Long-Term Course and Outcome of Panic Disorder

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The longitudinal course of panic disorder is an issue of critical clinical and research importance. For many patients, panic disorder may be a manifestation of an underlying, lifelong predisposition to anxiety with a chronic course, often requiring ongoing maintenance therapy. In this paper, we review some of the pertinent follow-up studies of patients with panic disorder treated with antidepressants, high-potency benzodiazepines, and cognitive behavior therapy, as well as data from longitudinal studies.
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Examining the longitudinal course and treatment outcomes of panic disorder is critically important to the clinician and patient for understanding the likely acute and long-term response to treatment. Information about the course of illness fosters assessment of the differential response of patient subtypes to therapeutic interventions, facilitates assignment of treatment interventions by patient subtype, and increases the clinician's ability to determine a patient's potential for recovery or relapse during and after treatment.

FOLLOW-UP STUDIES OF TREATMENT OF PANIC DISORDER

Studies examining the long-term outcome of patients treated for panic disorder suggest that, although most patients improve after treatment is started, many remain symptomatic. In a recent review of studies of the long-term outcome of panic disorder, Roy-Byrne and Cowley[1] note that the efficacy of different interventions for panic disorder depends on the outcome being assessed (Table 1). While a substantial number of patients become panic free with treatment, response rates decline when other outcome domains, including phobic anxiety and avoidance, generalized anxiety, functional impairment, and global levels of severity, are considered. A consensus conference on assessment of outcome for panic disorder research underlined the importance of considering multiple outcome domains in assessing response to treatment.[2]

Table 1. Long-Term Outcome of Panic Disorder*

Outcome	Rate (%)	Range (%)
Panic-free	54	30–83
Phobic avoidance remission	31	18–64
Development of depression	29	12–60
Absence of functional impairment	50	33–61

*Adapted from Roy-Byrne and Cowley.[1]

Follow-up studies of patients with panic disorder treated with antidepressants, high-potency benzodiazepines, and cognitive behavior therapies are consistent with the notion that panic disorder is a chronic condition. For example, Noyes et al.[3] followed up a group of patients who started treatment with tricyclic antidepressants. Two thirds of the patients discontinued the initial antidepressant treatment, half because of side effects. Although three quarters of the patients experienced moderate levels of improvement, only 14% were free of symptoms. Furthermore, more than half of patients who experienced at least moderate improvement during treatment and attempted to discontinue the tricyclic antidepressant relapsed, most within 2 months after discontinuation.

Follow-up studies of patients entering clinical trials of high-potency benzodiazepines report similar findings. In a 1.5-year follow-up of patients with panic disorder entering a placebo-controlled trial of alprazolam and clonazepam, we[4] found that 78% of the patients remained on medication during the follow-up period. Doses of benzodiazepines generally were decreased or remained the same, and 57% of patients were panic free at follow-up. In a 2.5-year follow-up study of patients starting treatment with alprazolam and behavior therapy,[5] 43% of patients treated with alprazolam were in remission and doses were decreased during the follow-up period, allaying concerns about potential dose escalation. However, as in our study,[4]

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benzodiazepine doses were often kept the same or decreased even though many patients were still at least somewhat symptomatic. Whether those who remained symptomatic may have benefited from an increased dose of the high-potency benzodiazepine or continued dosing at acute levels remains unknown, but it is a question of considerable clinical importance.

In a follow-up study of patients 2 to 6 years after participating in the Cross-National Collaborative Panic Study and receiving initial treatment with imipramine or alprazolam,[6] 31% of patients had recovered over the follow-up period. Fifty percent had an intermediate course of illness characterized by mild or recurrent symptoms, and 19% had a severe chronic course.

