

Clinical Guidelines for Establishing Remission in Patients With Depression and Anxiety

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© Depression and anxiety exist together more often than as separate syndromes. Comorbid major depression substantially worsens the clinical outcome of patients with anxiety disorders such as panic disorder, social phobia, and generalized anxiety disorder. Although previous treatment guidelines have addressed depression and anxiety separately, we have developed guidelines that more closely approximate the types of patients seen in clinical practice. These recommendations focus on scales to measure all symptoms (anxiety and depression) and propose full remission and functional recovery as the goal of treatment. Objective guidelines for remission include maintaining the Hamilton Rating Scale for Depression total score at ≤ 7 and the Hamilton Rating Scale for Anxiety total score at 7 to 10 or even lower—rigorous, challenging, but appropriate goals to restore patients to a normal functional state.

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Despite intensive investigation into the pathophysiologic course and treatment outcomes of depression and anxiety, considerable confusion persists regarding 2 fundamental questions asked in clinical practice: What is the realistic expectation of how healthy any patient with these disorders can become with treatment? and How can we get patients into remission in a typical clinical practice setting? Most randomized controlled trials of pharmacologic and nonpharmacologic treatments of anxiety disorders and depression do not evaluate remission—which we define here as both symptom resolution and resolution of any functional impairments caused by the depression or anxiety disorder or both. Instead, studies have generally focused on short-term clinical symptom response rates. In addition, these studies, as well as clinical consensus guidelines, have used widely varying definitions of remission.^{1–3}

An additional challenge in extrapolating the results of trials in highly defined patient subgroups into practical clinical treatment guidelines is the considerable overlap between major depressive disorder (MDD) and anxiety disorders such as panic disorder, social phobia, and generalized anxiety disorder (GAD) in primary care and among psychiatric outpatients. The majority of controlled studies

of depression exclude patients with other psychiatric disorders, including anxiety, and most controlled studies of anxiety exclude patients with depression.

Faced with these challenges, we sought to develop guidelines for evaluating remission in patients with these 4 frequently comorbid disorders and to recommend specific physician- or patient-rated evaluation tools and cutoff points that can be used in clinical practice. Because there is considerable overlap in the symptoms and clinical presentation of depression and the anxiety disorders, we considered it particularly useful to recommend general and broad outcome measures that cover the entire range of symptoms, rather than look at the specific distinguishing symptoms of each of the 4 disorders separately. We believe this approach is more relevant to what is seen typically in clinical practice and to the goal of achieving full remission for more patients. Clearly, therapies must focus more on addressing the global aspects of the disorders, including disparate symptom domains and various symptomatology, rather than merely resolving specific symptoms. Such a shift may increase the likelihood that individual patients will achieve remission rather than a partial response.¹

The largest database from which to derive information on assessing remission is available for MDD. We have extended findings from this area of research to provide additional information on treating patients with comorbid depression in panic disorder and social phobia—areas in which the database has expanded substantially in recent years. For patients with GAD, the most recent revisions to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) have considerably refined the criteria for identifying this disorder.⁴ However, to our knowledge, no published guidelines define remission in patients with this

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Table 1. Guidelines for the Remission of Depression^a

Phase	Goals	Time Course	Physician-Rated Scale	Patient-Rated Scale
Acute	Reduce symptoms to nonpathologic level	6–8 wk	HAM-D score ≤ 7	CGI score = 1 ^b
Continuation	Extend and maintain improvement and induce remission; resolve functional impairments	4–9 mo	HAM-D score ≤ 7 ; Sheehan score ≤ 1 (mildly disabled)	CGI score = 1 ^b
Maintenance	Maintain remission and reduce recurrence	4–5 mo	HAM-D score ≤ 7	CGI score = 1 ^b

^aAbbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, Sheehan = Sheehan Disability Scale.

^bAlternatively, clinician could use 70% improvement on another patient-rated scale as the criterion for remission.

disorder. Hence, the current document represents the first attempt at providing the practicing clinician with a practical outcome measure for GAD.

