

# The Road to Recovery in Panic Disorder: Response, Remission, and Relapse

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A standard set of definitions and criteria for the terms commonly used in panic disorder research is required to aid clinicians in their management of patients with panic disorder. Furthermore, the use of a simple, psychometrically sound assessment procedure such as the Panic Disorder Severity Scale, which considers all of the essential domains of panic disorder, will provide clinicians with an appropriate instrument for diagnosing and monitoring patients. The use of this more comprehensive scale for monitoring patients should alert clinicians to the reemergence of associated symptoms of panic disorder and allow for the rapid modification of treatment. By responding quickly to the recurrence of symptoms, a full relapse may be prevented.  
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The history of the diagnosis and treatment of panic disorder began with the identification of the disorder in the 1960s.<sup>1</sup> It was the observation of the key symptom, the panic attack, that led to recognition of the disorder. Panic is defined as a specific type of anxiety, characterized by the abrupt onset and rapid crescendo peak of prominent autonomic symptoms, often seeming to come “out of the blue.” This discrete type of anxiety can be differentiated from more persistent worry about daily life events, which characterizes generalized anxiety disorder.

The diagnostic criteria for panic disorder have evolved from DSM-III, through DSM-III-R, to DSM-IV to encompass the component of persistent, intercurrent anxiety. Thus, according to DSM-IV, panic disorder is diagnosed when an individual experiences recurrent panic attacks along with fearful anticipation of panic or of frightening consequences or implications of these attacks. Often, anticipation of panic leads to agoraphobic symptoms. Frightened of the recurrence of panic, such patients do not want to be in places or situations where they believe they could be either physically or socially trapped, or alone and unable to get help. Thus, to describe the clinical syndrome of panic disorder, we must include panic attacks (both full

and “limited symptom” episodes), anticipatory anxiety about the possibility of having a panic attack, and phobic symptoms. Since anxiety and phobic symptoms frequently focus on feared bodily sensations, this type of fear should be considered. Panic disorder causes substantial functional impairment and contributes to high utilization of medical facilities in futile efforts to find dreaded physical causes for the symptoms. To characterize the status of panic disorder adequately, we must include a measure of functional impairment.

Since the identification of panic disorder, considerable work has gone into developing efficacious treatments for it, and there are now specific treatments, both pharmacologic and cognitive behavioral, with proven efficacy. Other psychotherapeutic approaches are currently being tested. It is important to keep in mind that a treatment is considered efficacious if it is shown reliably to reduce symptoms better than a no-treatment control group (i.e., difference is statistically significant), with the control usually a placebo for medication and wait-list for psychotherapy. It is important to remember that there is no particular amount of symptom improvement needed to declare efficacy. However, for the clinician and the patient, the extent of improvement is vitally important. This is one reason why clinicians sometimes consider research results not to be relevant to their practice. Often the question the patient asks is “Will I be cured?” For any medical treatment, the optimal outcome is “cure” or full recovery from illness, by which we mean long-term and essentially complete remission of symptoms, based upon amelioration of the specific etiologic factor(s) conferring vulnerability to the illness. Full recovery also implies there is no continued need for treatment. For example, recovery from

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diabetes would entail identifying and correcting the underlying pathology related to the etiology of insulin deficiency so as to eliminate the need for exogenous insulin.

Although advances have been made such that treatments with proven efficacy are now available, most psychiatric illness has a chronic course, with a minority of patients recovering fully following an episode of illness. The amount of data about etiology and pathogenesis of panic disorders is increasing. Other than psychoanalysis, which is based on an unproven set of assumptions, poorly operationalized techniques, and the absence of outcome measures, the goal of most current proven efficacious treatments is good clinical response with remission of symptoms, rather than full recovery. Maintenance treatment is recommended for many disorders, especially following recurrent episodes of illness. Panic disorder fits this general description.