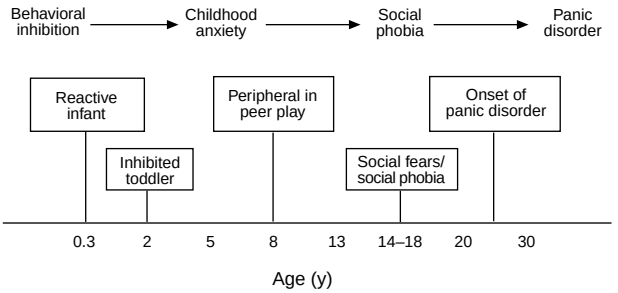
A recent follow-up study of patients treated with cognitive behavior therapy[7] also suggests that while patients improve over time with treatment, many remain symptomatic. The investigators reported that, at a 2-year cross-sectional follow-up, 75% of patients who underwent an acute course of panic control therapy were panic free, and 57% exhibited high end-state functioning. However, when criteria for outcome included high end-state functioning and no further need for treatment, the number of responders dropped to 48%. When outcome criteria were made even more stringent and included persistent high end-state functioning demonstrated at both Months 3 and 24 of follow-up as well as a panic-free state lasting a year and no further need for treatment, the number of patients who could truly be considered in remission and required no further intervention dropped to 21%. This well-conducted follow-up study underscores the need for a longitudinal perspective in assessing patients' response to treatment. Although effective pharmacologic and cognitive behavior interventions are available for treating panic disorder, few patients experience sustained remission without the need for additional or ongoing treatment.

NATURALISTIC LONGITUDINAL STUDIES OF PANIC DISORDER

Although few data are available from systematic, prospective studies of the course of panic disorder, emerging evidence supports the view of panic disorder as a chronic condition characterized by prolonged periods of illness interspersed with relatively brief periods of remission. Keller et al.[8] reported that, in patients with panic disorder treated naturalistically, a 39% probability of achieving remission over 1 year dropped to 17% if the panic disorder was complicated by agoraphobia. Approximately one third of patients relapsed within a year of remission.

In the Massachusetts General Hospital longitudinal study of panic disorder,[9] approximately 50% of patients achieved remission at some point during a 2-year follow-up period, with 21% experiencing sustained remission, 14% multiple episodes of relapse and remission, and 15% remission followed by sustained relapse. Fifty percent of patients were persistently symptomatic. It should be noted, however, that relatively few patients in these studies[8,9] received cognitive behavior interventions; hence, additional research is needed to determine whether these findings generalize to patients treated with cognitive behavior therapy.

Figure 1. Anxiety Diathesis*



*From Rosenbaum et al.[12], with permission.

PREDICTORS OF OUTCOME

Converging lines of evidence from animal studies, family and twin studies, and studies of temperament in children at risk for anxiety disorders suggest that panic and other anxiety disorders in adulthood may represent one manifestation of an underlying constitutional vulnerability or diathesis for anxiety. This diathesis model posits a familial, probably genetic, constitutional vulnerability to anxiety that is likely reactive to developmental and psychosocial experiences and predisposes the person to difficulties with anxiety manifested over time—behavioral inhibition and fearfulness in infants, social isolation and separation difficulties in toddlers and children, social phobia in adolescents, and panic disorder in adults[10–12] (Figure 1).

A number of patient characteristics, including the extent of phobic avoidance, comorbid anxiety and depressive disorders, personality dysfunction, and anxiety sensitivity, are predictors of poor outcome in patients treated for panic disorder.[1,13] We have posited that patients with a diathesis for anxiety as manifested by histories of behavioral inhibition or anxiety difficulties during childhood will develop many of the characteristics associated with poor long-term outcome of panic disorder.

Work to date confirms the association between a history of significant anxiety difficulties during childhood and more complicated course of illness during adulthood.[11,14–16] Patients with a constitutional vulnerability to anxiety may have a lower threshold to dysphoric arousal as well as a predisposition for dysfunctional cognitive and behavioral patterns of fear and avoidance that may pro-

mote ongoing difficulties with anxiety.[17] Results from a study[18] examining the longitudinal course of naturalistically treated patients with panic disorder suggested that a childhood history of anxiety difficulties is linked with increased agoraphobic avoidance and comorbidity, which appear to be critical determinants of chronicity in adulthood. One implication of this link is that early intervention in children at risk for anxiety disorders should target reduction of avoidance and prevention of comorbidity as ways of improving the long-term course of anxiety in adulthood.

