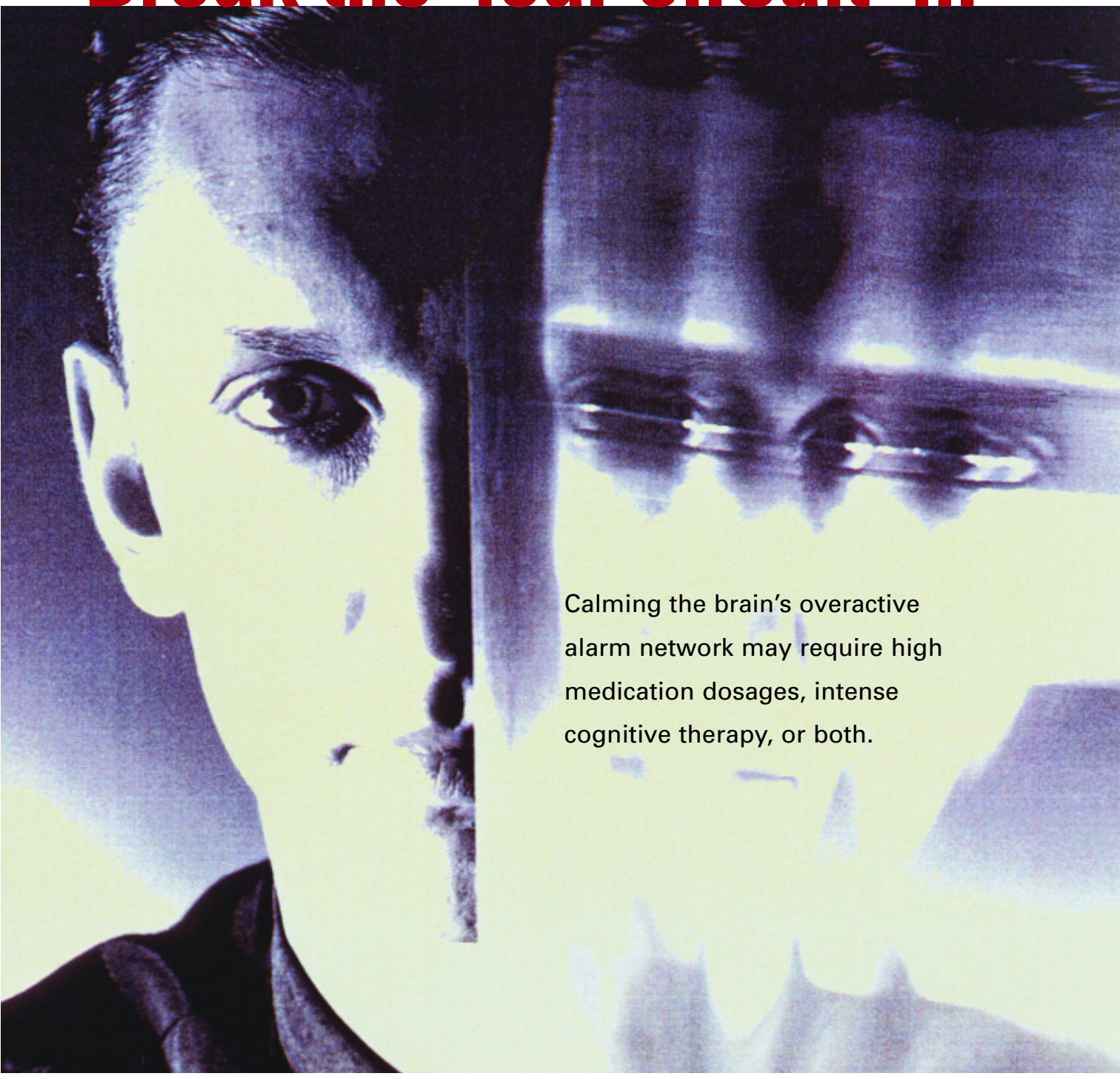
Break the 'fear circuit' in



Calming the brain's overactive alarm network may require high medication dosages, intense cognitive therapy, or both.

