Treatment-Resistant Panic Disorder

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Although effective pharmacologic and psychosocial treatments are available for panic disorder, many patients continue to experience residual anxiety symptoms, recurrent panic attacks, or continuing impairment and distress. Selecting the appropriate treatment for such patients can be confounded by factors such as comorbid disorders (both psychiatric and medical), psychosocial complications, and physiologic provocations. The clinician must assess these factors before an optimal therapeutic strategy can be designed. *(J Clin Psychiatry 1997;58[suppl 2]:61–64)*

Despite expanding research on the nature and treatment of panic disorder and newly emergent pharmacologic strategies and multicomponent cognitive behavior interventions, the treatment-resistant patient remains a challenge to the clinician. The pharmacopoeia for treating panic disorder is extensive and includes agents of several classes with reported efficacy, such as antidepressants (e.g., serotonin selective reuptake inhibitors [SSRIs], tricyclic antidepressants, and monoamine oxidase inhibitors), high-potency benzodiazepines (e.g., alprazolam and clonazepam), some anticonvulsants, antiadrenergic drugs, and others. In addition, certain cognitive behavior strategies target cessation of panic attacks as well as elimination of concomitant agoraphobic avoidance and anticipatory anxiety. Although the effectiveness of these pharmacologic and psychosocial interventions has been demonstrated in controlled clinical trials, many patients continue to experience residual symptoms, recurrent panic attacks, or continuing impairment and distress. Furthermore, high rates of comorbid Axis I and Axis II disorders, extensive avoidance behavior, and other confounding factors emphasize the complexity of panic disorder and its treatment.

Both patient-related (e.g., comorbidity and medical illness) and drug-related (e.g., dose and duration of treatment) factors may contribute to symptom persistence, suggesting a clinical approach to the assessment of the treatment-resistant patient.

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TREATMENT APPROACHES

Few systematically obtained, prospective, controlled data are available to guide the selection of treatment for patients with treatment-resistant anxiety disorders. Moreover, clinical trial data only partly inform clinical practice. Often, patients selected for clinical research studies are younger and healthier than the general patient population. They also tolerate treatment with placebo, receive single-agent treatments with inflexible dosing schedules, are lost to follow-up because of side effects or inefficacy, and do not suffer significant comorbid psychiatric disorders. With such limited data to guide initial treatment selection in the clinical setting, it is no surprise that little consensus exists on therapeutic algorithms for patients with panic disorder, particularly for those who do not respond to initial treatment or remain symptomatic despite adequate drug doses.

Naturalistic studies[1–3] indicate that most patients in clinical settings have both chronic and recurring symptoms, with rates of continuing panic attacks ranging from 40% to 80% at 1.5- to 6-year follow-up assessments. Data from a prospective, long-term study conducted at Massachusetts General Hospital[3] confirm these results. Of the first 100 patients entered, only 46% experienced a remission that lasted 2 months or longer, and about one third of patients experienced a remission that lasted 6 months or more during the course of their disorder. The presence of a comorbid anxiety disorder significantly decreased the likelihood of a patient experiencing remission and was also associated with increased phobic avoidance, personality disorders, and higher rates of anxiety sensitivity. One methodological difficulty lies in determining whether persistent and recurrent symptoms represent treatment resistance inherent to the disorder or result from suboptimal therapeutic intervention.[4–7]

Reports[8] indicate that adults with panic disorder who suffered from childhood anxiety disorders experienced panic attacks and phobic avoidance at a younger age than

those without such a history. They also were more likely to have agoraphobia (often characterized by more severe phobic avoidance) and had a significantly higher mean score on the Anxiety Sensitivity Index (a measure of the tendency to react with fear to bodily sensations) than patients who did not meet the criteria for early anxiety disorders. This clinical profile is considered a risk factor for symptom persistence and signals a need for vigorous, multimodal, sustained treatments.

COMORBIDITY

Patients with panic disorder often have other psychiatric disorders, including affective disorders (e.g., depression), other anxiety disorders (e.g., social phobia and agoraphobia), substance abuse, and personality disorders (e.g., dependent or histrionic personalities). Comorbid conditions affect the course and outcome of panic disorder, often increasing levels of overall distress, and are conducive to both diagnostic error and treatment resistance. Studies suggest that one half to two thirds of patients with panic disorder report past or present major depression, indicating that depression may emerge despite ongoing treatment.[9,10] Determining the specific symptoms of anxiety (e.g., agoraphobia, generalized anxiety disorder, and specific or social phobia versus spontaneous panic) in a panic patient who does not respond or only partially responds to treatment is important, since the most effective interventions for one comorbid anxiety disorder may not be so for another. By recognizing comorbid conditions, the clinician can design individual therapeutic interventions that maximize response, such as optimizing antidepressant treatment for persisting depression or adding exposure therapy for agoraphobia.