Since most research on the treatment of panic disorder has been conducted as relatively brief efficacy trials (6–12 weeks in duration), there is little to guide the clinician in deciding how long to treat patients and/or how to optimize treatment. The purpose of this article is to define a strategy by which clinicians can utilize and extend existing research data and methods to make decisions about individual patients. We suggest that physicians monitor the effects of treatment on key symptoms and use standard and clinically meaningful definitions for response, remission, and relapse as way stations on the road to recovery. We provide some preliminary published information on the long-term track record of treatment of panic disorder and suggest possible ways of optimizing the likelihood of recovery, or at least remission from panic.

### MEASURING OUTCOMES IN PANIC DISORDER

Most practicing psychiatrists were not trained to monitor symptoms in a systematic way, but increasingly are asked to do so. One way of determining how well a patient is doing is to regularly follow the progress of key symptoms. To do this, it is useful to have simple, but psychometrically sound, measurement tools. Key symptoms of panic disorder are those that comprise diagnostic criteria, i.e., recurrent unexpected panic attacks, intercurrent anxiety or concern about attacks, implications or consequences of attacks or behavior change related to attacks (anticipatory anxiety), and, for patients with agoraphobia, anxiety about having symptoms in situations where escape or getting help may be difficult. Phobic situations are avoided or endured with marked distress. It is also helpful to have a simple, standard measure of functional impairment in work, social, and family life. How do we measure these key areas?

The standard method of assessing panic attacks, strongly endorsed by experts in the field, is the panic di-

ary. The patients are given a preprinted form or booklet and asked to carry it with them and record panic episodes as they occur. It is worth noting the advantages and disadvantages of this type of measure. The advantages are that this is the standard accepted method, that it may be the most accurate, and, importantly, that such monitoring has documented therapeutic effects. The disadvantages are that such assessment tends to focus on panic frequency, not severity, that patients often fail to record panic as instructed, and that it can encourage the possibly artificial separation between types of panic, e.g., spontaneous, situational, full, limited symptom.<sup>2</sup> On balance, however, following the recently released American Psychiatric Association Panic Disorder Guidelines,<sup>3</sup> we recommend the use of diary monitoring.

Similarly, the standard method of measuring anticipatory anxiety is a daily symptom diary. Again, the advantage of this approach is that it is a standard accepted method and may be most accurate. The disadvantages are that it may be difficult for patients to judge the percentage of the day spent worrying, and they often fail to record anxiety as instructed, waiting until the end of the day or the end of the week and taking away the advantage of on-line recording. The clinician also needs to consider other features of anticipatory anxiety, such as fear of the consequences of expected panic and ongoing fear of bodily sensations.

Phobic symptom assessment is somewhat more problematic since there is no standard measure. Commonly used measures include the Fear Questionnaire,<sup>4,5</sup> a behavioral avoidance test,<sup>6</sup> a global rating of main phobia or overall phobic symptoms,<sup>7</sup> and the Mobility Inventory for Agoraphobia.<sup>8</sup> In assessing phobic symptoms, we need to consider agoraphobia, sensation avoidance, and possible differences in the degree of anxiety and avoidance when the patient has a companion.

Many research studies include a measure of overall illness severity, which can also help in following a patient's progress. The Clinical Global Impressions scale (CGI)<sup>9</sup> is the most frequently used measure and is a single Likert-type rating of the level of severity. A similar measure is often used to assess improvement and has the advantage of making use of clinician judgment. As a single-item scale, it is psychometrically poor and has the added disadvantage that it is not consistently anchored, so a rating of "severe" may carry different meanings to different people.

An alternative strategy used by Keller et al.<sup>10</sup> is the Psychiatric Status Rating (PSR),<sup>11</sup> a simple, composite measure that has now been used in a large naturalistic follow-up study. However, its anchor points are somewhat arbitrary, a hierarchy of DSM diagnostic criteria are included, there are currently no psychometric data, and it is not widely used.

In addition to having a measure of overall severity, it is useful to have a measure of impairment in each area of panic symptoms. Again, there is no standard measure.

