The Pharmacotherapy of Panic Disorder

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Panic disorder is common and associated with significant morbidity and dysfunction. The pharmacologic treatment of panic disorder is aimed at reducing or eliminating panic attacks, avoidance behavior, anticipatory anxiety, and comorbid conditions—and substantially improving and normalizing overall function and quality of life. Antidepressants and benzodiazepines remain the current mainstays of pharmacotherapy for panic disorder, although other novel agents and strategies are becoming available and may add effective alternatives to the therapeutic armamentarium.

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Panic disorder is common, with a lifetime prevalence of 3.5%, according to the National Comorbidity Survey.[1] It is diagnosed in a 3:1 female-to-male ratio in patients with agoraphobia and a 2:1 ratio in patients without agoraphobia. Panic disorder has an average age at onset in the third decade of life, although, consistent with the relatively earlier age at onset of anxiety disorders in general, over half of adult patients report significant difficulties with anxiety during childhood.[2] Panic disorder may have a seemingly spontaneous onset, although many individuals identify a life stressor occurring prior to the onset of panic symptoms; however, once initiated, the disorder may have a persistent course even in the absence of the continuous presence of the precipitating stressor.[3]

Panic disorder is associated with significant physical, mental, social, and vocational dysfunction, as well as diminished quality of life, comparable to that of patients with chronic medical conditions or depression.[4] The dysfunction is greater in patients with comorbid mood or anxiety disorders. Although associated with excessive utilization of medical services[5,6] and perhaps increased risk of death from cardiovascular causes,[7,8] panic disorder may be unrecognized and untreated in half of affected patients in primary care settings[9,10] because of its predominantly somatic rather than psychological symptom presentation, particularly in medical settings.[11,12] Symptomatic and functional improvement, decreased utilization of medical resources, and reduction in overall costs are associated with treatment of panic in general medical settings.[13] Pharmacotherapy of panic disorder may also normalize the decreased heart rate variability that may be a risk factor underlying panic-related cardiac death, and thus may, although unproven at present, reduce associated mortality.[14,15]

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TREATMENT CONSIDERATIONS

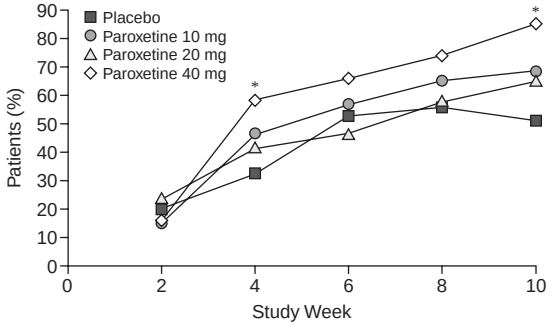
The goals for the treatment of panic disorder are to significantly reduce or eliminate panic attacks, avoidance behavior, anticipatory anxiety, and comorbid conditions and to substantially improve and normalize overall function and quality of life. Although this article will focus on pharmacologic treatment, both pharmacotherapy and cognitive-behavioral therapy have demonstrated efficacy for panic disorder in well-controlled clinical studies.

Development of an optimal treatment plan for an individual patient should include consideration of the patient's preference, particularly in the context of a review of the risks and benefits of each therapeutic intervention. In addition, the acuity of the distress and presence of significant comorbidities may help guide treatment selection; for instance, patients requiring rapid anxiolysis may require administration of benzodiazepines, whereas the presence of comorbid depression or substance abuse makes the case for administration of an antidepressant.

ANTIDEPRESSANTS

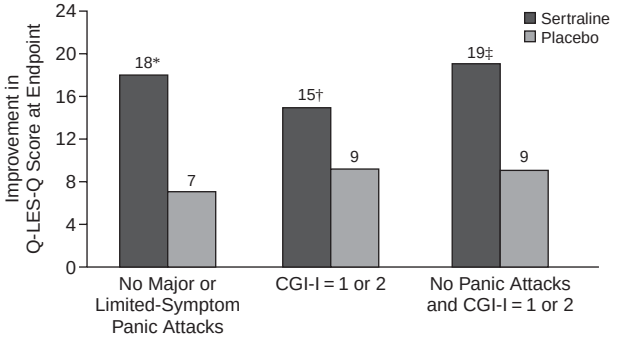
Antidepressants are often used as first-line treatments of anxiety disorders, including panic, because of their broad spectrum of efficacy against common comorbidities, especially depression, and the lack of the associated abuse and dependency liabilities that are associated with benzodiazepine administration.