Our overall objective in developing necessarily rigorous definitions of remission is to provide the clinician with clear markers of MDD, panic disorder, social phobia, and GAD as they attempt to restore their patients to functional normality—a state in which they cannot be distinguished from a person without the disorder. Striving for these results is appropriate but ambitious since remission should be expected in probably only $\leq 50\%$ of the patients typically seen in the clinic. This challenge is made more difficult given that data indicate that $\leq 30\%$ of depressed patients receive treatment matching that recommended in current, less rigorous guidelines.⁵ However, we believe that these aggressive goals focus our efforts more appropriately to benefit patients optimally. Remission, rather than response, should be viewed as the ultimate goal of any therapy. With these guidelines defining remission, we hope to renew efforts to improve therapeutic approaches that can more effectively achieve remission in an increasingly larger proportion of our patients.

REMISSION GUIDELINES FOR ANXIETY AND DEPRESSION

Major Depressive Disorder

Efforts to improve the treatment of MDD have led to the development of a number of treatment algorithms and clinical practice guidelines.³ With these efforts have come important shifts in concepts of the disorder itself and its treatment. For example, the importance of full remission of the disorder, whereby normal psychosocial functioning is restored and relapse and recurrence prevented, is now more strongly emphasized.

Aggressive and persistent treatment efforts are crucial in the management of MDD because of the high rates of both relapse and recurrence, estimated to occur in up to 85% of patients.⁶ Importantly, premature discontinuation of antidepressant treatment is significantly associated with the risk of relapse and recurrence.⁵ In turn, relapsing patients may be at greater risk of not receiving care for subsequent episodes of MDD⁷ or failing to respond to treatment. Further complicating discontinuation of antidepressant treatment and diagnosing depression recurrence or relapse are the data showing that patients with bipolar II disorder may

be misdiagnosed as having recurrent unipolar depression.⁸ Therefore, follow-up evaluations are imperative.

Depression practice guidelines commonly divide treatment into 3 phases: *acute treatment*, during which time the goal is to resolve symptoms; *continuation treatment*, during which time (generally 4 to 9 months) therapy is continued to ensure complete resolution of the index episode and prevent relapse; and *long-term maintenance*, during which time optimal therapy is continued to prevent the development of a new episode (i.e., recurrence).⁵ Although the length of the maintenance phase may vary, depending on the patient history and presence of comorbid anxiety, treatment should be continued for a minimum of 4 to 5 months beyond the continuation phase to reduce the risk of relapse.

We recommend the Hamilton Rating Scale for Depression (HAM-D) for assessing clinical response. The 21-item HAM-D is the most commonly used scale for rating the target symptoms of depression in clinical trials and is considered the gold standard of available tools.⁹ As noted in Table 1, the remission guidelines for depression that we have developed propose improvement down to a HAM-D total score ≤ 7 and Clinical Global Impressions (CGI) scale score of 1 (very much improved). Alternatively, the clinician could use 70% improvement on a patient-rated scale other than the CGI as the criterion for remission. The HAM-D cutoff point has previously been suggested as a stringent criterion for complete remission and may provide the advantage of separating those patients with a true response to therapy from those exhibiting nonspecific effects, placebo response, or spontaneous transient remission.^{10,11}

To illustrate this point, a recent pooled analysis of 8 studies compared the efficacy of venlafaxine, selective serotonin reuptake inhibitors (SSRIs), and placebo in achieving remission, as indicated by scores ≤ 7 on the HAM-D, in patients with moderate-to-severe MDD.¹² After 8 weeks of treatment, the remission rate for venlafaxine was 43% compared with 33% for SSRIs and only 21% for placebo. These data corroborate the usefulness of a criterion such as HAM-D score ≤ 7 in determining remission as a true pharmacotherapeutic response rather than merely a placebo response.

This and other studies raise the possibility that certain treatments or indications could lead to a higher percentage of patients responding, a more robust response, or a broader response (e.g., against depression and anxiety).

