasizes the characteristic of restriction in

breathing which was then present as a consequence of the real situation and is now almost invariably reinstated in the affect.

The clinical astuteness of Plato and Freud is noteworthy. Plato's epidemiologic statement about hysteria and women of child-bearing age is still accurate. Freud's hysterical patient reported a nocturnal panic attack. Nocturnal panic attacks are peculiar to panic disorder—social phobics and obsessive compulsives do not get them, and they occur in no other anxiety disorder.

Freud's Theories

Freud considered three distinct underlying causes of dyspnea as part of panic disorder. Initially, he thought dyspnea was due to a displaced fragment of coitus.⁷ Later, he thought dyspnea was due to the observation of the primal scene and identification with the participants in coitus who were frantically huffing and puffing.⁸

From here, Freud developed the notion of birth anxiety.⁶ Beyond the general idea of the contractions occurring during the passage of the fetus from the womb to the external environment, he was more specifically concerned about the interference in respiration that occurred during the birth process. Once again, Freud was grasping to understand the role of dyspnea.

Shortness of breath—dyspnea—is therefore one of the cardinal features of the spontaneous attack in panic disorder. Conversely, other anxiety states are not as well marked by dyspnea. For instance, social phobia—performance anxiety, public speaking anxiety—is classically marked by palpitations, sweating, and trembling, i.e., fear but not dyspnea.

EXPERIMENTAL PANIC ATTACK

Today, panic attacks can be produced experimentally by lactate infusions in panic patients.⁹ Furthermore, monoamine oxidase inhibitors (MAOIs) have been shown to block lactate-induced panic attacks. We were able to demonstrate that imipramine also blocked panics induced by sodium lactate.¹⁰ Thus, this psychopathologic state can be turned on and off in the laboratory, and related biochemical and physiologic processes can be examined in detail.

One of the first studies measured the response of the hypothalamic-pituitary-adrenal (HPA) axis to lactate infusion and surprisingly found that it was flat.^{11,12} During an experimentally induced panic attack, there were no increases in adrenocorticotrophic hormone (ACTH), cortisol, epinephrine, norepinephrine, and β -endorphins.

A lack of stimulation of the HPA axis was also found in people who were appropriately infused with carbon dioxide (CO₂) to induce a panic attack.¹³⁻¹⁵ In these experimental situations, as in clinical practice, panic is manifested

differently than fear. The symptoms of panic attack include shortness of breath (dyspnea), choking or smothering sensations, palpitations or tachycardia, chest pain or discomfort, sweating, and faintness.

CURRENT HYPOTHESES

Psychological Theories

Several theories have been proposed to clarify the etiology of panic attack. The most prominent of the psychological theories—the cognitive behavioral theory—considers panic attack as a form of misreleased fear.¹⁶ It has been postulated that people prone to panic have a catastrophizing attitude toward the possibility of severe and sudden illness. During the course of a day, innocuous stimuli occur that may seize their attention. They misinterpret these in a catastrophic way, which releases more autonomic symptomatology and increasingly frightens them; as a consequence, they experience a sudden, overwhelming panic attack.

Another psychological theory focuses on the phobia itself as being central and implies that a panic attack is a secondary reaction to the phobia.¹⁷ However, in many clinical cases, spontaneous panic attacks frequently occur in the absence of a phobic object, e.g., during a nocturnal panic attack.

Suffocation False Alarm Theory

The idea that a panic attack represents a suffocation false alarm underlies a physiocentric theory.¹⁸ The theory assumes that there is a monitor affecting the human central nervous system that has a regulatory threshold and, when exceeded, provides information on imminent suffocation.

