# Establishment of Remission Criteria for Anxiety Disorders

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Anxiety disorders such as generalized anxiety disorder, social anxiety disorder, panic disorder, and posttraumatic stress disorder are typically chronic conditions associated with high health care costs and are often accompanied by psychiatric comorbidity, including major depressive disorder, substance abuse, and other anxiety disorders. Anxiety disorders are associated with significant functional impairment in social, vocational, and familial spheres and with diminished overall quality of life. The following clinical overview provides informal guidelines for identifying remission in patients with an anxiety disorder. A systematic approach to treatment that includes patient education, encouragement of exposure, attention to relevant comorbidities, use of empirically proven pharmacotherapies, and psychosocial interventions of adequate intensity and duration will improve outcomes and move patients toward marked improvement and remission. *(J Clin Psychiatry 2003;64[suppl 15]:40–45)*

Anxiety disorders, such as generalized anxiety disorder (GAD), social anxiety disorder, panic disorder, and posttraumatic stress disorder (PTSD), are all marked by excessive anxiety that causes marked distress and/or interferes with function.[1] Clinical presentation, however, varies considerably depending on whether the anxiety is episodic as in panic attacks, persistent as in GAD, or situationally predisposed or cued as in phobic disorders and PTSD.[1]

Panic disorder is characterized by recurrent panic attacks. Whereas initial attacks occur spontaneously, over time they often become associated with places in which attacks have previously occurred or with any situation in which escape may be difficult or help unavailable in the event of an attack. The fear and avoidance of these situations, agoraphobia, is common among patients with panic disorder in clinical settings. Social anxiety disorder is characterized by excessive fear and avoidance of social or performance situations in which a person is exposed to possible scrutiny by others; the fear of embarrassment may be restricted to a few specific performance situations, such as public speaking, or more typically may be generalized across a range of social interactions. Generalized anxiety disorder involves excessive and uncontrollable worry about a number of situations; it persists for at least 6 months or more. PTSD is a condition affecting individuals exposed to a significant traumatic event involving the threat of death or serious harm. Affected individuals strive to avoid reminders of the trauma; they may become emotionally withdrawn, dissociate, uncontrollably reexperience the event, and develop symptoms of exaggerated emotional arousal and anxiety.[1]

When left untreated, anxiety disorders tend to persist over many years, with symptoms exhibiting a waxing and waning course related to changes in life demands, stressors, and exposure to feared situations.[1] Accruing experience has highlighted the clinical importance of achieving symptom remission for improved patient outcomes, and remission is gaining acceptance as an appropriate long-term treatment goal. The following discussion provides a broad overview of the epidemiologic and clinical features of GAD, social anxiety disorder, PTSD, and panic disorder; the personal and economic costs associated with these conditions; and strategies that clinicians can use to help patients achieve remission of anxiety disorder symptoms.

## BURDEN OF ANXIETY DISORDERS

Anxiety disorders are associated with significant impairment across multiple domains of work, social, and family function as well as diminished overall quality of life. Even when demographic factors and the presence of other psychiatric comorbidities are controlled for, daily activities, psychosocial function, and economic productivity are all negatively affected, suggesting that anxiety disorders independently contribute to such impairments.[2–8] For instance, Wittchen and colleagues[4] found

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**Table 1. Remission of Panic Disorder[a]**

| Subjective Goal | Objective Goal |
|---|---|
| No or minimal anxiety | HAM-A score ≤ 7–10 |
| No functional impairment | Sheehan Disability Scale score ≤ 1 on each item (mildly disabled) |
| No or minimal symptoms of depression | HAM-D score ≤ 7 |
| Essentially free of panic attacks | |
| No or mild agoraphobic avoidance | |

[a]Adapted with permission from Ballenger.[16]
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

**Table 2. Remission of Social Anxiety Disorder[a]**

| Subjective Goal | Objective Goal |
|---|---|
| Core symptoms of social anxiety have disappeared | LSAS score ≤ 30 |
| No or minimal anxiety | HAM-A score ≤ 7–10 |
| No functional impairment | Sheehan Disability Scale score ≤ 1 on each item (mildly disabled) |
| Core symptoms of depression have been resolved | HAM-D score ≤ 7 |

[a]Adapted with permission from Ballenger.[16]
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LSAS = Liebowitz Social Anxiety Scale.

