Remission Versus Response: The New Gold Standard of Antidepressant Care

Martin B. Keller, M.D.

As descriptors for the clinical course and treatment of depressive illness, terms such as *response*, *remission*, and *recovery* have evolved with our understanding of the disease, yet have been inconsistently applied as measures of outcome in clinical trials. Indeed, a wide variety of definitions may be found in contemporary study reports. This article reviews the breadth of definitions, the ways in which they affect interpretation of clinical study data, and their relationship to clinical practice. Therapeutic experience over the past decade indicates that remission is the optimal outcome of treatment, and patients said to have remitted generally are considered to be well. By some standards, however, patients may be considered in remission despite harboring one or two minor symptoms. The presence of residual symptoms, like continued functional or social impairment, is considered a strong predictor of relapse or recurrence. Wellness thus must be determined by symptom level, functional status, and increasingly (as our understanding of brain neurophysiology grows), the nature of pathophysiologic changes. The various factors that may predispose patients toward or away from a state of sustained recovery also are reviewed, helping to inform a concept of remission more consistent with true wellness. Defining such a target can serve to sharpen the focus of therapeutic intervention in the clinical environment. This dynamic is reinforced via the integration of current best therapeutic thinking in research settings, leading to clinical trials that more closely approximate an ideal, remission-focused treatment regimen. *(J Clin Psychiatry 2004;65[suppl 4]:53–59)*

The terms *response*, *recurrence*, *remission*, and *recovery* have evolved as the study of novel treatment strategies and new therapeutic agents has informed the clinical management of major depressive disorder (MDD). The relatively recent concept of remission has become a focus of attention as the psychiatric community has come to understand MDD as a chronic condition akin to illnesses such as diabetes or hypertension. Remission, now regarded as the optimal treatment goal, implies wellness, although the variety of ways that remission is defined in the psychiatric literature suggests that the actual levels of well-being experienced by "remitted" patients may vary substantially. A study, for example, may characterize a patient as remitted based on an impairment level decrease, but is the patient experiencing wellness? In other chronic illnesses, the level of wellness is most accurately judged in terms of symptoms, functional status, and pathophysiologic changes. Lacking a reliable physical marker of depression, clinicians must judge wellness based on levels of symptoms and functional impairment, with the outcomes of such assessments driving the nature of therapeutic intervention.[1]

The primary endpoint of most treatment studies to date has been relief of symptoms to a lesser (response) or greater (remission) degree as determined by various measurement tools. These targets, however, often are not consistent with sustained wellness because as many as half of all responders do not achieve remission[2] and, despite growing evidence that more fully remitted patients stay healthier longer, those classified as remitted may not be entirely free of symptoms and/or psychosocial impairment. Furthermore, trial durations and sample sizes most often are based on regulatory requirements for demonstrating statistical superiority over placebo rather than on the treatment goal of a sustained symptom-free state. Functional status routinely is not addressed in studies. The

From the Department of Psychiatry and Human Behavior, Brown University, Providence, RI.

Presented at the symposium, "Pharmacologic Treatments of Major Depression: Are Two Mechanisms Really Better Than One?" which was held on February 10, 2003, New York, N.Y., and supported by an unrestricted educational grant from Forest Laboratories, Inc.

Dr. Keller has been a consultant for or received honoraria from Bristol-Myers Squibb, Collegium, Cypress Bioscience, Cyberonics, Eli Lilly, Forest Laboratories, Janssen, Merck, Organon, Otsuka, Pfizer, Pharmacia, Pharmastar, Sepracor, Vela Pharmaceuticals, and Wyeth; has received grant/research support from Forest, Merck, Organon, Pfizer, and Wyeth; and has served on the advisory boards of Bristol-Myers Squibb, Cephalon, Cyberonics, Cypress Bioscience, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Merck, Mitsubishi Pharma Corp., Novartis, Organon, Pfizer, Pharmacia, Sanofi-Synthelabo, Scirex, Sepracor, Somerset Pharmaceuticals, Vela Pharmaceuticals, and Wyeth.

The author thanks Laurance Macke, B.A., for editorial assistance.

Corresponding author and reprints: Martin B. Keller, M.D., Department of Psychiatry and Human Behavior, Brown University, 345 Blackstone Blvd., Providence, RI 02906 (e-mail: martin_keller@brown.edu).

ultimate goal of pharmacotherapy research is reduction of disease burden, and yet in many ways clinical trials bear little resemblance to clinical practice. As we become better informed regarding the nature and progression of depression, it may be that changes in the scope and focus of clinical trial design are warranted to better reflect current best thinking in the treatment of MDD.