Figure 1. Patients Free of Panic During Paroxetine Treatment[a]



[a]Reprinted with permission from Ballenger et al.[16]
*p < .019 vs. placebo.

Figure 2. Quality-of-Life Improvement in Sertraline and Placebo Responders[a]



[a]Data from Rapaport et al.[18]
[b]Pairwise comparison of adjusted mean-change scores: *p < .001; †p < .007; ‡p < .003.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

The selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have become first-line pharmacotherapy for a number of mood and anxiety disorders, including panic, and have demonstrated efficacy in acute and longer term studies, with paroxetine, fluoxetine, and sertraline receiving U.S. Food and Drug Administration (FDA) approval for the panic disorder indication.[16,17] A randomized, placebo-controlled, fixed-dose, 10-week trial demonstrated the efficacy of paroxetine for the treatment of panic disorder, with approximately two thirds to three quarters of patients achieving panic-free status by the end of the acute trial (Figure 1).[16]

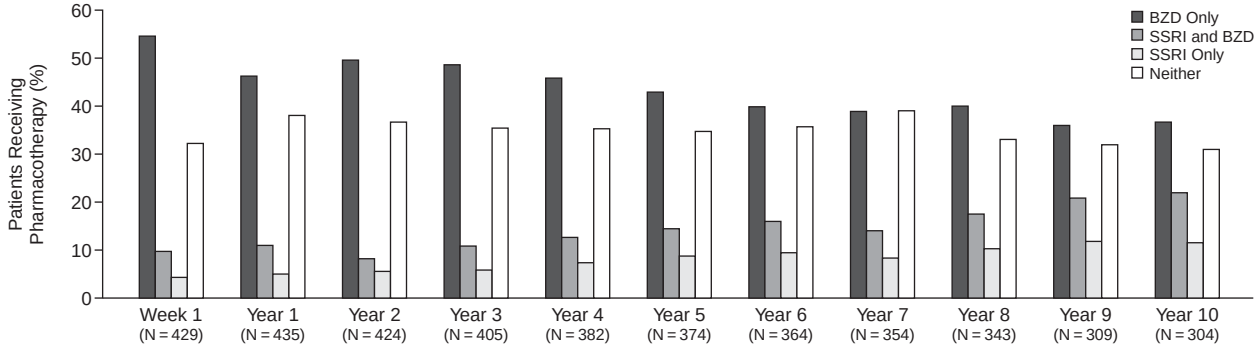
A study examining data from randomized, placebo-controlled studies of sertraline in panic disorder confirmed the efficacy of this SSRI for the condition.[18] It reported greater improvement in quality of life among patients receiving active treatment compared to those taking placebo, even among those who were responders by typical outcome criteria (e.g., panic-free), and affirmed the importance of assessing impact on quality of life in evaluating the effectiveness of treatment interventions (Figure 2). Although not FDA approved for the treatment of panic disorder, other SSRIs, such as escitalopram and citalopram, and SNRIs, such as venlafaxine, have demonstrated efficacy for panic disorder as well.[19,20]

The SSRIs and SNRIs are effective for many of the comorbidities associated with panic disorder, including depression, social phobia, generalized anxiety disorder, and posttraumatic stress disorder. In addition, they have no abuse or dependence liability and are less likely to negatively interact with alcohol compared to benzodiazepines. However, anxious patients, particularly those with panic disorder, may experience excessive activation, including insomnia, restlessness, jitteriness, agitation, and even exacerbation of panic associated with initiation of SSRIs and SNRIs and other antidepressants. As is true for the tricyclic antidepressants (TCAs) as well, SSRIs should be initiated at low doses (e.g., 12.5 mg/day of paroxetine controlled release; 25 mg/day of sertraline; 5–10 mg/day of escitalopram; 37.5 mg/day of venlafaxine extended release) in order to minimize increased activation, and then gradually titrated up to therapeutic doses. The SSRIs are associated with less weight gain and fewer anticholinergic effects, have a relatively benign cardiovascular profile, and are safer in overdose compared to the older antidepressants; in addition, they do not have the abuse liability in predisposed individuals associated with benzodiazepines. However, SSRI-associated side effects such as gastrointestinal distress and sexual dysfunction may be problematic for some treated patients, and the delay in time to therapeutic onset (typically at least 2–3 weeks) associated with antidepressant therapy may be problematic for patients requiring more acute anxiolysis.