Current PSYCHIATRY

resistant panic disorder

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When initial therapy fails to control a patient's panic attacks, a neuroanatomic model of anxiety disorders may help. This model proposes that panic sufferers have an abnormally sensitive brain "fear circuit."[1] It suggests why both medications and cognitive-behavioral therapy (CBT) are effective for treating panic disorder (PD) and can be used as a guide to more successful treatment.

This article explains the fear circuit model and describes how to determine whether initial drug treatment of panic symptoms has been adequate. It offers evidence-and experience-based dosing ranges, augmentation strategies, tips for antidepressant titration, and solutions to the most common inadequate response problems.

HOW THE FEAR CIRCUIT WORKS

Panic disorder may occur with or without agoraphobia. The diagnosis requires recurrent, unexpected panic attacks *(Table 1)*, with at least one attack followed by 1 month or more of:

- persistent concern about having additional attacks
- worry about the implications of the attack
- or significant change in behavior related to the attack.

Panic disorder is usually accompanied by phobic avoidance and anticipatory anxiety, and it often coexists with other psychiatric disorders. Anxiety disorders may share a common genetic vulnerabil-

Table 1

Panic attacks: The core symptom of panic disorder

A panic attack is a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and peak within 10 minutes:

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

Source: DSM-IV-TR

ity. Childhood experiences, gender, and life events may increase or decrease the probability that a biologically vulnerable individual will develop an anxiety disorder or depression.[1]

Fear circuit model. PD's pathophysiology is not completely understood, but evidence suggests that an overactive brain alarm network may increase vulnerability for PD *(Box)*.[1,2] Individual patients require different intensities of treatment to normalize their panic symptoms:

Mild to moderate PD (characterized by little or no avoidance and no comorbid disorders) often responds to either medication or CBT. A single intervention—such as using CBT to enhance the cortical inhibitory effects or using medication to reduce the amygdala's reactivity—may suffice for symptomatic relief.

Severe or complicated PD (characterized by frequent panic attacks, significant agoraphobia, and comorbid anxiety disorders or depression) may require high medication dosages, intense CBT/exposure therapy, or both to normalize more severely disrupted communication among the fear circuit's components.

ASSESSING TREATMENT OUTCOME

The goal of treatment is remission: a return to functioning without illness-related impairment or loss of quality of life, as if the patient had never been ill. In clinical practice, we can use validated, patient-rated assessment tools to document improvement in panic-related impairment, patient satisfaction, and quality of life—the real targets of treatment. Two useful tools are the Sheehan Disability Scale[3] and the Quality of Life Enjoyment and Satisfaction Questionnaire.[4]

With adequate treatment, achieving remission can take several months or more; without it, remission may never occur. The following guidelines can help ensure that you provide adequate treatment.

What is adequate CBT? When patients' symptoms fail to respond to CBT, the first step is to examine whether inadequate treatment is the culprit. At least 10 weekly CBT sessions administered by a "qualified professional" has been suggested as an adequate CBT trial for PD.[5] Unfortunately, qualified CBT therapists are not always available. If CBT referral is not an option, clinicians can provide patients with at least some elements of CBT, such as education about PD, information resources, and self-exposure instruction as indicated. For more information on CBT for PD, see *Related Resources* (page 22).