TOWARD A STANDARD

Perhaps the most significant effort toward establishing standards for the description of depression treatment outcomes occurred with the 1991 publication[3] of a proposed set of definitions and operational criteria produced by the MacArthur Foundation Research Network on the Psychobiology of Depression task force. According to the recommendations, *response* and *partial remission* are terms describing a period during which an individual no longer meets syndromal criteria for the disorder but continues to evidence more than minimal symptoms. Response may be considered the point at which partial remission begins, and although the term *response* implies the precedence of treatment, partial remission also may occur spontaneously. Remission is defined as a relatively brief period during which an individual is asymptomatic or has one or two symptoms to a mild degree; treatment is not a requirement because remission can occur spontaneously. Relapse describes a return to a fully symptomatic state during remission and is considered a reemergence of the current episode. Remission lasting longer than briefly is considered recovery (from the episode but not necessarily the illness) and can be spontaneous.

The operational criteria consist of score ranges and time periods (severity and duration, respectively) to aid patient assessment via 3 commonly used symptom measurement tools: the 21-item Beck Depression Inventory (BDI), the 17-item Hamilton Rating Scale for Depression (HAM-D-17), and the Schedule for Affective Disorders and Schizophrenia (SADS). Based on the sum of clinical experience and disease progression theory to date, the definitions and criteria were established as a starting point to be evaluated and revised as appropriate through future research. Indeed, the variability of symptom measurement tools and associated time periods used for patient classification (e.g., under HAM-D-17 criteria, patients must be asymptomatic for at least 6 months to be considered recovered, whereas SADS criteria require a minimum of 8 weeks) indicates a lack of true validity of any definition or criterion. It may be that the greatest value of the recommendations has been heuristic, with language and rationale reinforcing that MDD and its treatment are best regarded in terms of chronic rather than acute care.

The influence of the proposal by the MacArthur Foundation task force on clinical trial design in the 1990s, however, appears to have been somewhat modest. Despite publication of the first practice guidelines advocating remission as the goal of treatment in 1993,[4] relatively few randomized controlled trials of antidepressant treatments have addressed remission.[5–16] More typically, studies have used response, partial response, and/or full response as the primary outcome(s), and, in part, these targets gained a foothold as researchers conducting long-term studies explored ways to characterize interim results. Operational criteria for response and partial remission were not identified by the MacArthur Foundation task force beyond the implied inclusion of patients judged to be neither asymptomatic nor fully symptomatic, although one measure that has evolved—at least a 50% decrease from baseline score on a standardized symptom measurement scale—is perhaps the most consistently applied of any depression outcomes criteria.

The relative paucity of data regarding remission may be attributed to the fact that much of the published data on a given medication often comes from pivotal studies leading to regulatory approval, which typically require safety and efficacy only in the short term. Broadening the pool of response data further are the published interim results of longer trials, although studies directed toward the long-term goal of sustained patient wellness remain a minority.

Remission accordingly has proven a more difficult concept on which to obtain consensus. Some ambiguity may be detected in the MacArthur Foundation task force definition, by which patients experiencing "minimal symptoms" could be considered in full remission and perhaps in recovery. Although valid based on the stated rationale that "no increase in the intensity of the treatment regimen is required" for such patients, numerous studies[17–29] since have indicated that the presence of residual symptoms leads to poorer outcomes. These findings suggest that study designs allowing residual symptoms in remitted patients also should segregate asymptomatic remitters into a separate category for analysis, as reviewed elsewhere.[1] The majority of study reports, however, ignore this distinction.

In addition to the imprecise way in which remission often is defined, there has been little progress toward establishing standard operational criteria for remission. The absence of consensus is particularly evident in a pooled analysis of studies comparing venlafaxine with various selective serotonin reuptake inhibitors (SSRIs).[30] Only 8 of the 20 known trials satisfied the analysis inclusion criteria, and each of these studies defined remission in a different way: HAM-D-17 ≤ 7, HAM-D-17 ≤ 10, HAM-D-21 ≤ 7, HAM-D-21 ≤ 8, HAM-D-21 ≤ 10, HAM-D-21 $\geq 50\%$ decrease, Montgomery-Asberg Depression Rating Scale ≤ 10, and HAM-D-17 ≤ 10 plus Clinical Global Impressions Scale = 1. Although the authors minimized bias by assessing all patient records based on the MacArthur Foundation task force criterion for remission (HAM-D-17 ≤ 7), the wide variety of operational criteria used in the individual trials reminds us that there is no true validity to any

measure and that progress toward a standard, at best, has been slow.

PREDICTORS OF OUTCOME

Although consensus on MDD remission criteria remains out of reach at this time, psychiatry has been successful in characterizing factors that lead to incomplete remission, as well as numerous other conditions that may dispose a given patient toward or away from a state of sustained wellness. Continued accumulation of such data informs better trial designs, treatments, and care and ultimately helps in the drive to understand remission more fully.