The TCAs were, for a number of decades, the gold standard in pharmacotherapy for the treatment of panic disorder, but have been largely supplanted by the SSRIs and SNRIs because of their significant side effect burden over the longer term,[21] substantial toxicity in overdose, and lack of efficacy for some common comorbid disorders such as social phobia.[22] Because of its more potent serotonergic properties, some evidence suggests that clomipramine may be the most effective TCA for the treatment of panic disorder.[23] Selective serotonin reuptake inhibitors appear to be at least as efficacious as clomipramine in comparative trials but have a more favorable side effect profile.[24,25] Side effects are a common cause of treatment failure in TCA-treated patients with panic disorder.[26]

Monoamine oxidase inhibitors (MAOIs) are also effective for the treatment of panic disorder,[27] and although some clinicians believe them to be among the most com-

Figure 3. Pharmacotherapy Received by Panic Disorder Patients in the HARP Study (1989–2001)[a]



[a]Data from Bruce et al.[28]
Abbreviations: BZD = benzodiazepine, HARP = Harvard/Brown Anxiety Disorders Research Program, SSRIs = selective serotonin reuptake inhibitors.

prehensively effective agents for the treatment of panic and other mood and anxiety disorders, there are no definitive data addressing this issue. Despite their efficacy, the side effect profile of the MAOIs, including associated weight gain, orthostatic hypotension, and sexual dysfunction, along with the requirement of dietary monitoring and the risk of hypertensive crisis, has relegated their use to second or third tier, employed typically after safer and better-tolerated agents have proved ineffective.

BENZODIAZEPINES

Despite increasing emphasis on the use of antidepressants for the treatment of panic and other anxiety disorders, benzodiazepines are still widely used for these conditions. Although data from the Harvard/Brown Anxiety Disorders Research Program documented a small but steady rise in the number of patients getting SSRIs alone and in combination with benzodiazepines through the 1990s into the next decade, the most common type of treatment for patients with panic disorder actually remained benzodiazepine monotherapy (Figure 3).[28]

Compared to antidepressants, benzodiazepines have a rapid onset of action, favorable side effect profile, and the ability to be used on an "as needed" basis. However, regular use of benzodiazepines is associated with the development of physiologic dependence, necessitating that they be gradually tapered down when discontinued. Unlike antidepressants, benzodiazepines are not effective for the comorbid depression that frequently complicates the presentation of panic and other anxiety disorders. Although individuals predisposed to substance abuse may abuse benzodiazepines, they are very rarely misused in individuals without such a diathesis. Consistent with this assertion are results from a naturalistic study[29] examining patterns of benzodiazepine use in over 2000 Medicaid patients receiving these agents for a variety of reasons. The median dose of benzodiazepine remained constant over 2 years at 10 mg/day of diazepam milligram equivalents, and the incidence of escalation to a high dosage was only 1.6%, suggesting that long-term use of benzodiazepines does not frequently result in notable dose escalation.[29]

Benzodiazepines are often administered concurrently with antidepressants for the treatment of panic disorder. Although coadministration of a benzodiazepine at treatment initiation accelerates the response compared to antidepressant monotherapy[30] and may reduce early antidepressant-related stimulation, combined treatment beyond the first 4 to 6 weeks does not appear to be associated with better outcome by evaluation at 3 months compared to antidepressant monotherapy or patients receiving initial combined treatment followed by taper of the benzodiazepine.[31] For partial responders and nonresponders to antidepressant monotherapy, the addition of a benzodiazepine to treatment appears to be clinically useful, although there are few systematic data addressing this practice.

