Introduction

Defining Remission in Patients Treated With Antidepressants

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Achieving complete remission, or a state of "wellness," should now be considered the standard of care in the pharmacotherapy of depression, anxiety, and comorbid depression with anxiety. Since these are complex syndromes, especially when complicated by comorbidities, effective measurement of remission is difficult.

In the mid-1950s and 1960s, there was much skepticism regarding the use of drugs to treat psychiatric disorders, and psychoanalytic therapies predominated the ambulatory care of depressed people. Subsequent placebo-controlled drug trials indicated that tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) could demonstrate significant efficacy versus placebo. However, the challenge then, as it is now, was to provide a framework to successfully define a beneficial response. When using continuous measures such as the Hamilton Rating Scale for Depression,[1] responses of 60% or 50% reduction in symptom scores generally became the norm.[2] More recently, epidemiologic studies[3] and more extensive experience conducting clinical trials showed that the original standard of attaining 50% improvement is insufficient, and subthreshold depressive symptoms that remain after therapy are still associated with dysfunction.[4,5] In addition, residual symptoms may increase the risk of developing further depressive episodes.[3]

It has become apparent that the level of residual symptoms is an important outcome of treatment.[6–8] Currently, few patients treated achieve and maintain the total symptom-free state of full recovery, defined as a remission sustained over 4 to 6 months.[9] The article by Dr. Nierenberg and Ms. Wright summarizes the importance of full remission as an appropriate treatment objective.

Dr. Ninan describes a complex view of the components of psychopathology in his article, "The Functional Anatomy, Neurochemistry, and Pharmacology of Anxiety." Instead of being considered separate entities as was believed in the past, anxiety and depression are syndromes with varying degrees of overlap of clinical symptoms and pathophysiologic processes. This view is derived from both population-based and clinical perspectives.[10] These distinct diagnostic categories are mechanistically linked through the interplay and homeostasis of biogenic amines such as norepinephrine and serotonin,[11,12] and alterations in serotonergic and noradrenergic systems have been documented in both disorders. In general, data from clinical trials and neurobiologic studies suggest that abnormalities in serotonin function may be predisposing to noradrenergic hyperactivity, which in turn correlates with the anxious components of anxiety and affective disorders. Conversely, abnormalities that lead to hypoactivity of the noradrenergic system correlate with depression. The interplay and synergisms between these systems have important implications for treatment.

We can define normality as the capacity to vary, choose, and control the emotional, behavioral, cognitive, and interpersonal responses to a given situation. Those choices, however, are limited by the underlying psychopathologic characteristics of anxiety and depression. Ultimately, these alterations give rise to the psychopathologic states of anxiety or depression, in which the brain can be viewed as "hijacking" normal functions and substituting distorted patterns that halt mental development and maturation.

Instead of merely resolving the somatic and psychic signs and symptoms of disease, therapies for anxiety and depression should be aimed at restoring the patient to wellness. Currently, the agents most widely used to treat depression or anxiety generally have minimal mechanistic and therapeutic overlap, even though a patient frequently has both depression and anxiety. The most commonly used agents today predominantly affect one neurotransmitter system, resulting in rebalancing only one aspect of neural transmission. These drugs include benzodiazepines, some TCAs, MAOIs, and selective serotonin reuptake inhibitors (SSRIs).[13,14] Newer agents such as venlafaxine extended release (XR) have a dual action, inhibiting serotonin and norepinephrine reuptake. Such agents modulate complex interactions between the systems believed responsible for anxiety and depression and have important implications

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for treatment. For example, it has been suggested that antidepressant efficacy may be enhanced by treatments that act at multiple receptors, which can be achieved through either combinations of drugs or the discovery and use of agents with dual mechanisms of action. Such approaches may be necessary to achieve the newer objective of complete remission and may be especially relevant in severe depression, with or without comorbidities.

Dr. Ninan's review summarizes the neuroanatomic, neurochemical, and neuroendocrine correlates of perturbations in neurotransmitter systems resulting in anxiety and the common scenario of comorbid depression. His review also explores the potential benefits of treatments that interact with these systems and have a novel spectrum of activity and degree of specificity.