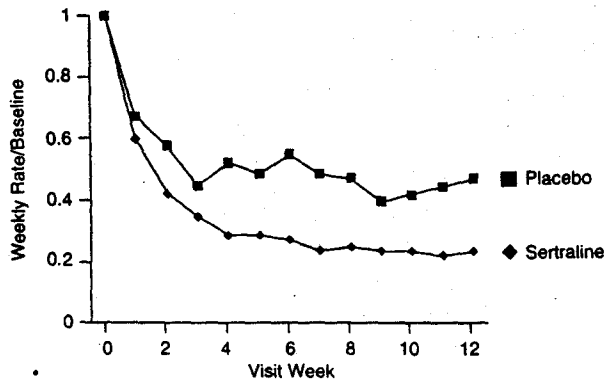
The primary physiologic indicators of suffocation are increasing levels of blood CO₂ and brain lactate. Since lactate is only formed during the process of anaerobic glycolysis—the metabolism of glucose in the absence of oxygen (O₂)—it seems more than a coincidence that these two potent panicogens are both indicators of putative suffocation.

Ondine's Curse

The existence of a suffocation alarm system has been validated by studies in people who lack this protective mechanism—children with congenital central hypoventilation syndrome (CCHS), so-called Ondine's Curse. These children are pink and healthy when born. When they go to sleep, however, they stop breathing, turn blue, and may die. It is necessary for nurses to shake them awake so that they start to breathe again. If these children go back to sleep and nobody notices, they may stop breathing again.

Babies with Ondine's Curse are very rare—about 1 in 100,000 live births.¹⁹ These children are kept alive primarily by forced breathing when they are asleep, using a

Figure 1. The Significant Decrease in the Frequency of Panic Attacks Over 12 Weeks Resulting From the Administration of Sertraline, Compared With Placebo*



*Data on file, Pfizer Inc.

technique known as phrenic driving. A radio frequency coil is implanted in the child's neck on the phrenic nerve, and a radio frequency generator sends out a pulse every 5 seconds to stimulate breathing throughout the night.

Children with Ondine's Curse have no feeling of suffocation. They do not know what it is like; CO₂ is not a respiratory stimulant for them, and if they are placed in a pure atmosphere of CO₂, they turn blue and have no awareness of their condition. In other words, panic disorder is a hypersensitivity of the suffocation alarm system and Ondine's Curse is a hyposensitivity.

ROLE OF SEROTONIN

Antidepressants with serotonin activity such as imipramine, which are effective in controlling panic disorder, seem to work by down-regulating the suffocation alarm system. Children with Ondine's Curse have little if any suffocation alarm system. When imipramine is given to these children during daylight hours, their breathing is interrupted.¹⁹ Conversely, when doxapram, a powerful respiratory stimulant used by anesthesiologists, is given to normal subjects, they are thrown into marked hyperventilation. If this drug is given to people with panic disorder, they experience a panic attack.²⁰

These responses seem to be pharmacologically related, since it has been recently shown that serotonin is extensively involved in respiratory regulation; depletion of serotonin in animals will cause hyperventilatory symptoms.²¹

Connection Between Ondine's Curse and Megacolon Disease

Another condition, megacolon disease, occurs in about 1 in 5000 live births.^{19,22} About a third of children with Ondine's Curse also have megacolon disease; there is a very high comorbidity of these two rare diseases.

Megacolon disease is a segmental absence of the myenteric plexus, which drives peristalsis. As a result, there is an area of the large intestine constricted as if by a rubber band; peristalsis is inhibited and the feces back up, resulting in an enlarged colon. Megacolon disease can be treated by excising the affected segment and reanastomosing the colon. It is noteworthy that the myenteric plexus is the only neuronal system outside the central nervous system that is serotonergic. Accordingly, there may be some stem defect in the serotonin system that is reflecting itself in both congenital central hypoventilation (Ondine's Curse) and peripheral hypocolonic peristalsis (megacolon syndrome).