**Table 3. Remission of Generalized Anxiety Disorder[a]**

| Subjective Goal | Objective Goal |
|---|---|
| No or minimal symptoms of anxiety | HAM-A score ≤ 7–10 |
| No functional impairment | Sheehan Disability Scale score ≤ 1 on each item (mildly disabled) |
| No or minimal symptoms of depression | HAM-D score ≤ 7 |

[a]Adapted with permission from Ballenger.[16]
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

**Table 4. Remission of Posttraumatic Stress Disorder[a]**

| Subjective Goal | Objective Goal |
|---|---|
| No or minimal PTSD symptoms | TOPS-8 score ≤ 5 or 6 |
| No or minimal anxiety | HAM-A score ≤ 7–10 |
| No functional impairment | Sheehan Disability Scale score ≤ 1 on each item (mildly disabled) |
| No or minimal symptoms of depression | HAM-D score ≤ 7 |

[a]Adapted with permission from Ballenger.[17]
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, TOPS-8 = Treatment Outcome PTSD Scale.

that individuals with "pure" GAD were more likely to perceive their health as fair or poor, to report significant role limitations due to emotional health, and to experience impaired social function compared with individuals without evidence of psychopathology.

These findings closely parallel those reported for other anxiety disorder populations. From a large cohort of health maintenance organization (HMO) enrollees, those with generalized social anxiety disorder were found to experience significantly reduced quality of life, characterized by a 10% lower probability of graduating from college, wages that were 10% less, and decreased professional achievements, compared with fellow enrollees who had no psychiatric diagnoses and who screened negative for social anxiety and depression.[3] PTSD is associated with increased rates of work loss and impairment, comparable to those seen with depression, and associated with an estimated $3 billion annual loss of productivity in the United States.[9] Using the United States National Comorbidity Survey and HMO-derived resource utilization data, Greenberg and colleagues[10] estimated that anxiety disorders, as a group, bore direct and indirect costs of approximately $63.1 billion in 1998 U.S. dollars. Direct psychiatric treatment costs accounted for only 31% of this total, while more than half of this amount ($34 billion; 54%) was attributable to nonpsychiatric medical treatments. To some extent, this cost distribution is related to inappropriate or inefficient treatment, possibly secondary to misdiagnosis.[10] It may also reflect the longer-term effects of the widespread failure of about 74% of individuals with current psychiatric disorders, including anxiety disorders, to seek and receive appropriate treatment.[10,11] Since remission is not commonly achieved even 1 year following detection,[12] the burden of such conditions is likely to persist over long periods of time.

Given evidence of the significant personal and societal burden associated with the anxiety disorders, the need for optimization of treatment to reduce and when possible eliminate the burden of illness is evident. Thus, there is growing consensus that, as with major depressive disorder,[13,14] the treatment goal for anxiety disorders should be remission.[15,16]

## REMISSION CRITERIA

Formal criteria for defining remission in a number of anxiety disorders, including panic disorder, social anxiety disorder, GAD, and PTSD, have been proposed in a series of consensus conferences addressing this issue (Tables 1–4).[16,17]

The proposed criteria reflect recognition that anxiety disorders exert negative effects across a number of domains of symptomatology and function.[18,19] Clinicians can assess progress in the treatment of GAD, social anxiety disorder, panic disorder, or PTSD based on the degree of reduction of the core symptoms of the given anxiety disorder (e.g., anxiety, panic attacks, phobic avoidance, reexperiencing of trauma, or physical symptoms of arousal), comorbid symptomatology (e.g., depression or alcohol abuse), and the resolution of functional

impairments across multiple domains of work, social, and family activity.