Commonly used measures include the Global Assessment of Functioning (Axis IV of DSM), the Social Adjustment Scale<sup>12</sup> and the Sheehan Disability Scale.<sup>13,14</sup>

We recently developed a new measure of severity and impairment called the Panic Disorder Severity Scale (PDSS),<sup>15</sup> using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)<sup>16</sup> as a model. The 7-item interview rates criterion symptoms separately on a 0 to 4 scale. Items include panic frequency, distress during panic, severity of anticipatory anxiety, agoraphobic fear/avoidance, fear/avoidance of physical sensations, and panic-related impairment in work and in social situations. We recommend the use of this scale as a single measure of key areas of panic disorder symptomatology. The scale has good psychometric properties, and its use eliminates the need for a complex algorithm.

### DEFINITIONS OF RESPONSE, REMISSION, AND RELAPSE

The most important reason for monitoring treatment results is to help guide clinical decisions. Use of standard measures of key symptoms assists in deciding when a patient has shown a clear response to treatment, when that response could be judged remission, and when a relapse has occurred. These decisions are linked to specific clinical behaviors. Clearly, if a patient does not respond to a treatment, the treatment should be changed. But what constitutes response? What might be reasonable criteria for clinically significant change in symptoms and/or impairment? Over what time period must such a response be seen for it to be considered stable and meaningful?

To answer the above questions, it is necessary to consider the typical course of symptoms of panic disorder. Panic attacks themselves are sporadic and highly variable in frequency. Some patients experience regular, daily panic attacks, but this is not the rule. Instead, persons with active panic disorder can have a period of several weeks in which no panic occurs at all, and then they might experience several episodes in a day or several over the next week. In spite of the fact that panic is the hallmark of the illness, panic is a useful measure only when it is followed over a prolonged period of time. At least 4 weeks is needed for a reasonably stable estimate of the presence or absence of panic attacks, and even with prolonged monitoring it may be difficult to say when there is a consistent, reliable decline from a pretreatment panic frequency level. In so far as assessment of panic frequency is used to determine response, it is important to remember that panic occurs in an attenuated form called "limited symptom episodes" that also need to be taken into consideration. These "minor" panic episodes can cause substantial distress and impairment.

The trajectory of anticipatory anxiety and phobic symptoms is more stable and less changeable. Anticipatory anxiety may begin at a low level following limited

symptom episodes of unexplained origin, but more commonly increases dramatically after several full panic attacks. Phobic symptoms usually take somewhat longer to develop but tend to be tenacious once established. Therefore, clear-cut improvement in severity of phobia symptoms can usually be taken as a reliable sign of response. But not all patients have phobic symptoms. Many show improvements in panic and anticipatory anxiety while change in phobia severity lags well behind. Thus, none of the individual key symptoms suffices as a marker of response in panic disorder. It is for this reason that we recommend use of an instrument such as the PDSS. How then might we define *response* in a uniform way?

The term *response* is not defined by DSM-IV. However, this terminology is widely used and is often utilized in research reports. Weise and colleagues<sup>17</sup> noted that investigators generally consider the endpoint CGI score to be the best indicator of improvement, where a rating of "much" or "very much" improved represents a positive response. There may also be a severity threshold, such as reduction of > 50% in panic frequency or a maximum score on the CGI severity rating.

An alternative way of judging clinically significant change has been proposed by a well-known psychologist researcher, Neil Jacobson.<sup>18</sup> His research group suggests that degree of improvement be assessed using a reliable change (RC) index, where  $RC = \text{individual } (x_2 - x_1) / S_{\text{diff}}$  and  $x_2 = \text{post treatment score}$ ,  $x_1 = \text{pretreatment score}$ , and  $S_{\text{diff}} = \text{SE of the difference score}$ . They further suggest that if  $RC > 1.96$ , then it is a significant change ( $p < .05$ ) and occurred by chance. This is a useful and rigorous method of establishing whether a stable change has occurred, although it does not help with the choice of instrument and it is somewhat inconvenient to use in everyday practice.

