

# Long-Term Management of Panic Disorder

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Panic disorder is a chronic, disabling condition that is often associated with a need for long-term clinical treatment. While a variety of pharmacotherapy options, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and benzodiazepines, are effective in reducing symptoms in the acute phase, a significant number of patients do not fully respond to initial treatment, and a large majority of patients experience relapse after medication discontinuation. Optimal long-term treatment of panic disorder involves attention to adequate medication dosing and adequate duration of treatment to achieve maximum improvement before discontinuing. Recent reports suggest the efficacy of adjunctive pharmacotherapies and combining pharmacotherapy with behavioral therapy to improve treatment response. Further research is necessary to determine the long-term effectiveness of these multifaceted treatment strategies among patients suffering from refractory panic disorder.

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**P**anic disorder is a chronic, distressing, and disabling condition that often appears to require ongoing treatment in clinical practice. Though a variety of pharmacologic and cognitive behavioral treatments appear to be effective for the acute treatment of panic disorder, a significant number of patients do not fully respond to initial treatment, and others relapse when treatment is discontinued. For instance, among studies examining the long-term efficacy of pharmacotherapy for panic disorder, Katschnig et al.<sup>1</sup> performed a 4-year follow-up investigation of 423 patients enrolled in the Cross-National Collaborative Studies for panic disorder. Thirty-one percent of these patients achieved continuous remission during the 4-year follow-up period, 50% continued to have mild to moderate symptoms or intermittent periods of remission, and 19% suffered from persistent, severe symptoms. A naturalistic, longitudinal study of patients in treatment for panic disorder at Massachusetts General Hospital<sup>2</sup> similarly found that up to 40% of over 250 patients achieved at least a 2-month period of remission, though close to two thirds of these experienced a relapse during the period of observation. Keller et al.<sup>3</sup> also performed a naturalistic, longitudinal study investigating remission and relapse rates in pa-

tients suffering from panic disorder and panic disorder with agoraphobia. At up to 91 weeks of assessment, patients with panic disorder with agoraphobia had only a 20% probability of experiencing even a 2-month period free of symptoms (Figure 1), a substantially lower rate than the same researchers observed using similar methodology in studies of depression<sup>4</sup> and bulimia.<sup>5</sup>

## PHARMACOTHERAPY OPTIONS FOR PANIC DISORDER

Tricyclic antidepressants (TCAs) such as imipramine and clomipramine were regularly used for the treatment of panic disorder through the early 1990s. Since then, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline have been more commonly used. However, despite a relatively favorable adverse-event profile, many patients are unable to tolerate the side effects associated with SSRI monotherapy, including initial anxiogenesis, as well as the delayed onset of therapeutic effects. Thus, despite current treatment guidelines recommending the use of SSRIs for panic disorder,<sup>6</sup> benzodiazepines remain commonly prescribed for this indication.<sup>7,8</sup> Interestingly, data from a longitudinal study in naturalistic treatment settings (Harvard/Brown Anxiety Research Project)<sup>7,8</sup> suggest that patients taking benzodiazepines have a comparable clinical course to those taking SSRIs.

Benzodiazepines are commonly coprescribed with antidepressants,<sup>7</sup> perhaps in the hope of reducing initial anxiogenesis to the antidepressant and improving response (Figure 2). However, though data on combined treatment do not suggest evidence of greater ultimate outcome compared with monotherapy,<sup>7,8</sup> initiation of combined therapy is associated with acceleration of response compared with antidepressant treatment alone.<sup>8,9</sup>

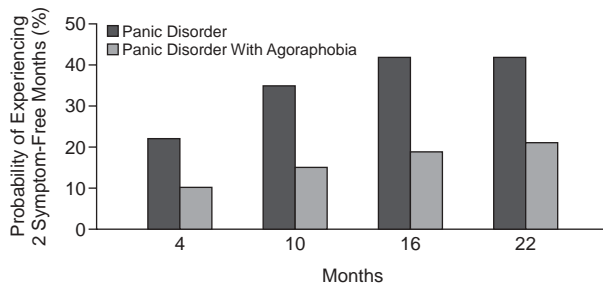
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Figure 1. Probability of Recovery From Panic Disorder and Panic Disorder With Agoraphobia<sup>a</sup>



<sup>a</sup>Data from Keller et al.<sup>3</sup>

## FOLLOW-UP STUDIES OF PHARMACOTHERAPY TRIALS

### TCAs

Noyes et al.<sup>10</sup> conducted a naturalistic 2.5-year follow-up study of 107 patients taking a TCA for panic disorder. Fifty patients (47%) remained on TCA treatment at the follow-up interview. Most patients (63%) showed improvement while taking the medication; of these, 32% had a persistent positive response and 12% remitted completely. Other patients who improved with treatment showed the recurrent pattern of improvement and relapse that is typical of patients with panic disorder.