Although both venlafaxine and SSRI treatment were significantly more effective than placebo in attaining remission, venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), was more effective than the SSRIs, showing an odds ratio of 1.90.¹² Interestingly, the robustness of this effect (overall) was confirmed by using various criteria for remission, some even more stringent than the 21-item HAM-D score ≤ 7 (e.g., HAM-D score ≤ 7 on the 17-item HAM-D).¹²

Other less specific criteria, such as a score of 1 (very much improved) or 2 (much improved) on the CGI or a 50% reduction from baseline on the HAM-D, are more appropriately used to evaluate symptom response rather than syndromal remission, because patients who achieve these goals often continue to exhibit significant residual depression.¹¹ Results of numerous studies suggest that the goal of HAM-D score ≤ 7 is obtainable in a large proportion of patients with individual disorders without comorbidities via a variety of pharmacologic and nonpharmacologic approaches. A further challenge is to achieve remission of depression when it is present with comorbidity and to maintain this improvement over the long term and prevent recurrences. Research is needed in this area to improve patients' mental health status, even to levels of the unaffected population (remission), and to resolve illness-associated functional impairments.

The Sheehan Disability Scale, which rates global disability in family, occupational, and social life, has been used widely in recent clinical trials. This scale has proved to be reliable and valid in multiple trials, especially those studying therapies for anxiety disorders. Resolution of functional impairment as marked by a Sheehan score ≤ 1 (mild disability) should effectively document full recovery (i.e., remission).

Panic Disorder and Social Phobia

More so than depression, panic disorder and social phobia are multidimensional disorders with various symptom domains in addition to the core features that distinguish them from other anxiety or mood disorders.^{1,2} Changes in these domains may serve as useful measures of treatment response.

Panic disorder. Despite the more recent development of effective treatments for panic disorder, standardized definitions of treatment response are lacking.^{3,13} In addition, although DSM-IV defines remission generally as stable absence of panic attacks,¹³ stable remission has been evaluated in controlled clinical trials only infrequently and definitions generally lack consistency and adequate specificity.

In recently published guidelines, response and remission were defined on the basis of almost complete resolution in 5 principal domains: panic attacks (the core feature of panic disorder), anticipatory anxiety, panic-related phobias, well-being/severity of illness, and functional and so-

Table 2. Guidelines for the Remission of Panic Disorder^a

Subjective Goal	Objective Goal	Time Course
Abolish core symptoms	No panic attacks (or rare)	6–12 wk
Minimize agoraphobic avoidance	Below DSM-IV level necessary to meet definition of agoraphobia	3–12 mo
Minimize anxiety	HAM-A score ≤ 7 –10 or 70% improvement on patient-rated scale	3–12 mo
Eliminate depression	HAM-D score ≤ 7 or 70% improvement on patient-rated scale	3–12 mo
Resolve functional impairments	Sheehan score ≤ 1 (mildly disabled)	3–12 mo

^aAbbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

cial impairment caused by the panic disorder.¹ At least 9 to 12 months of treatment were considered necessary to obtain remission in the majority of cases. Although the CGI score is the measure used most often in clinical trials to measure response in these domains, it is considered less adequate in terms of its psychometric properties than a tool such as the Panic Disorder Severity Scale.¹ The challenge in using either tool, however, is in dealing with the complexity created by multiple interrelated domains. For example, resolving panic attacks and the other features of panic disorder, such as agoraphobia, or comorbid features, such as depression, is complex and difficult. For instance, eliminating panic attacks is easier than resolving agoraphobia.

The presence of depression in a patient with panic disorder often appears to be the rule rather than the exception. In most trials, one third of patients with panic disorder are also depressed and fully two thirds become depressed over their lifetime.^{1,14,15} In fact, the clinician will likely encounter a patient with comorbid features, such as depression or substance abuse, that obscure the underlying panic disorder.^{14,15} Building on the guidelines developed by other clinician groups, we have defined remission in panic disorder here to encompass the scope of the functional problems exhibited by the majority of patients. The present guidelines (Table 2), therefore, include almost complete resolution of depressive symptoms (HAM-D score ≤ 7) and of global anxiety (Hamilton Rating Scale for Anxiety [HAM-A] score ≤ 7 –10), functional impairment (Sheehan score ≤ 1), and more commonly measured parameters (near absence of panic attacks and nearly complete resolution of agoraphobia). On the basis of this definition of remission, effective antidepressant activity would be considered an important feature of medications used to treat panic disorder.¹⁶ Comorbidity can complicate the treatment of panic disorder by requiring higher doses, longer duration of treatment, or additional or different pharmacotherapy. The optimal treatment of choice for panic disorder with comorbidity would be one with efficacy for both panic disorder and depression.¹ This is one of the reasons that the SSRIs