Several physiologic factors, including the presence of certain medical conditions and their treatment, can mimic the symptoms of a panic attack and contribute to chronicity. Such disorders include hyperthyroidism, hypoglycemia, congestive heart failure, cardiac arrhythmia, pheochromocytoma, audiovestibular dysfunctions, chronic obstructive pulmonary disease, and complex partial seizures. Anxiety-like symptoms in a medically ill patient may also reflect sensitivity to the side effects of medications, such as theophylline or other bronchodilators. Other physiologic factors in persisting anxiety symptoms include the excessive use of caffeine and substance abuse (e.g., marijuana or cocaine), which may produce panic-like symptoms and complicate the treatment of patients with panic disorder.[11] Treating the underlying medical illness or removing provocative treatment agents, selecting drugs with more benign side effect profiles, and using targeted cognitive behavior strategies may help achieve a therapeutic response in these patients.

The onset of panic disorder or the emergence of more intense and disabling panic symptoms typically follows identifiable antecedents, usually major life events, other psychosocial upheavals, or physiologic perturbations, and is relevant to identifying and improving interventions for the treatment-resistant patient. A variety of ongoing psychosocial stressors and interpersonal factors (e.g., marital distress, bereavement, dislocation, and personal or family conflicts) also can contribute to morbidity and interfere with treatment. Recurrent exposure to provocations of acute distress, such as loss or threat of loss, may be interpreted as a threat to personal security or attachment and may intensify panic symptoms or heighten the frequency of panic attacks.

Altered behavior patterns secondary to panic disorder can also impede treatment success. Patients with panic disorder and agoraphobia often develop intricate and restrictive behaviors—becoming prisoners to their own maladaptive coping strategies. With treatment, the freedom from panic attacks can in itself be anxiogenic, as the patient's limited but comfortable lifestyle is suddenly jeopardized. Ambivalence, frustration, anger, and guilt at the years of life lost to the limitations of the disorder may lead patients to retreat to their familiar sick-role surroundings rather than endure vulnerability in the face of novelty.

With panic disorder, it has been clinically useful and scientifically heuristic to view the panic attack as the primary pathogen responsible for the array of secondary symptoms, comorbidity, and course of illness. The focus on treating panic attacks may obscure the clinician's ability to recognize and evaluate many of the factors that contribute to persistent distress and impairment.

DRUG THERAPY AND COGNITIVE BEHAVIOR THERAPY

Several medications have well-documented acute efficacy for panic disorder and its complications; however, pharmacologic strategies related to agent selection, dosing adequacy, duration of treatment, and discontinuation of therapy can influence patient response. Antidepressants, chosen by most clinicians as the first-line treatment for panic disorder, are presumed to be better for conditions in which an underlying comorbid depression is present. The guidelines for adequate and optimal dosing of antidepressants for panic disorder are less clear than those for depression, particularly for the treatment-resistant patient. Most clinicians aim for the therapeutic levels used to treat depressed patients. In general, antidepressant treatment should be initiated at low doses to minimize early onset of adverse effects, such as jitteriness, and slowly titrated upward to a therapeutic level.

High-potency benzodiazepines are more rapidly effective for decreasing anticipatory anxiety and can be used in conjunction with an antidepressant when depression persists. Sedation and ataxia are the most common side effects associated with initiation of high-potency benzodiaz-

epine therapy and subsequent dose increases. However, these symptoms abate over time and with titration. Poor symptom control may be related to pharmacokinetics. Inadequate dosing of high-potency benzodiazepines (especially of short half-life agents) can result in interdose rebound anxiety, thereby contributing to continued symptomatology and chronicity and fostering a behavioral focus on "pill taking" or "clock watching" to control symptoms.[12] Therapeutic options include upwardly titrating the dose, increasing dose frequency, or switching to an agent with a longer half-life, such as clonazepam. When benzodiazepines are discontinued, a gradual taper augmented with cognitive behavior therapy can increase the likelihood of a successful taper and a positive long-term outcome.[12]

If continuing distress is related to nonsuppression of panic attacks, initial strategies may include trials with alternative antipanic medications or use of combination strategies, such as an antidepressant plus a benzodiazepine or an SSRI plus a tricyclic antidepressant. Adjunctive administration of buspirone[13] or treatment with valproic acid[14] has also proved effective for treatment-resistant panic disorder.

Cognitive behavior therapy as an intervention offers an alternative or supplement to medication and is highly effective for targeting the fear-of-fear cycle hypothesized by behaviorists to underlie panic disorder. The elements of cognitive behavior treatment include information on the nature of panic disorder and the fear-of-fear cycle, symptom management skills, cognitive restructuring that targets catastrophic misinterpretation of anxiety symptoms, interoceptive exposure aimed at eliminating the fear of anxiety sensations, and in vivo exposure aimed at eliminating phobic avoidance.[15,16] The specific cognitive behavior intervention, however, will vary with the disorder being treated, with different protocols for social phobia, agoraphobia, and severe personality disorder. Combined treatment with pharmacologic and cognitive behavior strategies has been shown to improve both the acute and long-term outcome of patients with panic disorder.[17,18] Cognitive behavior therapy can also benefit patients who remain symptomatic after receiving medication alone[19] and can augment the response to acute and maintenance benzodiazepine treatment.[20]