DSM-III-R and IV classifications both provide definitions of remission for panic disorder, even though clinicians and researchers rarely use them. Specifically, DSM-III-R<sup>19</sup> criteria for full remission of panic include the qualification: "During the past 6 months, there have been no panic or limited symptom attacks."<sup>19(p239)</sup> Mild panic disorder is defined as: "During the past month either all attacks have been limited symptom attacks or there has been no more than 1 panic attack."<sup>19(p239)</sup> Partial remission is declared to be "... intermediate between 'in full remission' and 'mild.'"<sup>19(p239)</sup> For agoraphobia, DSM-III-R criteria for full remission are that for at least 6 months, there have been no clinically significant agoraphobic symptoms (including distress during or in anticipation of exposure). The criteria for partial remission require that for at least 1 month (but less than 6 months) there have been no clinically significant agoraphobic symptoms (including distress during or in anticipation of exposure).

DSM-IV<sup>20</sup> no longer provides criteria for remission of a specific diagnostic category. Instead, remission is defined

generically, with partial remission described as “The full criteria for the disorder were previously met, but currently only some of the symptoms or signs of the disorder remain.”<sup>20(p2)</sup> Full remission is when “there are no longer any symptoms or signs of the disorder.”<sup>20(p2)</sup> This approach leaves open the critical clinical issue of what is meant by “any symptoms or signs of the disorder.”<sup>20(p2)</sup> Also omitted is the question of how long symptoms and signs must be absent to declare that a remission has occurred. Clearly, this definition is incomplete, and probably reflects a real problem in the field. It is difficult to know what the precise criteria for remission should be when there are little or no controlled longitudinal data to test the meaning of different definitions and different time periods.

In the field of panic disorder, several investigators have provided specific definitions of their own for determining remission. For example, Mavissakalian and Michelson<sup>21</sup> utilize a measure of high, medium, or low endstate functioning. Criteria include (1) minimal anxiety on behavioral avoidance test, (2)  $\leq 2$  on clinician global rating (score range, 0–5), (3)  $\leq 2$  on self-rated phobia severity (score range, 0–9), and (4)  $< 4$  on phobic anxiety and avoidance (score range, 0–9). A total score of 3 or 4 qualifies as high endstate functioning, while a total score of 1 or 2 is considered medium, and a patient is considered to have low endstate functioning if the total score is 0.

Another type of composite rating has been used by Faravelli and colleagues.<sup>22</sup> This group rates a “good response” when there is 1 or fewer mild symptoms (DSM-IV) within 2 or more months, where symptom severity is rated 0 to 4 or 0 to 8. “Amelioration” is 2 or more mild DSM symptoms, not meeting criteria for the disorder. A “poor” response is declared when the patient continues to meet criteria for the disorder.

Keller et al.<sup>10</sup> used the PSR to define specific criteria for 6 levels of symptoms for panic and agoraphobia (see Table 1). Keller’s group also defined remission: 8 consecutive weeks when both the panic and agoraphobia PSR scores are  $\leq 2$  is considered full remission, and when the PSR score is  $\leq 3$ , remission is considered partial. Relapse occurs if the patient experiences 1 week with a PSR of  $\geq 5$ .

Another way of tackling the problem is to use Jacobson’s criteria for clinically significant change. By using an instrument with normative data, a cutoff score is determined,  $c = (s_0X_1 + s_1X_0)/(s_0 + s_1)$  where  $X_1$  = pretreat mean for ill subjects,  $X_0$  = mean for normal subjects,  $s$  = respective SD. For an instrument without normative data, the cutoff score for clinically meaningful change for an experimental group = 2 SDs below mean of ill group.

We suggest that to consider a patient as having responded to a treatment, what is required is stable, reliable, clinically significant improvement following a treatment intervention. “Stable” refers to a specified time period during which the symptom level is more likely to persist than to change, and “reliable” refers to a change in symp-

**Table 1. Criteria for Panic and Agoraphobia Rating According to the Psychiatric Status Rating Scale\***

Criteria	Rating
<b>Panic</b>	
$\geq 1$ episode of panic/d	6
1 panic attack/wk	5
Persistent fear of panic	4
Limited symptom attack	3
No attacks, feels on verge of an attack but able to control it	2
None of the above	1
<b>Agoraphobia</b>	
Nearly or completely housebound, unable to leave home unaccompanied	6
Constricted lifestyle/endurance with great anxiety	5
Some avoidance, otherwise normal (travels unaccompanied when necessary, otherwise avoids)	4
Moderate situational anxiety, no avoidance	3
Slight situational anxiety	2
None of the above	1

\*Data from reference 10.

toms that is greater than the variance (between subjects and over time) of the measurement instrument. In standard clinical practice, the measurement instruments are often the clinicians themselves. It seems clear that this is a considerable burden and that use of ancillary standardized rating scales with good psychometric properties would be likely to improve the reliability and validity of judgments about clinical status.