Table 3. Guidelines for the Remission of Social Phobia

Subjective Goal	Objective Goal	Time Course
Abolish core symptoms	Little or no fear or avoidance of social situations as measured by functional improvement on a standardized scale ^a	6–12 wk
Minimize anxiety	HAM-A score \leq 7–10 or 70% improvement on patient-rated scale	3–12 mo
Eliminate depression	HAM-D score of 7 or 70% improvement on patient-rated scale	3–12 mo
Resolve functional impairments	Sheehan score \leq 1 (mildly disabled)	3–12 mo

^aFunctional improvement corresponds to a CGI score of 1 (very much improved) or 2 (much improved), a score of 1 (mildly disabled) on the Sheehan Disability Scale, or a 70% improvement on the Liebowitz Social Anxiety Scale (LSAS).

have become the treatment of first choice over the benzodiazepines, i.e., because of the higher antidepressant potency of SSRIs.¹

Social phobia. Little information is available on the most appropriate measures to assess clinical outcome in patients with social phobia. Controlled trials have typically focused on patients with generalized social phobia, who exhibit significant impairment in multiple social and occupational situations.¹⁷ Patients with limited social phobia have significant impairment related to 1 or 2 specific performance situations or public speaking. Symptom rating scales developed specifically for social phobia, such as the physician-rated Liebowitz Social Anxiety Scale (LSAS) and the patient-rated Duke Brief Social Phobia Scale or Fear of Negative Evaluation Scale, are the most standardized and widely used measures.^{2,17–20} The Sheehan Disability Scale and the CGI have been used with success in this patient population to measure, respectively, functional ability and well-being/overall disease severity—the 2 domains that in addition to symptoms constitute generally accepted parameters to measure treatment outcomes.²

As with depression and panic disorder, short-term treatment of social phobia in clinical studies rarely restores patients to fully functional status compared with healthy subjects.¹⁹ Studies of 10 to 16 weeks' duration have shown mean reductions in the LSAS score to $<$ 40 (generally representing a reduction from baseline of approximately 50%). These results were achieved with a variety of drug therapies, including the SSRI paroxetine,¹⁸ the traditional monoamine oxidase inhibitor (MAOI) phenelzine,²⁰ the reversible MAOI moclobemide,²⁰ and, in one trial, the benzodiazepine clonazepam.¹⁹ Up to 50% of patients treated with paroxetine achieve such a reduction in LSAS, as do up to 78% of patients treated with clonazepam.^{18,19} However, scores $<$ 40 on the LSAS still indicate the presence of residual psychopathology. We suggest a more rigorous criterion for full remission, based on an approximate 70% reduction of LSAS score, a comparable index of

Table 4. Guidelines for the Remission of GAD

Subjective Goals	Objective Goals	Time Course
Minimize anxiety	HAM-A score \leq 7–10 or 70% improvement on patient-rated scale	8–12 wk
Eliminate depression	HAM-D score \leq 7 or 70% improvement on patient-rated scale	3–6 mo
Prevent recurrence of depression	HAM-D score \leq 7 or 70% improvement on patient-rated scale	3–12 mo
Resolve functional impairments	Sheehan score \leq 1 (mildly disabled)	3–12 mo

functional improvement (a CGI score of 1 or 2), or a score \leq 1 on the Sheehan Disability Scale after treatment for 6 to 12 weeks (Table 3).