## STRATEGIES FOR TREATING TO REMISSION

Though remission is an appropriate therapeutic goal for patients with an anxiety disorder, it may be perceived as daunting given that, in controlled clinical trials and prospective observational studies, it is typically achieved in fewer than half of treated patients.[12,15] However, therapeutic strategies employed in a systematic fashion increase the proportion of patients with anxiety disorders who approach remission. Education is aimed at helping the patient gain an informed and realistic perspective on the nature of the illness, its impact on function, and the goal of improvement with an eye toward eventual remission. Patients should receive a balanced presentation of the benefits and drawbacks of the different pharmacologic and psychosocial treatment modalities, the need for adherence to treatment regimens to optimize outcome, the likelihood that gains with treatment may accrue over a period of months or longer, and the fact that many patients may require extended periods of treatment going on for months and even years in some cases to achieve and maintain full response. Instruction about the importance of gradual exposure to feared situations and how to accomplish this is a critical component of both pharmacologic and cognitive-behavioral therapies (CBTs) and should be frequently repeated and monitored during the course of treatment.

Patients who have been symptomatic for extended periods of time or since childhood may not have an adequate frame of reference to fully understand the limitations imposed by their anxiety and the possibilities for fuller function when anxiety is reduced. For these patients, a rapid achievement of full function may be less likely, and a period of training to develop lacking skills (e.g., social skills for those with social anxiety disorder) may be necessary to achieve full benefit. Initial reduction in the core symptoms of anxiety may reduce anticipatory anxiety and instill patients with a greater sense of control that will facilitate exposure to feared situations over time. Successful exposure leads to further reduction in anxiety.

Treatment addressing significant comorbidities, such as depression or substance abuse, is a necessary accompaniment to the therapeutic process. Gradual but repeated exposure to feared, avoided, and anxiety-provoking situations is critical for the realization of functional improvement and, ultimately, for the achievement of remission. For patients initially treated with pharmacotherapy, the reduction of core symptoms of anxiety may allow them to undertake the necessary exposure with the general encouragement and guidance of their clinician. For others, more formal behavioral or psychotherapeutic approaches may be required. Clinicians must regularly take time to confirm with patients that such exposure is occurring, since continued avoidance results in residual anxiety and continued impairment. Moreover, patients who do not successfully negotiate this intermediate step are likely to have difficulty in normalizing function. With the resolution of core anxiety symptoms and avoidant behaviors, functional impairments tend to diminish and patients may begin to realize their personal treatment goals.[15]

Optimizing treatment strategies to achieve these goals involves careful selection of therapeutic tools, based on presenting problems and symptoms, and the proper use of chosen therapies for an adequate amount of time. Exposure instructions should be part of the treatment for anxiety patients, even those for whom pharmacotherapy is the primary intervention.

Although full review of psychosocial therapy for anxiety disorders is beyond the scope of this article, data from a variety of sources demonstrate CBT to be at least comparably effective to pharmacotherapy in the acute and long-term treatment period, with evidence of perhaps greater sustained response following treatment discontinuation.[18] CBT targets maladaptive chains of thoughts, feelings, and behaviors and focuses on the learning of alternative behavior patterns; it involves administration of a variety of components, including provision of information, cognitive restructuring, exposure, and symptom management skills.[20] It can be used as an initial treatment alternative to pharmacotherapy, as a replacement, or in a combined treatment strategy to enhance outcome of treatment-refractory patients.