With this principle in mind, we suggest that patients be considered responders if they are much or very much improved on a clinical global improvement measure and have a PDSS score at least 30% below their baseline. Moreover, this level of improvement should be stable (or continuing to improve) for at least a month. Similar considerations hold for the judgment of remission. In the literature, the time frame for remission ranges from 2 to 8 months. We suggest that 6 months is an appropriate time period over which a patient could be considered to be in remission if he or she no longer meets diagnostic criteria for panic disorder or agoraphobia. For full remission, any residual symptoms should be at a frequency and intensity below a threshold level that would be clinically significant. We suggest that one way of determining this is to require that the PDSS score be  $\leq 3$ , with all individual items  $\leq 1$ . A patient who does not meet DSM-IV criteria for illness but has a PDSS score  $> 3$  would be in partial remission, as would one who meets the full criteria for less than 6 months.

### STRATEGIES TO IMPROVE REMISSION RATES

It may be possible to improve remission rates by simply using a better system to monitor the patient’s progress. If residual symptoms are identified clearly and the progress

of treatment can be mapped, clinicians may be induced to appropriately increase or possibly decrease medication dosage. This would be a strategy similar to the regular monitoring of blood pressure in a hypertensive subject. Such an approach would be useful because sometimes patients with panic disorder do not spontaneously talk about symptoms, hoping that if the symptom is not present now, it is gone for good. Systematically following outcome measures such as the PDSS may also alert clinicians to the recurrence of symptoms and the possibility of a relapse. Addressing such clinical situations quickly may prevent full relapse of the disorder and also optimize long-term outcome.

In addition to monitoring outcome, results may be improved if clinicians are aware of the specific cognitive-behavioral treatment strategies that target panic. If medication alone is insufficient, or if patients do not wish to continue to take medication, even after a good response, this treatment can be used. A recent report<sup>23</sup> also suggests that psychodynamic treatment may be useful in preventing relapse in severe (hospitalized) agoraphobic patients treated with medication. The use of adjunct targeted psychotherapy may thus help increase rates of remission and decrease relapse in these patients.

Many patients with panic disorder have comorbid conditions and life stresses that may contribute to exacerbation of panic symptoms. Awareness of these complications from the beginning of treatment is important, but it is especially useful when there are problems achieving remission and/or with relapse of symptoms.

It is important to recognize that the long-term goal for patients who have panic disorder is sustained full remission. While not all individuals may achieve this level of relief, and indeed current information suggests few do so, it should still be possible to approach this goal more closely through a systematic, rational approach to treatment.

## SUMMARY

We propose that a standard set of definitions and criteria for the terms commonly used in panic disorder research will assist clinicians in their management of patients who have panic disorder. Furthermore, the application of an assessment procedure such as the PDSS will provide clinicians with an instrument that considers all essential domains of panic disorder, namely, panic attacks, anticipatory anxiety, phobias, overall severity of illness, and functional disability. Achievement of full remission for all symptoms should be the goal for patients with panic disorder, and they can be considered to have reached this when they no longer meet diagnostic criteria for panic disorder or agoraphobia for 6 months or more. One way of determining remission is to require a PDSS score  $\leq 3$ , with all

individual items  $\leq 1$  for this time period. The use of the more comprehensive PDSS for monitoring patients who have panic disorder should alert the clinician to the re-emergence of associated symptoms and allow for treatment modification to be initiated. By responding quickly to the recurrence of symptoms, the clinician may prevent a full relapse.

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