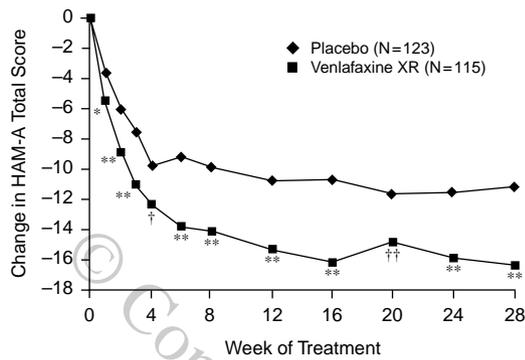
As with other mood and anxiety disorders, long-term treatment of social phobia—longer than 6 to 12 weeks—is generally required to achieve full remission. In addition, depression is one of the most frequent complications in patients with social phobia, often arising from the chronic isolation and functional disability that these patients experience.^{2,17} Approximately 40% to 50% of patients with social phobia will suffer comorbid depression at some point in their lives, with suicidal ideation present in nearly 30% to 55%.² For these reasons, the proposed remission guidelines include depression (HAM-D score \leq 7) as another measure of treatment outcome in addition to anxiety about avoidance of social situations (see Table 3) and functional impairment. Clinical trials suggest that these goals can be reached in the majority of patients with social phobia.^{18–20}

Generalized Anxiety Disorder

Recently reported trials of anxiolytics and antidepressants in patients with GAD or comorbid anxiety and depression form the basis for current recommendations on measuring treatment outcomes in GAD.^{21–25} Generally, no relevant guidelines have yet been developed. In addition to use of the HAM-A to measure global anxiety, the Covi Anxiety Scale and the CGI have been employed in some trials, although extensive experience with the HAM-A recommends its use.

As with the other disorders discussed, we recommend a goal of a score of 7 to 10 or less on the HAM-A or a comparable (i.e., 70%) reduction in score on a patient-rated scale (Table 4). Typically, it takes at least 8 weeks of robust treatment to achieve a score $<$ 10 on the HAM-A. This number was chosen as the upper limit on the basis of data showing it to be the cutoff point at which specific active treatment effects begin to be distinguishable from nonspecific placebo effects.²² In a recent large 12-week fixed-dose study of venlafaxine extended release (XR) and fluoxetine in outpatients with anxiety and depression, final scores on the HAM-A scale in responders were in the range of 10 to 15.²¹ Longer term treatment appears to be

Figure 1. Change From Baseline in Adjusted Mean HAM-A Total Scores (observed-cases analysis)^a



^aData on file, Wyeth-Ayerst Laboratories, 1998.

* $p = .003$ vs. placebo, ** $p < .001$ vs. placebo, † $p = .002$ vs. placebo, †† $p = .007$ vs. placebo.

necessary to reduce the HAM-A score to ≤ 10 . In a 6-month trial of venlafaxine XR in nondepressed outpatients with GAD with mean baseline HAM-A score between 24 and 25 (data on file, Wyeth-Ayerst Laboratories, 1998), significant reductions in the HAM-A scores were seen after 4 and 8 weeks of treatment. The final adjusted mean score was < 10 at week 28 (Figure 1). With the treatment extended beyond 8 weeks, about 70% of venlafaxine XR-treated patients maintained a HAM-A score < 10 , therefore meeting our criteria for remission.²³

GAD may play a particularly important role in the development of depression, with some data suggesting that GAD is actually a prodrome for MDD.^{26,27} As many as 40% of patients with GAD have comorbid MDD, and those without a current diagnosis of MDD can have a 50% risk of its developing within 1 to 2 years.²⁸ Therefore, it is particularly important again to incorporate depression measures in the remission guidelines for GAD (HAM-D score ≤ 7). Because of the extended time course of depression in GAD patients, it is recommended that treatment be continued for at least 12 months to ensure remission of both anxiety and depression. Although functional impairment is somewhat less prominent in GAD, we again recommend a Sheehan score ≤ 1 as part of the criteria for remission.