The side effect burden of TCAs is a major hindrance to treatment in many patients. In the Noyes et al.<sup>10</sup> study, patients repeatedly discontinued their medication and were unable to optimize their dosage due to side effects, including overstimulation and weight gain. Eighteen patients (17%) reported that the side effects of the TCA were intolerable, and 37 patients reported "side effects" as the reason for discontinuing medication. Although relapse after discontinuation is a common issue of concern raised in regard to benzodiazepine therapy, it is worth noting that the majority of patients in this study of TCAs relapsed after discontinuing their medication as well.

Nagy et al.<sup>11</sup> conducted a follow-up study of 28 patients treated with a combination of imipramine and a 4-month course of cognitive-behavioral therapy (CBT) for panic disorder. At a mean follow-up of 2.8 years, 17 patients (61%) were in remission. This relatively high remission rate may be due in part to the initial use of behavior therapy with the medication. Half of the patients were still taking medication at follow-up, although most were on a relatively low dose (mean = 74 mg/day), which was significantly less than at the end of the acute treatment period. It is possible that some patients who remained symptomatic might have benefited from higher doses of imipramine or ongoing CBT, although these remain untested hypotheses. Twelve patients included in this study experienced increased anxiety when the medication was tapered. However, medication discontinuation was unblinded, so some of the discontinuation

effects may have been due to anticipatory anxiety by the patients.

### SSRIs

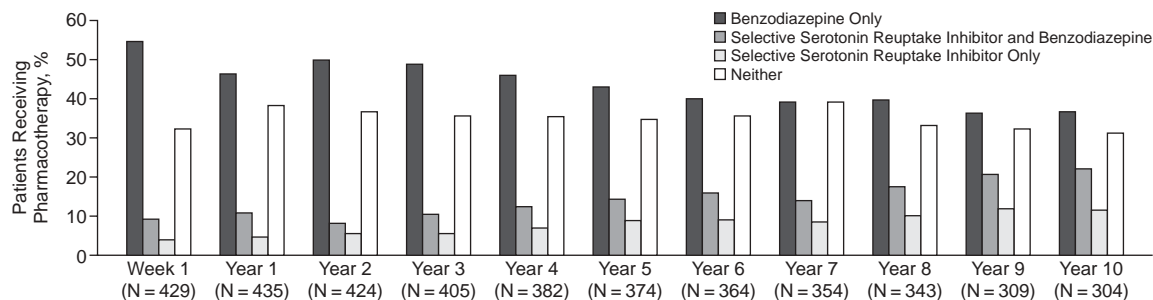
There are now data on longer-term use of SSRIs for panic disorder. Burnham et al.<sup>12</sup> conducted a long-term double-blind efficacy trial of paroxetine in the prevention of panic disorder relapse. Patients who had completed a 3-month maintenance phase taking paroxetine without relapse were randomly assigned to either continue treatment with paroxetine or switch to placebo. At the end of 3 more months, 30% of the patients taking placebo relapsed, compared with 5% of those remaining on paroxetine.

Rapaport et al.<sup>13</sup> performed a longitudinal follow-up study of patients who participated in acute treatment trials of sertraline. Three hundred ninety-eight patients who completed one of three 10-week acute trials were given open-label sertraline for a year. Of these, 214 completed the year, and 207 of the completers responded. One hundred eighty-three of the completers who responded were randomly assigned to a further 28 weeks of treatment with either sertraline or placebo. Ongoing therapy maintained benefit for the patients who continued treatment with sertraline, whereas those switched to placebo were more likely to have exacerbation of panic symptoms and discontinue medication due to insufficient clinical response.