OTHER AGENTS

A number of anticonvulsants have demonstrated suggestive evidence of efficacy for panic disorder. In small studies, valproic acid,[32,33] although not carbamazepine,[34] was effective for panic disorder. Gabapentin was significantly effective for panic disorder of moderate severity in a placebo-controlled, double-blind study at doses of 600 to 3600 mg/day.[35] Novel anticonvulsants in development or currently available, including pregabalin, tiagabine, and levetiracetam, appear to have anxiolytic effects and may prove effective for the treatment of panic disorder,[36–38] although formal testing for this indication has not been reported to date. Although bupropion is generally considered ineffective for panic disorder on the basis of an early negative study,[39] clinical experience and more re-

cent work[40] suggest bupropion may have some antipanic efficacy as well.

Some reports suggest that buspirone may be useful as an adjunct to antidepressants and benzodiazepines for the treatment of panic disorder,[41] but it does not appear to be effective when used alone.[42] Similarly, although useful at times as augmentation, β-blockers (e.g., propranolol) do not appear to be useful as first-line pharmacotherapy for the treatment of panic disorder, although a small, double-blind, placebo-controlled trial suggested the efficacy of augmentation with the β-blocker pindolol (2.5 mg t.i.d.) for patients with panic disorder that is persistently symptomatic despite treatment with fluoxetine.[43]

LONG-TERM PHARMACOTHERAPY

Most naturalistic studies of panic disorder suggest that it is characterized by a chronic, relapsing course for many patients.[44,45] Remission rates over time with pharmacotherapy are generally in the range of 20% to 50%, with relapse rates of 25% to 85% after treatment discontinuation.[46, 47] In a study of 51 patients treated to remission with imipramine and then randomized in double-blind fashion to withdrawal of treatment after 6 months versus 12 to 30 months, there was no difference in relapse rates following discontinuation (approximately 37% in both groups). This finding suggests that the critical determinant of persistent benefit following treatment discontinuation may be robustness of improvement before treatment is discontinued rather than duration of treatment.[48]

Although acute treatment and longer term treatment are clearly effective for panic disorder, 30% to 80% of patients continue to experience panic attacks, anticipatory anxiety, and/or avoidance behavior up to 6 years after initiating treatment.[49, 50] Simon and colleagues[51] reported results from a naturalistic study demonstrating that nearly half of patients with panic disorder achieving remission with a variety of pharmacotherapies relapsed within a 24-month follow-up period. Controlled studies examining long-term treatment of panic disorder with SSRIs report rates of relapse of 3% to 13% for patients maintained on treatment for up to 70 weeks.[52–54] However, the relative brevity of study duration and examination of a rarefied clinical trial population limit the applicability of data from these studies. Additional study is necessary to establish the optimal duration of treatment for panic disorder, examine the relative benefit of strategies to optimize response over the maintenance period, and identify patients who may be candidates for successful and sustained discontinuation of therapy.

CONCLUSIONS

A variety of pharmacologic options exist for the treatment of panic disorder. Although antidepressants and benzodiazepines remain the current mainstay of pharmacotherapy for panic disorder, other novel agents and strategies are becoming available and may add effective alternatives to the therapeutic armamentarium. Maximizing the degree of improvement prior to initiation of treatment discontinuation appears to be a critical determinant in preventing relapse. The relative benefit of different options for the treatment of patients remaining symptomatic despite initial therapy is an issue of critical clinical importance, and further systematic evaluation of this area is warranted.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Carbatrol, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), diazepam (Valium and others), escitalopram (Lexapro), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), levetiracetam (Keppra), paroxetine (Paxil and others), pindolol (Visken and others), pregabalin (Lyrica), propranolol (Inderal, Innopran, and others), sertraline (Zoloft), tiagabine (Gabitril), valproic acid (Depakene and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, buspirone, carbamazepine, citalopram, clomipramine, diazepam, escitalopram, gabapentin, imipramine, pindolol, propranolol, valproic acid, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of panic disorder; and levetiracetam, pregabalin, and tiagabine are not approved for the treatment of anxiety.

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