CONCLUSION

The design of therapeutic strategies to enhance the outcome of patients with treatment-resistant panic disorder begins with a detailed, systematic review of relevant factors in the etiology, symptomatology, and comorbidity of the disorder, as well as medical, physiologic, and psychosocial provocations. For some treatment-resistant patients, the next step is as simple as increasing the dose of an antipanic drug or switching from one agent to another to decrease side effects that limit treatment adequacy. For other patients, treatment response results from recognizing persistent phobic avoidance, anxiety sensitivity, or catastrophic misinterpretation of somatic symptoms and optimizing cognitive behavior therapies. In some cases, the intervention ensues from identifying an exogenous predisposing factor, such as an illness or use of other medications. For many treatment-resistant patients, the answer lies in understanding the complexity and interactions of interpersonal and psychosocial forces at work in their lives.

Before layering agent upon agent or treatment upon treatment to target panic attacks, the clinician should recognize persisting symptoms and comorbid disorders, medication-related issues, and physiologic and psychosocial factors. By identifying the nature and causes of persistent distress, the clinician can select appropriately targeted interventions. For many patients, panic disorder is one expression of a lifelong anxiety diathesis. These patients require vigorous multimodal efforts to decrease distress and optimize treatment. The clinician must ensure that the patient receives an adequate dose of medication initially and extended maintenance treatment as necessary, with the expectation that some residual impairment may be unavoidable.

Drug names: alprazolam (Xanax), buspirone (BuSpar), clonazepam (Klonopin), valproic acid (Depakene and others).

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Discussion

Treatment Resistance

Dr. Ballenger: In a treatment-resistant patient with panic disorder, the issue of exactly what to do next is not critical. Panic disorder is a chronic condition, and many things can be done. What you do next is less important than that you keep trying to find ways to improve the patient's well-being. You do not automatically exclude treatment, such as high-potency benzodiazepines, tricyclic antidepressants, or behavior therapy, that might be helpful. I do not know which approach you take next, just that you must keep trying to determine what is best for the patient. You try to hold onto your gains and achieve additional gains. Sometimes you have to give up some gains when you switch treatments. However, you do not stop until you believe the patient is as well as possible with a treatment that makes sense over the long term. With all the available drug and behavior therapies, we may never determine the absolute right treatment algorithm.

Dr. Davidson: You also should share that vision up front with the patient. You do not know whether you need to try 1 option or 15 options. The patient needs to be prepared for that.

Dr. Rosenbaum: We need to change the mindset of clinicians who restrict what they offer patients to one approach: "Here is the treatment, now tell me the problem."

Dr. Ballenger: Clinicians should be committed to vigorous, adequate treatments. That is, if you start on a particular course—whether benzodiazepine, tricyclic antidepressant, or psychotherapy—you should prescribe a high enough dose or continue the treatment for an adequate period of time before considering something else.

Dr. Jefferson: It can be difficult to determine where to draw the line. If a patient is only partially responding to various treatments, do we continue on with endless therapeutic zeal or do we settle for a partial improvement?

Dr. Rapaport: Practitioners also need to be versed in obtaining quantifiable data to determine the effectiveness of treatment, both in terms of symptom relief and functional impairment. We need to educate primary care physicians about the use of rating scales to obtain objective data.

Drug Therapy for Treatment-Resistant Patients

Dr. Rosenbaum: What is the next step if a patient with panic disorder does not respond to your drug of choice? Do you switch to a different drug or alter your treatment?

Dr. Pollack: It depends on whether the patient has no response or a partial response. It also depends on whether the patient is experiencing side effects or tolerating the medication well.

Dr. Davidson: If a patient does not respond at all to a serotonin selective reuptake inhibitor (SSRI) given at an adequate dose, I would consider adding another agent, such as clonazepam, or switching to another drug, such as a tricyclic antidepressant.

Dr. Jefferson: Drug therapy for a treatment-resistant patient is less well defined for panic disorder than for depression, and it is not that well defined for depression.

Cognitive Behavior Therapy

Dr. Barlow: We are working on ways to make behavior therapy more user friendly by decreasing some of the complexities, providing various manuals, and reducing the amount of time the therapist is involved. Patients may benefit from some of these changes, not only those with panic disorder but those with other disorders as well.

Chronicity

Dr. Rosenbaum: Biological models suggest that the longer patients are symptomatic, the more severe the panic disorder, based on late gene expressions. In other words, allowing the disorder to continue may activate genes that predispose the patient to chronicity, whereas vigorous early and sustained treatment may prevent that from occurring.

Dr. Charney: The lower prevalence of panic disorder in elderly patients suggests that something happens over time, even if the disorder is not treated.

Dr. Jefferson: Thus, long-term treatments may not be effective over time.

Dr. Rosenbaum: Are we conferring chronicity by our repeated attempts to discontinue treatment?

Dr. Ballenger: I think putting patients on and taking them off treatment and watching them relapse is not good. Although the trend is toward discontinuing medication as soon as possible, I would tend to maintain the drug regimen. If pharmacotherapy is effective, why stop it?