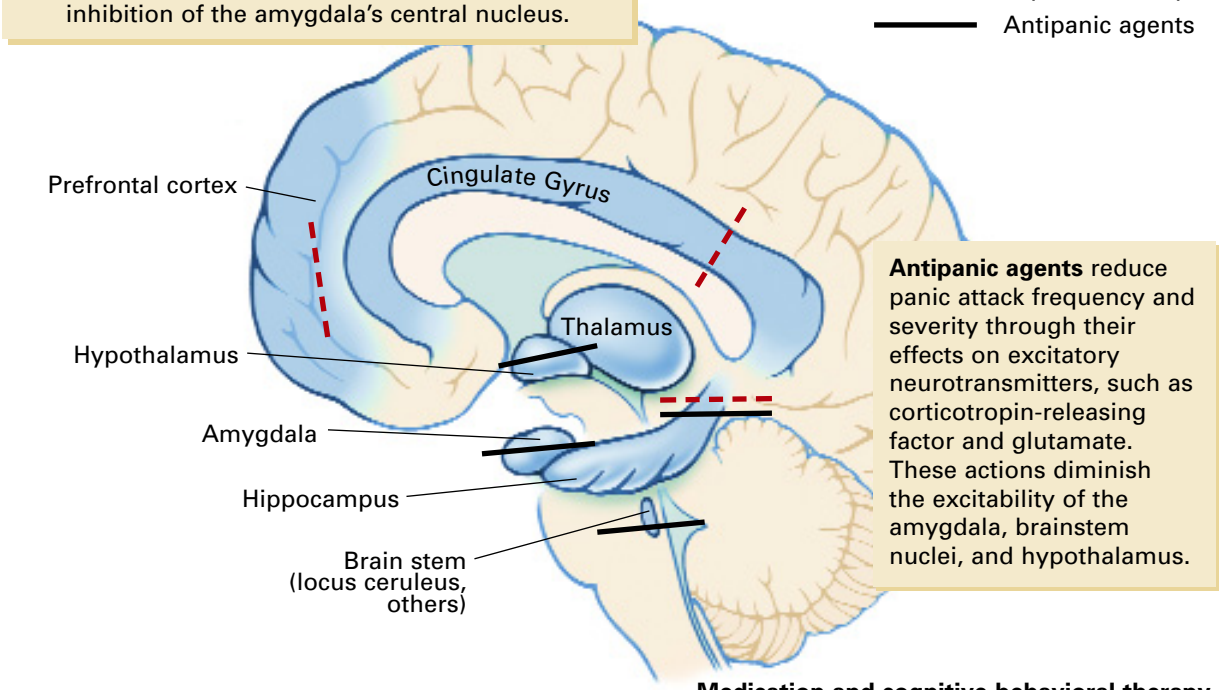
What is adequate drug treatment? Noncompliance with medication because a patient fears adverse effects or has insufficient information can easily thwart treatment. Before treatment begins, therefore, it is important to establish your credibility. Provide the patient with information about PD, its

Box

How an abnormal 'fear circuit' may trigger panic attacks

Cognitive-behavioral therapy and exposure therapy exert their beneficial effects in panic disorder by:

- extinguishing conditioned fear at the amygdala and hippocampus
- reducing distorted, catastrophic thinking in cortical processing, thus enhancing cortical inhibition of the amygdala's central nucleus.



Antipanic agents reduce panic attack frequency and severity through their effects on excitatory neurotransmitters, such as corticotropin-releasing factor and glutamate. These actions diminish the excitability of the amygdala, brainstem nuclei, and hypothalamus.

An inherited, abnormally active brain alarm mechanism—or "fear circuit"—may explain panic disorder, according to a theoretical neuroanatomic model.[1] Its hub is the central nucleus of the amygdala, which coordinates fear responses via pathways communicating with the hippocampus, thalamus, hypothalamus, brainstem, and cortical processing areas.

The amygdala mediates acute emotional responses, including fear and anxiety. The hypothalamus mediates physiologic changes connected with emotions, such as release of stress hormones and some changes in heart rate. The prefrontal cortex is involved in thinking and memory and may be instrumental in predicting the consequences of rewards or punishments. In vulnerable individuals, defects in coordinating the sensory input among these brain regions may cause the central nucleus to discharge, resulting in a panic attack.

Medication and cognitive-behavioral therapy may reduce fear circuit reactivity and prevent panic attacks by acting at different components of the fear circuit. When the amygdala's central nucleus no longer overreacts to sensory input, anticipatory anxiety and phobic avoidance usually dissipate over time.[2,3] Thus, the fear circuit model integrates the clinical observation that both cognitive-behavioral therapy and medication are effective for treating panic.[1]

Abnormal interactions among components of this oversensitive fear circuit also may occur in social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder, and depression.[1] In these disorders, communication patterns among the parts of the hypothesized circuit may be disrupted in different ways. The clinical observation that anxious individuals often become depressed when under stress is consistent with this model and with the literature.

ILLUSTRATION BY MARCIA HARTSOCK

treatment options, and what to expect so that he or she can collaborate in treatment *(Table 2)*.

Antidepressants are preferred as first-line treatment of PD, even in nondepressed patients. Selective serotonin reuptake inhibitors (SSRIs) are recommended for PD because of their comparable efficacy and tolerability compared with older antipanic agents.[6] SSRIs are also effective against other anxiety disorders likely to co-occur with PD.[7]

Many panic patients are exquisitely sensitive to activation by initial antidepressant dosages. Activation rarely occurs in other disorders, so its appearance suggests that your diagnosis is correct. Clinical strategies to help you manage antidepressant titration are suggested in *Table 3*.

