

# Panic Disorder as a Chronic Illness

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Panic disorder is a chronic illness that waxes and wanes, and the prognosis is worse with comorbid agoraphobia, depression, or personality disorder. Both medication and cognitive-behavioral therapy have been found helpful in acute treatment trials of panic disorder. However, recent studies suggest that therapeutic gains are lost in many instances when treatment is stopped after short-term medication or cognitive-behavioral therapy. Thus, maintenance treatment appears necessary for many panic patients. Patients appear relatively stable during medication maintenance, but studies of maintenance psychosocial treatment for panic disorder have not yet been reported. Whether combined medication and psychosocial treatment lead to more durable effects after treatment discontinuation than are seen with individual treatments also remains to be determined. *(J Clin Psychiatry 1997;58[suppl 13]:5-8)*

David Barlow's<sup>1</sup> model posits a biological vulnerability that renders people susceptible to panic attacks and panic disorder. Some kind of false alarm goes off that leads to the first panic attack. The victim then begins to learn those cues, so that anything that begins to suggest that another panic attack is coming renders great anxiety.<sup>2</sup> Those with the greatest psychological vulnerability to worrying about and being terrified by further attacks are also most prone to develop agoraphobia. This model suggests that both psychopharmacologic and cognitive-behavioral interactions should be helpful in treating panic disorder and agoraphobia.

## NATURAL COURSE OF PANIC DISORDER

Older follow-up studies<sup>3</sup> conducted prior to the establishment of DSM-III criteria found that 40% to 60% of the patients originally diagnosed with anxiety neurosis showed either no change or slight improvement. More recent follow-up studies of up to 12 years' duration found that 15% to 48% of the patients showed no change or only slight improvement.<sup>4</sup> These are the earliest evidence of chronicity.

The ongoing Harvard/Brown Anxiety Disorders Research Program (HARP) study<sup>5</sup> is providing useful infor-

mation on the natural course of panic disorder. Remission was strictly defined as no panic attacks or phobic avoidance for at least 8 consecutive weeks. A relapse was considered to have occurred if the patient experienced one panic attack or a return of significant avoidance for 1 week. With those criteria, 39% of patients with uncomplicated panic disorder showed full remission at 1 year and 49% cumulatively at 18 months. Patients with panic disorder and agoraphobia showed lower remission rates (17% at 1 year, 20% at 18 months) and high relapse rates, compared to patients without comorbid agoraphobia. These findings suggest that panic disorder has a more chronic course and longer episodes when agoraphobia is present. This is of particular concern for clinicians, since up to 50% of people with panic disorder develop agoraphobia. Using more stringent relapse criteria, the investigators also found high rates of chronicity and relapse (Keller MB, written communication, 1996).

Roy-Byrne and Cowley<sup>6</sup> have summarized naturalistic studies of panic disorder and found the literature to have these limitations:

- Lack of control or standardization of treatment over follow-up
- Use of clinical, rather than epidemiologic, samples
- Samples that differ in comorbidity
- Subject attrition that limits the ability of the remaining sample to be representative
- Lack of uniformity across studies on dependent measures and in outcome criteria

Given these limitations, suggested negative determinants of outcome include the presence of agoraphobia, depressive symptoms, generalized anxiety, and maladaptive personality traits. Any of these features complicating panic disorder leads to a less favorable outcome.

Conclusions of the long-term follow-up studies as summarized by Roy-Byrne and Cowley<sup>6</sup> are that while most

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patients improve, few are cured. The majority of patients seem to require long-term treatment and have chronic, residual symptoms. Panic attacks appear to resolve more readily than phobic avoidance or generalized anxiety. Finally, there is a need to design treatments for subgroups with poorer outcomes.

Major depression occurs frequently in patients with panic disorder (50%–65% according to DSM-IV), including 20% to 30% of treated patients during follow-up. Risk factors for major depression are a history of depression or poor treatment response of the panic disorder.

There has been controversy about suicidal behaviors in panic disorder. One position (articulated by Weissman and colleagues<sup>7</sup>) is that suicidal behaviors occur more frequently than expected and are not related to comorbid depression; they are somehow inherent in the panic disorder itself.