Dr. Feighner's article continues to explore the emerging information linking anxiety and depression. Our understanding of the relationship between anxiety and depression traditionally has focused on the neurobiologic, clinical, and nosologic distinctiveness of these disorders. Newer concepts point to a continuum of disease presentation, with anxiety and depression being viewed as different phenotypic expressions that share a common underlying neurobiologic substrate.[15–17] In this model, situated in the middle is a newly defined category of mixed anxiety-depression characterized by subsyndromal, but chronic, symptoms of both disorders.[18] Because the activity of various neurotransmitter systems is intimately linked within the brain, changes in serotonergic neurotransmission may be accompanied by changes in the noradrenergic and other neurotransmitter systems.

Epidemiologic, longitudinal, and family history studies support a model that closely links anxiety and depression. Up to 95% of depressed patients experience symptoms of anxiety. In addition, the prevalence of specific comorbidities of major depressive disorder (MDD) and anxiety disorders is 58% in the United States. Anxiety states, in a similar fashion to generalized anxiety disorder (GAD), typically occur at an earlier age than MDD and usually precede the development of depressive states. Some investigators have hypothesized that GAD may actually be a prodrome for MDD, and the observation of clustering of anxiety and depression in families of affected patients supports this idea. Relatives of patients with comorbid anxiety and depression are twice as likely to have depression as relatives of patients with depression alone. Clearly, the evidence exhibits a link between anxiety, depression, and possibly other psychobiologic comorbidities.[19,20]

Despite these findings, several factors continue to confound our ability to more precisely define this relationship and raise important questions regarding the neurobiochemistry of these disorders. The benzodiazepines are effective in treating generalized anxiety and panic, at least in the short term, with a notable bias toward resolving the somatic manifestations of anxiety. In general, however, with the exception of alprazolam, these agents as a class are not effective as antidepressants when used alone, and in particular, benzodiazepines have minimal efficacy in improving the core symptoms of depression. Differing responses support the idea of differing underlying mechanisms. In addition, as the core diagnostic criteria for anxiety disorders become better defined, the validity of earlier studies wanes. For example, the core features of GAD have evolved considerably, with the current focus highlighting the chronicity of the disorder and the consistent presence of excessive worries or fears. Older studies of this disorder included patient populations that, today, may poorly represent those with the clinical disorder as currently defined. To better understand the relationship between anxiety and depression, it might be useful to review the anxiolytic effects of traditional antidepressants such as the TCAs and MAOIs, as well as the newer ones, such as the SSRIs, nefazodone, mirtazapine, and venlafaxine XR. The differential responses of patient subgroups to these agents could help to further map the neurochemistry of depression and anxiety.

The strong association between GAD and depression has clinical consequences, because patients with these disorders tend to have poorer prognoses. Clinical wisdom has suggested that antidepressants be a part of the treatment strategy for GAD. Despite this suggestion, traditional therapies for anxiety, such as the benzodiazepines and buspirone, have shown little efficacy in the treatment of depression. Conversely, antidepressants have a long history of use in the treatment of anxiety disorders. The potential use of one agent to treat either or both conditions may have important implications for improving outcomes and making GAD easier to treat, from both a patient and clinician perspective. This type of clinical improvement may help to achieve the desirable clinical endpoint of remission, or wellness.

Improving the treatment of GAD may be a particularly important objective in the primary care setting. A study by Lecrubier and Hergueta[21] found that general practitioners tend to underrecognize depression and overrecognize anxiety. As a consequence, depressed patients misdiagnosed with an anxiety disorder were treated more often with anxiolytics than with antidepressants, and only 13% of all depressed patients received antidepressant treatment. Further, treatment choices did not necessarily improve when the underlying psychiatric disorder was accurately identified. Of the 11.4% of patients with anxiety-depressive syndrome identified by primary care physicians, most were treated with anxiolytics. Thus, given the extraordinary overlap between GAD and depression and the challenges of treating the spectrum of their complex symptomatology, the effectiveness of one agent for both is an attractive concept.

Underrecognition, misdiagnosis, and inadequate treatment of GAD also significantly impact recovery rates.

Therapy initiated within the first 6 months of depression results in the highest rates of recovery, which steeply decline thereafter.[22] In contrast, substantially fewer patients (approximately 10%) with GAD recover within 6 months, and this rate barely approaches 40% at 5 years. Inadequate treatment may also play a significant role in the high relapse rates seen in patients treated for this disorder. The somatization of GAD likely contributes to the challenges of proper diagnosis and highlights the need for therapies that improve both the psychic and somatic manifestations of this disorder.