TREATMENT IMPLICATIONS OF GUIDELINES

Given the striking frequency of comorbidity of anxiety disorders and depression, it appears judicious to use agents that offer protection against both disorders. Antidepressants—the tricyclic antidepressants (TCAs), MAOIs, and SSRIs—have been used extensively in treating the anxiety related to panic disorder or obsessive-compulsive disorder and appear to be as effective as the benzodiazepines in this regard.^{3,4,16} Aside from alprazolam, benzodiazepines are not effective in reducing the depressive

symptoms that often accompany anxiety disorders and therefore are probably not the optimal choice for treating the frequently comorbid spectrum of anxiety and depressive disorders. Furthermore, although the benzodiazepines may reliably reduce anxiety in the short term, these drugs have significant drawbacks during extended therapy, most notably the risk of dependence and withdrawal syndrome during discontinuation.¹⁶

Treatment of social phobia has been less well studied than treatment of panic disorder. The SSRI paroxetine has been shown to reduce the fear and anticipatory anxiety associated with social phobia as well as to improve measures of disability. Whether paroxetine will exhibit the same robust efficacy in meeting the current goals for attaining long-term remission remains to be studied. However, as with panic disorder, an antidepressant agent that addresses both the anxious and depressive domains of social phobia appears to provide the best opportunity for achieving these goals. Whether agents with both serotonergic and noradrenergic activities such as venlafaxine XR will provide more frequent and more robust efficacy needs to be studied.

There are only a few studies of antidepressants in patients with GAD.¹⁶ Experimental data suggest that agents with both serotonergic and noradrenergic neurochemical effects may be ideally suited for the treatment of anxiety and comorbid depression.^{29–31} Recent studies assessing the effects of venlafaxine XR have shown robust efficacy in reducing the core feature of GAD (excessive worry) as well as the associated symptoms of depression and global anxiety. As a result, this agent was approved by the U.S. Food and Drug Administration for use in patients with GAD.^{23–25} At present, venlafaxine XR is recommended as first-line therapy in treating GAD, and it may have special efficacy in the comorbid anxious and depressed patient. This hypothesis was recently supported by results of a 12-week study comparing venlafaxine XR with the SSRI fluoxetine in treating comorbid anxiety and depression.²¹ In this study, response rates on the HAM-A, defined as a 50% reduction from baseline, were significantly greater in the venlafaxine XR-treated group than in the fluoxetine-treated group at week 12 ($p < .05$). Additional data are needed to provide further support for this potentially important concept.

Our global recommendation is that, as clinicians, we concentrate our efforts on achieving remission in as many patients as possible. The suggested goals for reductions in scores on the HAM-D (to ≤ 7) and HAM-A (to $\leq 7–10$) obviously need to be used flexibly in the context of overall patient populations. Individual patient goals may differ depending on factors such as baseline values, patient history, and the specific clinical milieu. Although not specifically addressed in the guidelines, augmentation therapy, for example buspirone in patients who do not respond to SSRI or TCA monotherapy, may play an important role in

achieving remission in a subset of patients.³² Additionally, switching to an agent with a different underlying mechanism of action, such as from an SSRI to an agent with dual neurotransmitter effects such as venlafaxine XR, an SNRI, may produce a more robust effect in some nonresponders or partial responders.

CONCLUSIONS

Optimal treatment across the spectrum of anxiety disorders commonly associated with depression has remained elusive. Previously developed guidelines have provided a firm base of recommendations for achieving a good response in the short term. Specific guidelines that focus on remission and the frequently observed concomitance of depression in all the anxiety disorders are needed. Therefore, the current guidelines have been developed with the goal of providing broader but specific measures of recovery applicable in panic disorder, social phobia, and GAD—specific for recovery and focusing on attaining full remission. Full remission is a crucial goal of pharmacologic and non-pharmacologic therapy alike, since it represents a clinical scenario in which the patient is completely free of symptoms or is only mildly symptomatic, fully functional, and essentially indistinguishable from healthy counterparts. Although challenging, these preliminary guidelines provide an opportunity for optimizing clinical care and should encourage the development and study of therapies with greater potency and wider effectiveness.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), clonazepam (Klonopin and others), fluoxetine (Prozac), paroxetine (Paxil), phenelzine (Nardil), venlafaxine XR (Effexor XR).

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