Another position (HARP study and others<sup>8</sup>) is that suicidal behaviors in patients with panic disorder appear to be related to comorbid depression. Other contributing factors to suicidal behavior in patients with panic disorder include substance abuse, eating disorders, posttraumatic stress disorder, personality disorders, and early onset anxiety or depressive disorder.

Overall, these studies suggest that panic disorder is a chronic illness that waxes and wanes and, at times, leads to suicidal behavior. The prognosis is worse with the presence of agoraphobia, depression, or personality disorders. The prognosis for untreated panic disorder is not known.

### **LONG-TERM COURSE AFTER ACUTE MEDICATION TREATMENT, BASED ON FOLLOW-UP STUDIES**

Acute treatment with medication includes tricyclics (the first documented efficacious treatments), high-potency benzodiazepines, monoamine oxidase inhibitors (MAOIs), and serotonin selective reuptake inhibitors (SSRIs). In single-medication trials, there is approximately a 50% to 60% acute response rate. When nonresponders are treated with second and third medications, the response rates rise.

Acute treatment, however, does not usually lead to lasting remission. In a 1- to 4-year follow-up (mean interval = 2.5 years) after an acute imipramine trial,<sup>4</sup> 80% of the people were symptomatic, 50% reported panic attacks during the 3 months before follow-up, and 40% reported phobic avoidance. Follow-up of patients 3 years after an acute diazepam-alprazolam-placebo study<sup>9</sup> showed 41% of patients were well or markedly improved, while 60% showed continuing symptoms. In a 2- to 6-year follow-up of the Upjohn Cross-National study comparing alprazolam and placebo or alprazolam, imipramine, and placebo for 8 weeks, 19% of patients had a severe, chronic course, 31% recovered, and 50% had recurrent or mild, chronic

symptoms.<sup>10</sup> A methodological limitation of the studies is that there is no control over or standardization of treatment for the long term.

There is also some evidence that panic disorder patients, even when they are successfully treated, have some continued biological abnormalities. Coplan and others<sup>11</sup> showed that patients with panic disorder had a blunted growth hormone response to a clonidine challenge that signifies a noradrenergic disturbance, and this did not normalize even though patients improved while taking an SSRI.

Findings of studies of long-term course after acute medication treatment indicate that a majority of patients continue to show some symptoms after treatment, although only a minority of patients continue with severe symptoms. Therefore, maintenance treatment may be indicated for many panic patients.

### **Maintenance Medication Effects**

Mavissakalian and Perel<sup>12</sup> have done the most informative studies of medication maintenance treatment in panic disorder. Reduced maintenance-dose imipramine for 12 months following a 6-month acute treatment lowered the relapse rate during that time. In another study, longer imipramine treatment lowered the subsequent relapse rate after medication was stopped.<sup>13</sup>

A naturalistic follow-up<sup>14</sup> of patients taking imipramine for 1 to 4 years showed that side effects caused 35% of the patients to end treatment and that most of these patients went on to relapse. These patients might have done better with the SSRIs due to the greater tolerability of these agents. Response to alprazolam also appeared stable over at least 6 months of maintenance treatment.<sup>15,16</sup>

Medication maintenance data show that:

- Patients are relatively stable during medication maintenance
- Increasing side effects or medication tolerance is not seen, with the exception of weight gain, with imipramine<sup>14</sup>; however, side effects, such as weight gain, caused 35% to stop imipramine treatment in the naturalistic follow-up study cited above
- Six to 18 months of treatment appear useful in reducing relapse

Remaining questions about the long-term medication treatment<sup>4,9,14,17</sup> are listed below, followed by provisional answers:

- *What medication is most suitable?* The SSRIs may be preferable because of lower rates of side effects, although tricyclic antidepressants, high-potency benzodiazepines, and MAOIs have been shown to be efficacious
- *Are there patients who can stop medication without relapse?* Patients may be able to stop after an extended period of being panic free and overcoming avoidance
- *What is the optimal duration of treatment?* It appears that treatment of at least 6 to 12 months' duration after a

patient is panic free and has overcome avoidance is preferable

- *Does panic disorder improve if behavior therapy is added for agoraphobia?* Unfortunately, we do not know from the existing data
- *Residual agoraphobia predicts relapse, but is it a marker for worse illness or is it something that can be altered by treatment?* The data suggest that there will be better long-term stabilization if the residual agoraphobia is eliminated
- *Does tolerance develop to long-term treatment?* The available data suggest generally not, although some patients have occasional slips
- *What are the long-term adverse effects of antipanic drug treatment?* Sexual dysfunction with SSRIs and weight gain with tricyclics can be problematic, although both classes of drugs are generally well tolerated
- *How do medications, behavior therapy, and the combination compare in long-term benefits and risks?* We need research studies to answer these questions
- *What message should we give patients about long-term treatment?* Panic disorder, while treatable, often requires chronic treatment

As should be clear from the answers to the above questions, further research is needed on the long-term treatment of panic disorder.