In clinical settings, two naturalistic studies suggested that more-favorable outcomes are associated with antipanic medication dosages shown in *Table 4* as "possibly effective"—and that most patients with poor medication response received inadequate treatment.[8,9] *Table 4*'s dosages come from those two studies—published before the efficacy studies of SSRIs in PD—and from later studies of SSRIs and the selective norepinephrine-serotonin reuptake inhibitor (SNRI) venlafaxine.[7,8,10]

The lower end of the "probably effective" range in *Table 4* represents the lowest dose levels generally expected to be effective for PD. Not all agents in the table are FDA-approved for PD, nor are the dosages of approved agents necessarily "within labeling." Some patients' symptoms may resolve at higher or lower dosages.

Some patients require months to reach and maintain the "probably effective" dosage for at

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Table 2

Prescription for success in treating panic disorder

Relieve patient of perceived burden of being ill
Explain the disorder's familial/genetic origins
Describe the fear circuit model
Include spouse or significant other in treatment

Build patient-physician collaboration
Explain potential medication side effects
Describe the usual pattern of symptom relief (stop panic attacks → reduce anticipatory anxiety → decrease phobia)
Estimate a time frame for improvement
Map out next steps if first try is unsuccessful
Be available, especially at first

Address patient's long-term medication concerns
Discuss safety, long-term efficacy
Frame treatment as a pathway to independence from panic attacks
Use analogy of diabetes or hypertension to explain that medication is for managing symptoms, rather than a cure
Discuss tapering medication after sustained improvement (12 to 18 months) to determine continued need for medication

Table 3

Tips to help the patient tolerate antidepressant titration

Be pre-emptive
Before starting therapy, explain that low initial dosing and flexible titration help to control unpleasant but medically safe "jitteriness" known as antidepressant-induced activation

Tell the patient that activation rarely occurs in disorders other than PD ("Its appearance suggests that the diagnosis is correct and that we're likely on the right track")

Be reassuring
Tell the patient, "You control the gas peddle—I'll help you steer" (to an effective dose)

Be cautious
Start with 25 to 50% of the usual antidepressant initial dosage for depression (*Table 4*); if too activating, reduce and advance more gradually

Activation usually dissipates in 1 to 2 weeks; over time, larger dosage increments are often possible

Be attentive
Use benzodiazepines or beta blockers as needed to attenuate activation

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least 6 weeks. Short-term benzodiazepines can be used to control panic symptoms during antidepressant titration, then tapered off.[11] We categorize patients who are unable to tolerate an "adequate dose" as not having had a therapeutic trial—not as treatment failures.

No controlled studies of PD have examined the success rate of switching to a second antidepressant after a first one has been ineffective.[12] In clinical practice, we may try two different SSRIs and venlafaxine. When switching agents, we usually co-administer the treatments for a few weeks, titrate the second agent upward gradually, then taper and discontinue the first agent over 2 to 4 weeks. We use short-term benzodiazepines as needed.

Partial improvement. Sometimes overall symptoms improve meaningfully, but bothersome panic symptoms remain. Clinical response may improve sufficiently if you raise the medication dosage in increments while monitoring for safety and tolerability. Address medicolegal concerns by documenting in the patient's chart:

- your rationale for prescribing dosages that exceed FDA guidelines
- that you discussed possible risks versus benefits with the patient, and the patient agrees to the treatment.

When in doubt about using dosages that exceed FDA guidelines for patients with unusually resistant panic symptoms, obtain consultation from an expert or colleague.