### Benzodiazepines

Nagy et al.<sup>14</sup> performed a follow-up study (mean = 2.5 years) of 60 patients with panic disorder receiving an initial 4-month course of alprazolam and behavioral group treatment. At follow-up, 18 patients (33%) were in remission, 30% of patients had discontinued treatment with alprazolam, and 60% were taking a reduced dose of the medication. The average daily dose of alprazolam taken by patients who were still prescribed the medication at follow-up had dropped from 3.1 to 1.8 mg/day, even though 60% of patients remained symptomatic. These findings are reflective of the tendency to reduce benzodiazepine dosage to allay concern about abuse or dependence even in the face of persistent symptomatology, a practice that often results in suboptimal treatment and incomplete response.

A 1-year follow-up study<sup>15</sup> examined 50 patients who had been enrolled in an acute 4-month trial of clonazepam.<sup>16</sup> Nine of these patients were treatment naïve, and 41 had a history of prior poor response or difficulty tolerating other available treatments. Of the patients enrolled in the acute trial, 78% showed significant improvement with treatment. Thirty-one of these patients were available for follow-up a mean of 54 weeks later. Of these patients, 20 remained on clonazepam, and 18 retained their positive response. The average Clinical Global Impressions-Severity of Illness scale scores declined from 4.6 to 1.6, representing an improvement from the moderate to severe range of severity into the borderline ill range. The patients who discontinued

Figure 2. Pharmacotherapy Received by Patients With Panic Disorder in the Harvard/Brown Anxiety Research Project, 1989–2001<sup>a</sup>

<sup>a</sup>Data from Bruce et al.<sup>7</sup>

clonazepam did so primarily because of a lack of efficacy and side effects such as irritability, sedation, and depression.

Pollack et al.<sup>17</sup> also studied the long-term outcome of 59 patients who were enrolled in a 6-week randomized trial of alprazolam, clonazepam, or placebo.<sup>18</sup> At an average follow-up of 1.5 years, 57% of patients who were initially treated with medication were panic free. Seventy-eight percent of participants were on medication at follow-up, although the average daily dose of alprazolam had decreased from 3.2 to 1.9 mg and the average daily dose of clonazepam decreased from 2.3 mg to 2.0 mg. A greater duration of panic disorder, agoraphobic avoidance, and comorbid social phobia were all associated with poor outcome at follow-up.

Worthington et al.<sup>19</sup> reported on a 2-year naturalistic, longitudinal study of 204 patients with panic disorder. The nature of the study allowed for a participant population that closely resembled the patient pool found in most clinical practices, with common comorbidities such as depression and other anxiety disorders. Forty-six percent of the patients studied were taking clonazepam alone (N = 57) or in combination with an antidepressant (N = 36). The patients' average severity of illness decreased over time in both the group taking clonazepam alone and the group taking clonazepam in combination with an antidepressant. At the 2-year follow-up, 51.5% of patients who were taking clonazepam alone and 63.6% of the patients taking clonazepam in combination with an antidepressant were in remission. Mean doses of clonazepam ranged from 1 to 2 mg/day, with 50% of patients decreasing and 33% increasing their doses during the 2-year period, and no significant difference between baseline dose and dose at year 2 evaluation. The maintenance of significant improvement over time without escalation of dose suggests there was not significant development of therapeutic tolerance to the benzodiazepine.

#### MINIMIZING CHANCES OF RELAPSE AFTER DISCONTINUATION OF TREATMENT

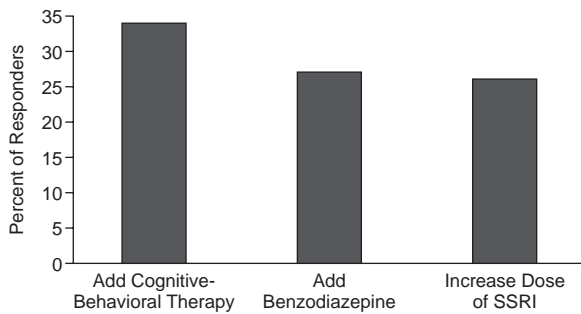
In a recent study examining imipramine therapy for panic disorder with agoraphobia, Mavissakalian and Perel<sup>20</sup> assessed 51 patients who were in remission at the end of 6