#### **WHAT DO WE KNOW ABOUT LONG-TERM EFFECTS AFTER ACUTE PSYCHOSOCIAL TREATMENT?**

Panic control treatment, a cognitive-behavioral treatment for panic attacks, has a number of components including slow abdominal breathing, cognitive therapy, and interoceptive exposures (spinning patients, hyperventilating them, and getting them to be less afraid of aversive autonomic arousal). Existing psychosocial treatments have approximately a 60% response rate, and long-term studies show that deterioration does occur,<sup>18</sup> suggesting that some form of psychosocial maintenance therapy might be helpful.

In a 24-month follow-up<sup>18</sup> of patients after panic control therapy versus relaxation (cross-sectional look at one point in time), 81% in the exposure group were panic free at follow-up compared with 36% in the relaxation group. However, only 53% in the exposure group had high end-state functioning (free of panic and phobic avoidance).

The response rates over a longitudinal course are less encouraging. In another sample from Barlow's group,<sup>19</sup> 48% had high end-state functioning at 24 months; 27% had high end-state functioning at 3 and 24 months; and 21% had high end-state functioning and no panic attacks at 3 and 24 months. A study of a single point in time examined cross-sectionally showed results similar to those previously published.

Conclusions from the follow-up of acute psychosocial treatment show that with longitudinal as well as cross-sectional evaluation, residual, recurrent symptoms are often evident. These data suggest that maintenance treatment for psychotherapy is necessary as well.

#### **MAINTENANCE PSYCHOSOCIAL TREATMENT EFFECTS**

The effects of maintenance psychosocial treatment in panic disorder are unknown; there are no published data.

#### **COMBINING AND COMPARING MEDICATION AND PSYCHOSOCIAL TREATMENT**

How do medications and psychosocial treatment compare for panic disorder? Findings to date appear to vary depending on the site of the study.

Work from Iowa<sup>20</sup> (a site of the psychopharmacologic expertise) showed a 90% response rate for fluvoxamine-treated patients versus a 50% response rate for those receiving cognitive therapy only. In contrast, at Oxford<sup>21</sup> (a site expert in psychotherapy), cognitive therapy resulted in a better response rate than imipramine. Given results such as these, collaborative studies between expert psychotherapists and psychopharmacologists are needed to generate findings with maximum credibility and ability for generalization.

Such a study in panic disorder is the four-center trial by Barlow, Gorman, Shear, and Woods comparing panic-control therapy, imipramine, imipramine plus therapy, placebo plus therapy, and placebo alone. This study is focused on acute treatment. We look forward to receiving the data when they are available. The long-term course after combined treatment also needs more study. Cognitive therapy may help the durability of treatment gains after treatment discontinuation.<sup>22</sup>

In summary, we can discern the following about the chronicity and long-term treatment of panic disorder:

- Panic disorder is often chronic, but responds well to both acute and maintenance drug and psychosocial treatments
- Residual agoraphobic avoidance may require additional treatment, because it does not always remit on its own
- Agoraphobic avoidance may be a significant predictor of long-term poor outcome
- Further research is needed on the long-term treatment of panic disorder to determine which patients require maintenance therapy
- Acute combined treatment looks superior to the individual modalities in terms of percentage of acute responses. However, many patients seem to do well with medication or panic control therapy alone. If so, then some patients should probably not get combined treat-

ment at the outset, unless its results prove to be much more lasting following treatment discontinuation. Being able to discern the most appropriate treatment for each patient at the outset (patient-treatment matching) is going to require substantial further research.

*Drug names:* alprazolam (Xanax), clonidine (Catapres), diazepam (Valium and others), fluvoxamine (Luvox), imipramine (Tofranil and others).

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