Serotonin Selective Reuptake Inhibitors (SSRIs)

Serotonin must be involved in respiratory regulation since the tricyclic antidepressants (TCAs) and MAOIs are effective in panic disorder, while those antidepressants that do not affect serotonin, such as bupropion or maprotiline, do not seem to be useful in treatment.^{23,24}

The SSRIs are probably among the most effective drugs for panic disorder. Figure 1 shows a significant decrease in frequency of panic attacks over 12 weeks when sertraline is compared with placebo.²⁵

CLINICAL TESTS OF THE SUFFOCATION ALARM THEORY

The suffocation alarm theory implies that any time people with panic disorder are in a situation of putative suffocation, they are likely to panic. A rise in the blood level of CO₂ might be interpreted as a physiologic sign of suffocation in sleep, relaxation, pregnancy, childbirth, and hyperventilation.

Sleep and Relaxation

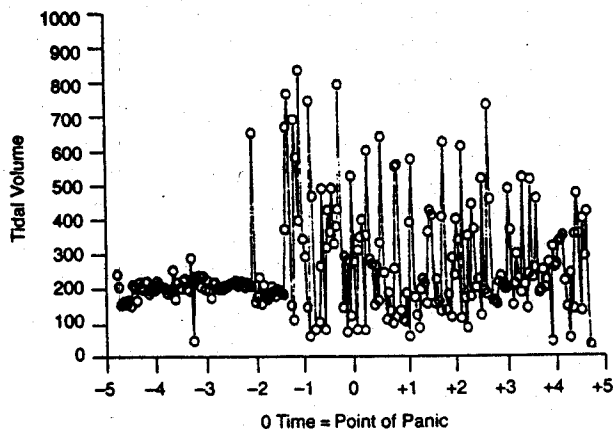
Patients with panic disorder panic during sleep, but they do not panic while dreaming during REM sleep. They panic in the transition (stage 3/4) of deep sleep and deeper sleep,^{26,27} which is the period when blood CO₂ is beginning to rise significantly.

Paradoxically, patients with panic disorder often panic when they try to relax. Half of these patients are chronic hyperventilators and when they try to relax, they stop hyperventilating and their blood CO₂ rises dramatically. The rise in blood levels of CO₂ when people sleep and when they relax accounts for the high positive correlation observed between these two situations.

Pregnancy and Childbirth

From a cognitive perspective, pregnancy can be thought of as a period of excessive risk for panic disorder, given all the internal, putatively dangerous sensations that can be ambiguously interpreted. However, during pregnancy, the establishment of a placenta requires the produc-

Figure 2. Hyperventilation in Panic Disorder Caused by an Infusion of Lactate in Patient 528*



*Klein DF. 1993. Unpublished data.

tion of the female reproductive hormone progesterone, which is also a strong respiratory stimulant. Starting in Week 10 of pregnancy, blood CO₂ steadily falls, leading to a compensatory respiratory alkalosis. Since blood CO₂ is low, the threshold of the suffocation alarm system is decreased. Therefore, pregnancy is actually a protected period against panic disorder, and the rate of panic attack falls drastically as pregnancy progresses.

During labor and childbirth, there is a large increase in endogenous stimuli, along with marked pain, uncertainty, and the recognition of the possibility of death. However, women with panic disorder do not panic during childbirth; their experience is entirely different. Because of hyperventilation that occurs during childbirth, this is the period of lowest blood CO₂ that has ever been measured in any natural situation. Rather than being a cause of panic attacks, hyperventilation provides protection against panic during childbirth.

Following expulsion of the placenta, progesterone levels fall and blood CO₂ increases. The period of protection against panic disorder ceases postpartum and the attack rate of women with a history of panic disorder again rises.²

HYPERVENTILATION

Direct evidence for the involvement of hyperventilation in panic disorder comes from the measurement of tidal volume during lactate infusion studies.²⁸ As a patient is slowly infused with lactate, breathing is regular and the tidal volume is stable. At a certain point, the patient may sigh, continue regular breathing and then suddenly, within a single breath, become dyspneic, entering a hyperventilatory state that continues for about a minute before the panic itself registers (Figure 2).