months of treatment. Patients were randomized in double-blind fashion to discontinue treatment either after 6 months or after a range of 12 to 30 months. Contrary to prior reports by these authors,<sup>21</sup> there was no decrease in relapse rates (approximately 37% in both groups) following treatment discontinuation associated with longer- versus shorter-term treatment of remitted patients. These results suggest that while ongoing treatment appears to exert a prophylactic effect, the critical issue regarding maintenance of benefit following treatment discontinuation may not be the duration of treatment as much as the level of symptom severity before treatment is discontinued. Such findings underscore the importance of maximizing improvement or achieving remission status before considering treatment discontinuation in order to increase the likelihood of maintaining improvement if treatment discontinuation is elected.

#### MAXIMIZING CHANCES OF REMISSION IN LONG-TERM TREATMENT

Though many patients may experience a reduction in panic disorder symptoms during acute treatment, optimal outcomes seem to be reliant on achieving remission before treatment is tapered or discontinued. There is a difference of opinion on the best way to advance short-term improvement into the long term. Scott et al.<sup>22</sup> surveyed psychiatrists (N = 483) who were members of the American Society for Clinical Psychopharmacology or the Anxiety Disorders Association of America on "next-step" strategies for partial responders to antipanic pharmacotherapy. The physicians were presented with a case of a patient with panic disorder who received 6 weeks of treatment with an SSRI and showed improvement but was still symptomatic. Participants were then provided with a list of 11 "next-step" treatment options among which to choose. The 3 most common interventions chosen were to add CBT (34%), add a benzodiazepine to the SSRI (27%), or increase the dose of the SSRI (26%) (Figure 3). However, as of yet, there are few systematic data addressing the relative benefits of these or other interventions for the treatment of partial responders or nonresponders to initial therapy.

Figure 3. Treatment Choice for SSRI-Refractory Panic Disorder: Results From a Survey of 483 Psychiatrists<sup>a</sup>



<sup>a</sup>Data from Scott et al.<sup>22</sup>

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

### Combination Treatment With SSRIs and Benzodiazepines

Goddard et al.<sup>9</sup> performed a study of the benefits to patients of initiating treatment for panic disorder with a combination of sertraline and clonazepam compared with the SSRI alone. Twenty-five study participants were given sertraline and clonazepam (with the benzodiazepine tapered off after a few weeks) and 22 participants were given sertraline and placebo. The patients taking sertraline and clonazepam in combination showed greater improvement in weeks 1 and 3 of the study than did the group taking sertraline alone. However, by about week 5, when clonazepam taper began, both groups were doing equally well. Although both groups improved during treatment, there was no additional benefit accrued at week 12 (study endpoint) from having initially received the combination treatment.

Pollack and colleagues<sup>8</sup> performed a similar study to the Goddard et al. trial,<sup>9</sup> with the addition of a group of patients who remained on combined treatment over the duration of the trial. Sixty patients, all of whom were being treated with the SSRI paroxetine, were randomly assigned to 1 of 3 groups: those who received paroxetine and clonazepam in combination, those who received paroxetine and clonazepam in combination for 5 weeks and were then tapered off the clonazepam, and those who received paroxetine and placebo. Similar to the study by Goddard et al.,<sup>9</sup> the groups given clonazepam with the SSRI showed faster improvement initially, but there was no additional benefit from taking clonazepam in combination with paroxetine past the first 5 or 6 weeks. By the 12th week of the study all 3 groups were showing similar levels of improvement. This study suggests that initiating treatment with benzodiazepines in combination with SSRIs provides faster symptom relief than SSRIs alone, but there is no benefit for most patients in maintaining the benzodiazepine past the first month or two of treatment, and it can often, at that point, be gradually tapered off. The question remains, however, as to whether adding a benzodiazepine for partial responders or nonresponders to initial antidepressant treatment is

helpful. Clinical experience suggests the potential efficacy of this intervention, but there are no systematic data to date directly addressing this issue.

### Behavioral Treatments

There is increasing awareness of the efficacy of CBT for the treatment of panic and other anxiety disorders. Administration of CBT offers the hope that once patients learn its principles and application, they will be able to serve as their own therapists in the event that symptoms emerge, without the need for ongoing treatment or additional interventions. However, some long-term data suggest behavior therapy may offer a pattern of therapeutic benefits similar to those found with pharmacotherapy—with some patients fully remitted and many others improved but not necessarily fully and persistently symptom free.