Reported response rates for CBT in panic disorder, for example, are relatively high, with panic-free rates reported as high as 85% but with lower rates for high end-state function (a more comprehensive measure that may be considered as a surrogate of remission) on the order of 70% in one study.[21] However, a report by Brown and Barlow[22] that tracked patients for 2 years after they participated in an acute CBT program for panic disorder documents a variable course for the treated disorder, with periods of clinical worsening and reemergent symptoms for more than three quarters of patients despite the fact that the majority of patients were panic free or met criteria for high end-state function at some time during follow-up. Thus, even with CBT, many patients require ongoing or intermittent interventions to maintain remission, and the optimal strategy to provide ongoing treatment to maintain benefit over time is an important issue for the field to address. In addition, administration of CBT may be limited by the lack of availability of trained providers in most settings to administer empirically based treatments and the increased initial work required on the part of patients that may seem unacceptably daunting to some.

Studies examining combined treatment with pharmacotherapy and formal CBT suggest some additional benefit over either intervention alone.[23] The magnitude of this effect, though, may not be large enough in the average

patient to warrant recommendations for the widespread application of initial coadministration of a formal course of CBT with medication. However, accruing experience does suggest that coadministration of the alternative therapeutic modality for partial or nonresponders to initial treatment (e.g., CBT for medication-refractory patients) may well offer significant additional benefit.[24] The combination of pharmacotherapy and psychotherapeutic strategies may be a particular consideration for those with comorbid symptoms, lengthy periods of illness, or refractory symptoms.

In considering pharmacotherapy for the anxiety disorders, a number of drug classes, including the benzodiazepines; the azapirones (buspirone, for GAD only); and the antidepressants, including the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and, more recently, selective serotonin reuptake inhibitors (SSRIs), such as paroxetine or sertraline, and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, have been shown to be effective. In addition, novel pharmacologic strategies including the use of atypical neuroleptics and anticonvulsants are being examined and utilized to improve outcome in partial responders and nonresponders to initial treatment.[24] In choosing among the wide array of available pharmacotherapeutic options, clinicians should consider efficacy, spectrum of action, and safety and tolerability, with an eye toward optimizing outcome over the acute and long term.

## EFFICACY

Current recommendations for the pharmacotherapy of the anxiety disorders often advocate initiation of treatment with an antidepressant, with the rationale that these agents will be effective for the anxiety and the comorbid depression that often complicate the presentation. Treatment of 2 or more comorbid conditions with a single agent may help to improve long-term patient compliance by reducing polypharmacy, simplifying drug regimens, and improving tolerability. The SSRIs and SNRIs have largely supplanted the TCAs and MAOIs as first-line agents because the newer antidepressants are comparably effective with a more favorable side effect profile lacking the anticholinergic properties, effects on cardiac conduction, induction of orthostatic hypotension, lethality in overdose, and need for careful dietary monitoring (in the case of the MAOIs) that complicated treatment with the older agents. In addition, the SSRIs and the SNRI venlafaxine have a broader spectrum of activity than do the TCAs, which appear ineffective for social phobia and obsessive-compulsive disorder (with the exception of clomipramine for obsessive-compulsive disorder). The SSRIs and SNRI do not have abuse liability in contrast to the benzodiazepines, but in general they may take 2 to 3 weeks to exert significant therapeutic benefit.

Though generally well tolerated, use of the SSRIs and SNRIs can be associated with some adverse effects, including jitteriness with initiation of treatment, sedation, sexual dysfunction, gastrointestinal symptoms, occasional increased blood pressure at higher doses of venlafaxine, weight gain, and sleep disturbance. However, these side effects are generally manageable for most patients in practice with the use of careful titration and augmentation strategies when necessary.[24]

Benzodiazepines remain widely prescribed for the treatment of a variety of anxiety states because they reduce anxiety quickly (in hours or days rather than weeks), can be used on a situational basis, and are generally well tolerated. However, they can cause some side effects, including sedation, ataxia, and cognitive impairment, and can be dangerous in combination with alcohol. Benzodiazepines may cause physiologic dependence after a few weeks of maintenance therapy and may be abused by those predisposed to abuse of alcohol or other substances (although people without such a predisposition do not abuse these medications and often take subtherapeutic doses because of misplaced concerns about "addiction"). Of particular concern, benzodiazepines alone are generally ineffective for the comorbid depression that often accompanies anxiety and may, at times, worsen the mood disorder. In addition, there is concern in the case of PTSD that early administration of hypnotics or benzodiazepines may be associated with persistence of symptomatology over time.[25,26]