Using benzodiazepines. As noted above, adjunctive use of benzodiazepines while initiating antidepressant therapy can help extremely anxious or medication-sensitive patients.[11] Many clinicians co-administer benzodiazepines with antidepressants

Table 4

Recommended drug dosages for panic disorder

Class/agent	Possibly effective (mg/d)	Probably effective (mg/d)	High dosage (mg/d)	Initial dosage (mg/d)	Confidence level
SSRIs					
Citalopram	<20	20-60	>60	10	++
Escitalopram	<10	10-30	>30	5	++++
Fluoxetine	<40	40-80	>80	10	++
Fluvoxamine	<150	150-300	>300	25	++++
Paroxetine*	<40	40-60	>60	5-10	++++
Sertraline*	<150	150-300	>300	12.5-25	++++
SNRI					
Venlafaxine	<150	150-300	>300	18.75-37.5	++
Benzodiazepines					
Alprazolam*	<2	2-8	>8	0.5-1.0	++++
Clonazepam*	<1	2-4	>4	0.25-0.5	++++
Tricyclics					
Clomipramine	<100	100-200	>200	10	++++
Desipramine	<150	150-300	>300	10	++
Imipramine	<150	150-300	>300	10	++++
MAOIs					
Phenelzine	<45	45-90	>90	15	+++
Tranylcypromine	<30	30-70	>70	10	+
Antiepileptics					
Gabapentin	100-200	600-3,400			++
Valproate (VPA)	250-500	1,000-2,000			++

* FDA-approved for treating panic disorder

Confidence: + (uncontrolled series) +++ (>1 controlled study)
++ (at least 1 controlled study) ++++ (Unequivocal)

Table 5

Solving inadequate response to initial SSRI treatment of panic disorder

Problem	Differential diagnosis	Suggested solutions
Persistent panic attacks	Unexpected attacks	
	Inadequate treatment or duration	≥Threshold dose for 6 weeks Try second SSRI Try venlafaxine
	Situational attacks	CBT/exposure therapy
	Medical condition	Address specific conditions
	Other psychiatric disorder	Rule out social phobia, OCD, PTSD
Persistent nonpanic anxiety	Medication-related	
	Activation (SSRI or SNRI)	Adjust dosage, add BZD or beta blocker
	Akathisia from SSRI	Adjust dosage, add beta blocker or BZD
	Comorbid GAD	Increase antidepressant dosage, add BZD
	Interdose BZD rebound	Switch to longer-acting agent
	BZD or alcohol withdrawal	Assess and treat as indicated
	Residual anxiety	Add/increase BZD
Residual phobia	Agoraphobia	CBT/exposure, adjust medication
Other disorders	Depression	Aggressive antidepressant treatment ± BZDs
	Bipolar disorder	Mood stabilizer and antidepressant ± BZDs
	Personality disorders	Specific psychotherapy
	Medical disorder	Review and modify treatment as indicated
Environmental event or stressor(s)	Review work, family events, patient perception of stressor	Family/spouse interview and education Environmental hygiene as indicated Brief adjustment in treatment plan(s) as needed
Poor adherence	Drug sexual side effects	Try bupropion, sildenafil, amantadine, switch agents
	Inadequate patient or family understanding of panic disorder and its treatment	Patient/family education Make resource materials available

BZD: Benzodiazepine
CBT: Cognitive-behavioral therapy
GAD: Generalized anxiety disorder
OCD: Obsessive-compulsive disorder
PTSD: Posttraumatic stress disorder
SNRI: Serotonin-norepinephrine reuptake inhibitor
SSRI: Selective serotonin reuptake inhibitor

over the longer term.[7] As a primary treatment, benzodiazepines may be useful for patients who could not tolerate or did not respond to at least two or three antidepressant trials.

Because benzodiazepine monotherapy does not reliably protect against depression, we advise clinicians to encourage patients to self-monitor and report any signs of emerging depression. Avoid benzodiazepines in patients with a history of alcohol or substance abuse.[7]

Other agents. Once the mainstay of antipanic treatment, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are seldom used today because of their side effects, toxicity in overdose, and—for MAOIs—tyramine-restricted diet. Their usefulness in resistant panic is probably limited to last-ditch efforts.

DISSECTING TREATMENT FAILURE

In uncomplicated PD, lack of improvement after two or more adequate medication trials is unusual. If you observe minimal or no improvement, review carefully for other causes of anxiety or factors that can complicate PD treatment *(Table 5)*.

If no other cause for the persistent symptom(s) is apparent, the fear circuit model may help you decide how to modify or enhance medication treatment, add CBT, or both.