Sighing and yawning are venerable signs of what was usually referred to in the 19th century as neurosis. Labora-

tory studies show that one sigh is the equivalent of three deep breaths and significantly reduces blood CO₂. When blood CO₂ rises uncomfortably close to the suffocation alarm threshold, sighing is an adaptive strategy, although it may not prevent a panic attack. A common but incorrect theory suggests that hyperventilation causes panic attacks.²⁹ Several studies show that when patients with panic disorder are hyperventilated in room air, they become dizzy and dysphoric. They are uncomfortable but do not panic. If these patients are hyperventilated with 5% CO₂, they will panic,^{28,30} although the CO₂ prevents them from developing respiratory alkalosis.

Hyperventilation has been considered a bad habit of thoracic breathing. Normal abdominal breathing uses the diaphragmatic pump. Some people, women in particular, are thought to have developed the habit of thoracic breathing for cosmetic reasons. This type of breathing may explain why there are more panic attacks in women than in men. Currently, there is an emphasis on breathing retraining—teaching people techniques to breathe abdominally rather than thoracically. Panic attacks may be associated with increases in diaphragmatic rather than thoracic breathing (Klein DF. 1995. Unpublished data).

Carbon Monoxide (CO) Poisoning

One of the implications of the suffocation false alarm theory is that anybody who is suffocating should panic. Indeed, any normal person suffocating should panic. Yet, when people suffocate from CO poisoning, they seem to die without panicking.

One of the monitors for suffocation may be the carotid body, which measures the blood levels of both CO₂ and O₂. It recently has been shown that CO is an inhibitory neurotransmitter within the carotid body. Perhaps the reason that CO does not cause panic is that it sabotages the alarm system. The direct implication, then, is that CO acts as an antipanic agent. Work currently is in progress to see if CO₂ panicogenesis can be blocked by an admixture that includes CO.

PHARMACOLOGIC DISTINCTIONS IN PANIC DISORDER

Panic disorder can be differentiated by patient symptoms and the response to different pharmacologic agents. As previously emphasized, the cardinal sign of panic attack is dyspnea. Imipramine blocks the symptoms of clinical panic as well as the panics produced by lactate, bicarbonate, CO₂, and probably isoproterenol as well. While these agents do not activate the HPA axis, panic attacks caused by them are accompanied by marked respiratory symptoms. Furthermore, these agents have little effect on normal subjects and are specific for patients with panic disorder.

There are other agents that have been reported to cause panic, among them *m*-chlorophenylpiperazine (*m*-CPP),

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yohimbine, caffeine, β -carboline, and flumazenil. However, no respiratory symptoms characteristic of a clinical panic attack have been reported with the use of these agents.

While *m*-CPP is indeed serotonergic and capable of increasing obsessions in patients with OCD, the symptomatology of this disorder and the effects of the challenge do not include dyspnea.

Yohimbine is the main agent on which the noradrenergic theory of panic disorder is based. However, the effects of yohimbine are not blocked by imipramine. Yohimbine stimulates the HPA-mediated release of both cortisol and MHPG (3-methoxy-4-hydroxyphenylglycol).^{31,32}

Studies with caffeine have led to various adenosine theories of panic disorder, but its effects are not blocked by imipramine (Uhde TW, personal communication). Caffeine causes the release of cortisol.³³

Flumazenil is a benzodiazepine blocker. Its effects have been described as resembling those of γ -aminobutyric acid (GABA)-inverse agonists in panic patients (like β -carboline).³⁴ Importantly, it induces palpitations but not dyspnea.

Finally, β -carboline is an inverse GABA agonist with marked HPA activation.