Clearly, a number of needs are unmet in the diagnosis and treatment of GAD among both primary care patients and those seen by specialists. As noted, agents such as the benzodiazepines and buspirone may alleviate anxiety, but they have little effect against the depression commonly occurring with this disorder. Treatment with antidepressants has opened a new arena of investigation in the treatment of GAD, and increasing evidence supports the role of pharmacotherapy with a dual mechanism of action.

Dual serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine XR have properties that make them effective treatment for depression while also treating comorbidities such as GAD. In contrast to the older tricyclics and related heterocyclic antidepressants, venlafaxine XR generally has a more favorable adverse effect profile and greater patient tolerability because it does not have affinity for the histamine and acetylcholine receptor sites.[23] Dr. Sheehan's review presents information regarding the use of venlafaxine XR in anxiety disorders and summarizes the recent double-blind, placebo-controlled clinical trials that highlight its substantial efficacy combined with a rapid onset of action, its dose-response characteristics, and its safety in this patient population.

Despite the necessity of achieving full remission in treated patients and the intensive investigation into the pathophysiologic course and treatment outcomes of patients with depression and anxiety, considerable confusion exists regarding two fundamental questions in clinical practice. Specifically, what can realistically be expected in terms of wellness for these patients with treatment, and how can we get as many patients as possible to this desired endpoint in the course of typical clinical practice? Dr. Ballenger's article reviews the clinical guidelines for achieving remission in patients with depression and anxiety.

Randomized controlled trials of pharmacologic and nonpharmacologic treatments for anxiety and depression generally do not evaluate remission, defined here as functional normality. These studies usually focus on short-term clinical symptom response rates. When the term *remission* is used, either in the published results of these trials or in clinical consensus guidelines, the definitions have varied widely in their consistency and specificity.[24–26] An additional challenge in extrapolating trial results of highly defined subgroups of patients into practical clinical guidelines is the considerable overlap between MDD and anxiety disorders such as panic disorder, social phobia, and GAD among both primary care and psychiatric outpatients. Most controlled studies of depression and anxiety as separate entities include only patients with one or the other—not both—and generally exclude patients with other psychiatric comorbidities and disorders.

Faced with these challenges in 1998, Ballenger, Rush, and colleagues[24–26] sought to develop guidelines for evaluating remission in depression, panic disorder, and social phobia. These guidelines recommend specific physician-rated evaluation tools and cutoff points that can be used in clinical practice or more easily translated into patient-rated scales. Because considerable overlap exists between symptomatology and clinical presentation of depression and anxiety disorders, the investigators considered it particularly useful to provide recommendations for outcome measures that incorporate a variety of symptomatologies. This effort was the goal, rather than looking at the core-defined symptoms of each of the 4 syndromes separately. The group believed this approach was more relevant to what is typically seen in clinical practice and possibly provides a better way to achieve the goal of true remission and freedom from relapse. The group concluded that, clearly, therapies must focus more on addressing the global aspects of the syndrome, including disparate domains and various symptomatologies, rather than resolving the core symptoms of the disease. Such a shift may make it more likely that individual patients will receive optimal care, rather than merely adequate care.

The largest database containing information on assessing remission is available for MDD. Ballenger, Rush, and colleagues[24–26] have extended findings from this area of research to provide additional information on treating comorbid depression in panic disorder and social phobia, areas in which the database has expanded significantly in recent years. With the most recent revisions to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), the criteria for identifying patients with GAD[12] have been refined considerably. In general, there are no published guidelines defining remission in patients with this disorder.

Hence, the participants of the Depression/Anxiety Working Group developed the current document to provide the first attempt at devising a practical measure of remission for GAD using depression as a working model. The overall objective of the Working Group—to develop rigorous definitions of remission—will provide clinicians an accurate concept of what to strive for in treating patients with depression and GAD to restore them to functional normality and wellness. Functional normality is defined as a state in which these patients cannot be distinguished from a person without the disorder. Striving for these results is an ambitious undertaking, and expectations

are that they can be achieved in only 50% or fewer of the patients typically seen in clinics. However, by providing aggressive goals, it is felt that the Working Group more appropriately focused efforts that ultimately most benefit the patients. Remission, rather than response, should be viewed as the ultimate goal of any therapy. It is hoped that these current guidelines defining remission will result in a renewed effort to improve therapy approaches that will achieve remission in an increasingly larger proportion of patients.

Drug names: alprazolam (Xanax and others), buspirone (BuSpar), mirtazapine (Remeron), nefazodone (Serzone), venlafaxine XR (Effexor XR).

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