For example:

- If panic attacks persist, advancing the medication dosage (if tolerated and acceptably safe) may help. Consider increasing the dosage, augmenting, or switching to a different agent.
- If persistent attacks are consistently cued to feared situations, try intervening with more-aggressive exposure therapy. Consider whether other disorders such as unrecognized social anxiety disorder, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD) may be perpetuating the fearful avoidance.
- If the patient is depressed, consider that depression-related social withdrawal may be causing the avoidance symptoms. Aggressive antidepressant pharmacotherapy is strongly suggested.

AUGMENTATION STRATEGIES

Medication for CBT failure. Only two controlled studies have examined adding an adequate dose of medication after patients failed to respond to exposure/CBT alone:

- One study of 18 hospitalized patients with agoraphobia who failed a course of behavioral psychodynamic therapy reported improvement when clomipramine, 150 mg/d, was given for 3 weeks.[13]
- In a study of 43 patients who failed initial CBT, greater improvement was reported in patients who received CBT plus paroxetine, 40 mg/d, compared with those who received placebo while continuing CBT.[14]

Augmentation in drug therapy. Only one controlled study has examined augmentation therapy after lack of response to an SSRI—in this case 8 weeks of fluoxetine after two undefined "antidepressant failures." When pindolol, 2.5 mg tid, or placebo were added to the fluoxetine therapy, the 13 patients who received pindolol improved clinically and statistically more on several standardized ratings than the 12 who received placebo.[15]

An 8-week, open-label trial showed beneficial effects of olanzapine, up to 20 mg/d, in patients with well-described treatment-resistant PD.[16]

Other well-described treatment adjustments reported to benefit nonresponsive PD include:

- Adding fluoxetine to a TCA or adding a TCA to fluoxetine, for TCA/SSRI combination therapy[17]
- Switching to the selective norepinephrine reuptake inhibitor reboxetine, 2 to 8 mg/d for 6 weeks after inadequate paroxetine or fluoxetine response (average of 8 weeks, maximum dosage 40 mg/d).[18] (Note: Reboxetine is not available in the United States.)
- Using open-label gabapentin, 600 to 2,400 mg/d, after two SSRI treatment failures.[19]
- Adding the dopamine receptor agonist pramipexole, 1.0 to 1.5 mg/d, to various antipanic medications.[20]

Augmenting an SSRI with pindolol or supplementing unsuccessful behavioral treatment with "probably effective" dosages of paroxetine or clomipramine could be recommended with some confidence, although more definitive studies are

needed. As outlined above, some strategies[17-20] might be considered if a patient fails to respond to two or more adequate medication trials. Anecdotal reports are difficult to assess but may be clinically useful when other treatment options have been exhausted.

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The fear circuit model may help you decide whether more-intense drug treatment, CBT, or both may improve panic symptoms. Adequate therapeutic trials can increase the chances of success when initial treatment has failed. Some patients benefit from higher-than-approved medication dosages, if tolerated.

Bottom Line

Related resources

- Barlow DH. *Anxiety and its disorders: the nature and treatment of anxiety and panic*. New York: Guilford Press, 1988.
- Craske MG, DeCola JP, Sachs AD, Pontillo DC. Panic control treatment of agoraphobia. *J Anxiety Disord* 2003;17:321-33.
- National Institute for Mental Health: Panic Disorder http://www.nimh.nih.gov/publicat/fearandtrauma.cfm
- Anxiety Disorders Association of America http://www.adaa.org/

DRUG BRAND NAMES

Alprazolam • Xanax
Citalopram • Celexa
Clomipramine • Anafranil
Clonazepam • Klonopin
Desipramine • Norpramin
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Gabapentin • Neurontin
Imipramine • Tofranil
Olanzapine • Zyprexa
Phenelzine • Nardil
Pindolol • Visken
Paroxetine • Paxil
Pramipexole • Mirapex
Reboxetine • Vestra
Sertraline • Zoloft
Tranylcypromine • Parnate
Venlafaxine • Effexor

DISCLOSURE

Dr. Lydiard receives research support from GlaxoSmithKline, Eli Lilly and Co., Organon, Sanofi-Synthelabo, Cephalon, UCB Pharma, and Merck & Co. and he is a speaker for or consultant to Pfizer Inc., Eli Lilly and Co., Solvay Pharmaceuticals, AstraZeneca Pharmaceuticals, and Forest Pharmaceuticals.