In general, clinical panic involving only tachycardia, sweating, and trembling responds more readily to alprazolam than to imipramine. When dyspnea is also involved, imipramine is more effective than alprazolam.³⁵

SEPARATION ANXIETY

A final observation of interest is that there is a high incidence of childhood separation anxiety in adult patients with panic disorder. One theory suggests that there is a linkage between separation anxiety and suffocation false alarm via the endorphin system.¹⁸

Research with animal models has shown that endorphinergic deficits increase both separation anxiety and CO₂ sensitivity.³⁶ In current clinical studies, lactate infusions are being given to normal subjects after their endorphinergic system has been blocked by naloxone, in an attempt to convert them into lactate responders. None of the patients panicked in the small sample group in these current studies, but their blood pressure increased and they experienced considerable anxiety. There is no known pharmacologic reason why the combination of lactate and naloxone should cause a sudden increase in blood pressure, which occurs in panic disorder (Klein DF, 1995. Unpublished data). Like other proposed hypotheses, this one needs to be explored further to validate the hypothesis that phasic endorphinergic deficits play a role in both separation anxiety and panic disorder.

QUESTIONS AND ANSWERS

Question: *What is your recommendation for treating panic disorder in clinical practice?*

Answer: I originally used imipramine in the treatment of patients with panic disorder, and it continues to be a useful drug. We have done studies with alprazolam, and, at least in our hands, the drug seems to be less effective than imipramine in more severe patients—those whose panics were marked by dyspnea.

When we did our initial studies with fluoxetine, we found that the drug was overstimulating to about half the patients.³⁷ They felt extremely agitated and distressed. We reduced the initial dose from 20 mg to 5 mg. With some patients, you may have to further lower the dose to 2.5 mg or 1.25 mg. Fluoxetine is an excellent drug, but it has to be used in extremely low doses in treating patients with panic disorder.

When sertraline was introduced, the available dose was 50 mg, and that is too high for many patients. We use 25 mg, and that seems quite acceptable to most patients. I have shifted from fluoxetine to sertraline for two reasons. First, many of my patients have atypical depression. If an SSRI does not work, the patient should be switched to an MAOI. That is simpler to do with sertraline than with fluoxetine. It is not really a question of differential efficacy, but rather of easy tactical management. A recent sertraline trial in panic disorder has documented its efficacy in a placebo-controlled trial.

I have had very little experience with either paroxetine or fluvoxamine, but my colleagues tell me that these agents cause some sedation. At the present time, I use one SSRI, sertraline. I begin with a very low dose, 25 mg, and do not increase the dose for 3 weeks. Then I raise the dose gradually. Using that routine, I avoid nausea and diarrhea in almost all patients.

Question: *Please explain the issue of abdominal breathing and account for the observation that rebreathing into a paper bag seems to abort anxiety attacks in some patients?*

Answer: An analog double-blind study of breathing into a paper bag found that the results described by the questioner were based entirely on a placebo effect.³⁸ Since panic attacks are typically short, the placebo effect was sufficient until the panic attack dissipated naturally.

Most forms of respiratory training that reduce thoracic and promote abdominal breathing require the patient to breathe slowly and shallowly, rather than deeply. This type of retraining, which seems to be counter-intuitive, may nevertheless make sense because about half the patients with panic disorder are chronic hyperventilators. These patients typically have a low blood level of CO₂ and breathing slowly and shallowly boosts their CO₂ level.

Chronic hyperventilation may lead to a deafferentation hypersensitivity. In other words, the low level of CO₂ increases receptor sensitivity to this gas. Increasing the levels of CO₂ by breathing shallowly may decrease the deafferentation hypersensitivity.

The pathologic decrement in the suffocation alarm system seems to wax and wane. Respiratory retraining may eliminate the deafferentation hypersensitivity component and, if the primary suffocation alarm hypersensitivity has waned, normality may be restored.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), doxapram (Dopram), flumazenil (Romazicon), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), isoproterenol hydrochloride (Isuprel and others), maprotiline (Ludiomil), naloxone (Narcan and others), paroxetine (Paxil), sertraline (Zoloft), yohimbine (Yoon and others).

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