Perhaps not surprisingly, benzodiazepines and antidepressants are often combined. The available evidence, though limited, suggests that this combination accelerates response compared with an antidepressant alone, but beyond the initial 4 to 5 weeks, combination treatment does not confer additional benefit beyond that seen with monotherapy.[27,28]

## DOSING AND DURATION OF TREATMENT

Anxiolytic treatment should be initiated at low doses and gradually increased to minimize treatment-emergent adverse events. Preparing the patient for the 2 to 4 weeks of expected lag in onset of symptom relief usually seen with antidepressant agents will help to prevent premature discontinuation of treatment. For remission, it may be important to identify optimally effective dose levels. Although the available data at present do not permit definitive evaluation of the impact of increasing the dose beyond typical levels for partial or nonresponders to initial therapy, clinical experience suggests that this may sometimes be a useful strategy. The data are clearer about the salutary effect of longer duration of treatment on outcome. For instance, Londborg and colleagues[29] examined outcome of treatment with sertraline for patients with PTSD in a 24-week, open-label extension study following participation in a 12-week, double-blind, randomized, placebo-

controlled trial. They found that 92% of acute-phase responders maintained their response during the full 6 months of continuation treatment; of particular note, 54% of acute-phase nonresponders converted to responder status during continuation therapy. About a quarter of the improvement in severity ratings occurred during the continuation phase.

In GAD, there is emerging evidence as well suggesting that patients continue to improve over time during treatment. In an analysis pooling data from 2 long-term, randomized, placebo-controlled studies with venlafaxine extended release, 58% of the venlafaxine-treated patients achieved responder status (≥ 50% reduction in Hamilton Rating Scale for Anxiety [HAM-A] score) at week 8, which increased to 66% at month 6 (compared with placebo-treated patients for whom the parallel numbers during that time period were 32% and 39%, respectively; venlafaxine vs. placebo, $p < .001$ at 8 weeks and at 6 months) .3[0] Rates of remission (HAM-A score ≤ 7) increased during the period from week 8 to month 6 from 32% to 43% for venlafaxine but remained about the same for placebo (15% to 19%, respectively; venlafaxine vs. placebo, $p < .001$ at 8 weeks and at 6 months). Of particular note, 64% of nonresponders to venlafaxine at week 8 became responders by month 6 compared with only 26% of those taking placebo (treatment-by-time interaction effect, $p < .001$), and 61% of responders taking venlafaxine achieved remission status during that time period compared with 39% of placebo-treated patients (treatment-by-time interaction effect, $p = .007$).

Thus, the available data support the importance of treatment adherence over time as patients and clinicians may expect to see continued improvement following initial treatment, with nonresponders during the acute phase responding over time and with partial responders achieving more robust results during maintenance-phase therapy.

## CONCLUSION

Most patients with an anxiety disorder experience significant comorbidity and impairments across multiple domains of function. Moreover, with the typically early onset of such disorders and the tendency toward recurrence, many of these individuals may suffer impaired function to varying degrees over a large portion of their lives. With the recognition of the high prevalence of anxiety disorders and the associated burden on affected individuals and society in general comes the impetus to improve outcome and to focus on remission as an appropriate therapeutic target. Patient education, encouragement of exposure, utilization of empirically proven pharmacotherapies, and psychosocial interventions administered in sufficient doses over adequate periods of time offer the promise of improved outcomes for individuals affected by these distressing and disabling disorders.

*Drug names:* buspirone (BuSpar and others), clomipramine (Anafranil and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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