Brown and Barlow<sup>23</sup> reported a study of the long-term effectiveness of a standard course of behavior therapy for patients with panic disorder. They followed up with patients up to 2 years after a standard acute course of CBT. Cross-sectional assessments of outcome showed that 75% of patients were panic free at follow-up and 57% were in high end-state functioning. However, only 1 in 5 of the patients experienced complete and persistent relief of symptoms requiring no additional behavioral or pharmacologic intervention over the 2-year follow-up period.

Although behavioral therapy is widely acknowledged as effective in the treatment of panic disorder, its application is limited by the lack of availability of trained therapists able to administer empirically validated forms of CBT. As a result, relatively few individuals with anxiety disorders receive CBT.<sup>24</sup>

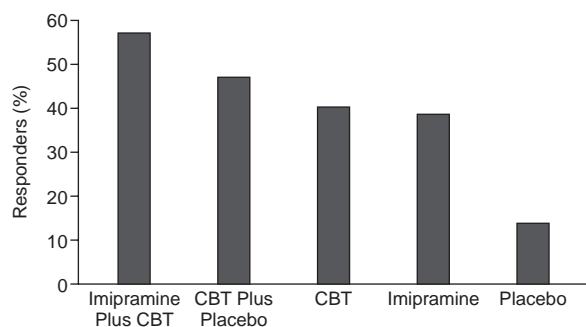
### COMBINATION PHARMACOTHERAPY AND BEHAVIOR THERAPY

Combining pharmacotherapy and behavior therapy is emerging as a treatment strategy for patients who are either partially responsive or nonresponsive to initial treatment. Although there is evidence that adding behavioral therapy to pharmacotherapy improves treatment outcome,<sup>25</sup> data on adding pharmacotherapy to behavior therapy are less clear.

Barlow et al.<sup>26</sup> studied the relative effectiveness of pharmacotherapy with imipramine, CBT, and the combination of the 2 in the treatment of panic disorder. Patients were randomly assigned to one of 5 groups: imipramine only, CBT only, placebo only, a combination of the 2 active treatments, or a combination of CBT and placebo. Patients were treated for 3 months. Those who responded to treatment were given maintenance treatment of the same type for 6 months. At the end of the 6-month maintenance phase, the response rate for the group given a combination of imipramine and CBT was somewhat better than the response rates for the groups given imipramine alone, CBT alone, or either of the groups given placebo (Figure 4), although it is not clear that the



**Figure 4. Treatment Response Rate With Cognitive-Behavioral Therapy (CBT) Plus Imipramine Versus Monotherapy<sup>a</sup>**



<sup>a</sup>Data from Barlow et al.<sup>26</sup>

magnitude of the effect warrants the routine application of formal combined treatment for all patients. In practice, combined treatment is often difficult because most psychiatrists and primary care doctors are not able to administer CBT, necessitating that patients see 2 separate practitioners and resulting in additional financial and logistical burdens on the patient and practitioners. Identification of individuals requiring initial combined treatment and those who might respond to monotherapy with either CBT or pharmacotherapy or their sequential application is an issue of clinical import. In addition, the development of a system for integrating an effective and time-efficient CBT into a standard psychiatric or primary care visit for patients with panic disorder remains an important unmet need.

## CONCLUSION

Available pharmacotherapies as well as CBT have clear efficacy for the acute and long-term treatment of panic disorder, but many patients remain symptomatic despite their routine application. Treatments combining different pharmacotherapies and pharmacotherapies with behavior therapy appear to be promising strategies for patients who are partial responders or nonresponders to initial interventions, but systematic data addressing this issue are critically needed. Optimal use of available agents and psychosocial therapies and their combination, as well as the development of novel strategies, are necessary to improve outcomes for patients suffering with this distressing and often disabling disorder.

*Drug names:* alprazolam (Xanax and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), imipramine (Surmontil, Tofranil, and others), paroxetine (Paxil and others), sertraline (Zoloft).

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, clomipramine and imipramine are not approved by the U.S. Food and Drug Administration for the treatment of panic disorder.

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