DISCONTINUATION-RELATED DIFFICULTIES

Numerous studies have documented high rates of difficulty associated with discontinuation of antipanic treatment.[19] While acute difficulties with withdrawal or rebound are more common with patients treated with benzodiazepines, relapse is a significant problem across all treatments. Most patients taking high-potency benzodiazepines or antidepressants for panic disorder have recurrent symptoms, usually within a fairly short period of time, and many have to restart some form of pharmacotherapy or cognitive behavior therapy.[20]

Beyond the benefits accrued from a more conservative tapering of medication, no pharmacologic strategies, including the use of anticonvulsants, antidepressants, β-blockers, or buspirone, have demonstrated robust benefits in decreasing discontinuation-related distress or forestalling eventual relapse.[21] However, recently developed cognitive behavior therapy programs designed to reduce difficulties associated with benzodiazepine withdrawal have demonstrated effectiveness in patients with panic disorder and may decrease the likelihood of relapse in the future.[22,23]

CONCLUSION

Review of the longitudinal course and outcome of patients with panic disorder confirms the notion that, for many patients, panic disorder can be a chronic condition that requires ongoing maintenance therapy. The diathesis model for panic disorder, positing a constitutional predisposition for anxiety manifested early in childhood and variably expressed over time, provides a useful perspective for understanding the apparent chronicity of panic disorder. A variety of patient characteristics associated with early expression of anxiety difficulties, including degree of agoraphobia, anxiety sensitivity, comorbid anxiety, and affective and personality disorders, all confer poorer treatment response and increased chronicity in affected patients with panic disorder.

Although predicting the optimal duration of therapy for an individual patient is difficult, available evidence suggests that a substantial proportion of patients requires ongoing treatment for panic disorder. Thus, there is a critical need for effective, well-tolerated antipanic drugs, including the high-potency benzodiazepines and the new-generation antidepressants, as well as targeted cognitive behavior therapy, that optimize outcomes and enhance patient comfort and compliance over time. Future research should focus on developing optimal treatment algorithms for pharmacologic, cognitive behavior, and psychotherapies and their combinations; novel therapeutic strategies; and early interventions in persons at risk for anxiety disorders to decrease long-term morbidity.

Drug names: alprazolam (Xanax), buspirone (BuSpar), clonazepam (Klonopin), imipramine (Tofranil and others).

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Discussion

Panic Disorder, Agoraphobia, and Chronicity

Dr. Ballenger: The strongest predictor of panic disorder chronicity is agoraphobia. Does this mean that agoraphobia is more difficult to treat or that it is not being treated?

Dr. Barlow: Over the past 10 years, in our zeal to develop panic control treatment, we may have short-changed the treatment of agoraphobia.

Dr. Shear: Agoraphobia may not be just a disorder of panic attacks. It may be a multicomponent disorder, of which panic attacks are just one part.

Dr. Barlow: In terms of optimizing treatment for agoraphobia, reports in the literature are beginning to suggest that exposure therapy can be administered more intensely in a briefer period of time. We are now studying a new approach to exposure therapy that originated in Germany. This structured, individualized, highly intense program is implemented by a trained mental health worker over 3 to 10 days. Even for the most severe disorders, patients are given no information that would arouse anticipatory anxiety, although they do understand the type of commitment they must make to the program. They also must pay for the program up front. The mental health worker then takes the patient on a train, to the airport, across country, and so on. Patients are exposed over a brief period of time to whatever causes them the most trouble yet is important to them, such as taking a train to visit family members. Results have been far superior to graduated exposure therapy. Whether this approach will work in the United States is unclear.

Dr. Shear: What has been the long-term outcome of this program?

Dr. Barlow: They report that over 5 years, 75% of patients with panic disorder and agoraphobia remain cured. Once they treat the agoraphobia, the panic attacks go away.

Dr. Pollack: Although we all hope to cure every patient, it's important to remember that panic disorder is a chronic condition for many patients. We have had a hard time coming to terms with this. Panic disorder is difficult to completely cure. A 75% sustained remission rate without ongoing treatment is rarely possible using current approaches.

Dr. Jefferson: We are dealing with a syndrome. In most cases, we are not treating what I view as the intrinsic biological pathology. Interventions may work for awhile, but until we can treat the core cause, the disorder will not go away.

Dr. Marshall: We can look at this as whether the glass is half empty or half full. In our study, panic symptoms became mild or intermittent in more than 80% of patients. That's better than the treatment of almost any medical condition other than a few infections. We make most of our patients a lot better, but we cannot cure them with our current technology.

Dr. Pollack: One of the big questions is, What is making panic disorder chronic? You can get miracle cures by treating panic symptoms with medication. However, do you leave the patient vulnerable to the return of symptoms when treatment is discontinued? Even with nonpharmacologic treatments, you see fluctuations in and persistence of symptoms over time.

Dr. Barlow: Another issue is that we do not yet know what is the optimal maintenance treatment for panic disorder.