Length of major depressive episode is positively associated with the likelihood that a patient will experience residual symptoms.[17] This relationship is illustrated in Table 1, which divides study subjects who recovered from an episode either asymptomatic or with residual symptoms according to episode length (onset to recovery). Other signs of chronicity such as the presence of dysthymic disorder or double depression[31] also are predictive of incomplete remission, as are medical comorbidity, older age, Axis I or II comorbidity, greater severity, and inadequate treatment.[32]

The implications of residual symptoms and incomplete remissions are numerous, costly, and potentially severe. In comparisons of patients with and without residual symptoms, the presence of symptoms has been a strong predictor of early relapse[17,18,33,34] and shorter duration between depressive episodes.[17,18] Similar conclusions emerge from studies of partial versus full remission[26,27] or recovery,[35] in which patients experiencing partial remission or recovery were at significantly greater risk of suffering relapse compared with those who had fully remitted or recovered. Additional consequences of failing to achieve remission include worse prognosis of Axis III disorders, increased utilization of medical services, sustained elevation of suicide and substance abuse risks, and increased risk of developing treatment-resistant depression.[36,37]

Beyond potential influence on the course of depressive illness, lingering symptoms and partial remission often impede psychosocial and professional functioning to a significant degree. A survey of data from more than 20,000 adults[21] found that individuals with major depression and those with subsyndromal depressive symptoms experienced similar levels of impairment in multiple domains of functioning. In a comparison of patients before and after 12 weeks of antidepressant therapy,[38] those achieving full remission experienced significant improvement across all domains of functioning (overall psychosocial adjustment, quality of life, work functioning, interpersonal functioning, and physical health) compared with those classified as responders. Measures of work impairment for which partial remitters compare poorly with fully remitted subjects include absenteeism, decreased productivity, interpersonal friction, distress, lack of interest, and dissatisfaction in the workplace.[20]

Table 1. Characterization of Major Depressive Episode (MDE) Recovery Status by MDE Length[a]

Duration of MDE[b]	Residual Symptoms, % (N = 82)	Asymptomatic, % (N = 155)
0–6 mo	6.1	28.4
6–12 mo	18.3	21.9
1–2 y	31.7	26.4
> 2 y	43.9	23.2

[a]Data from Judd et al.[17]
[b]From onset to recovery.

Perhaps not surprisingly, psychosocial impairment is considered a risk factor for recurrence. In a study of 320 subjects who, at intake into the National Institute of Mental Health Collaborative Depression Study,[39] had presented with unipolar major depression and had recovered during naturalistic prospective follow-up, the risk of recurrence 6 months later was positively associated with degree of functional impairment. This dynamic was confirmed in a naturalistic prospective follow-up study of 290 patients who had recovered from unipolar major depression during a 15-year period: moderate to severe psychosocial impairment during a euthymic period resulted in a 3-fold increased risk of recurrence at the next assessment (i.e., 6 or 12 months later). History of recurrence also is considered indicative of future risk,[40–42] with probability and number of prior episodes sharing a positive association.[34,43]

Treatment data accumulated over the past couple of decades also reveal factors that lead typically to more positive outcomes. Several studies[44–46] suggest that patients who respond more quickly and fully to antidepressants are more likely to sustain treatment gains than are those whose improvements come more slowly and/or less completely. Although definitions of early response varied among trials, full response in the first few weeks of therapy generally predicted wellness throughout the continuation phase of treatment, whereas partial response in the acute phase was less likely to bode well for patients.

The ability to sustain a robust response to treatment also appears to be a strong predictor of continued wellness. Recent unpublished data suggest that patients who experience a 4-week asymptomatic period face a significantly lower risk of relapse (Lewis Judd, M.D., unpublished data, January 10, 2003).

Maintaining therapeutic response is the goal for those who engage in long-term maintenance antidepressant treatment, another group with an elevated chance of sustained wellness. In trials of continuation and maintenance therapies of varying lengths, subjects who responded to an antidepressant and maintained treatment at the full therapeutic dose were less likely to experience symptom reemergence than those who continued therapy at a lower

dose[47] or discontinued medication altogether.[48–58] A pair of studies[48,59] suggested that after 6 months of wellness the risk of recurrence is not significantly greater for patients who discontinue versus those on maintenance therapy, although one of these studies[48] also concluded that patients who have suffered multiple recurrences face an elevated risk of recurrence and therefore continue to benefit from maintenance therapy beyond the first 6 months. Furthermore, a 5-year trial showed that patients who discontinued therapy after 3 years were at increased risk for recurrence, and that those who continued therapy benefited from the prophylactic effects.[60]

The sum of findings on factors that dispose patients toward or away from wellness supports the value of striving for a remission free from symptoms and functional impairment. A more extensive exploration of the research that gives structure to the evolving concept of remission is reviewed elsewhere.[1]

BETTER TO BE BETTER

Judd et al.[17] have argued against the notion that MDD patients with one or two symptoms to a minor degree could be considered recovered or remitted, advocating instead that the existence of subthreshold depressive symptoms constitutes a clinically relevant state of illness activity based on the risks associated with residual symptoms. Furthermore, continuing failure to acknowledge the therapeutic validity of this disease state implies that treatment of major depressive episodes in clinical settings may stop short of guiding patients to fully asymptomatic status, inadvertently contributing to the risk of recurrence. These conclusions are indicative of the continuing evolution of remission as a therapeutic construct: new information emerges to chip away invalid assumptions, leading toward a concept that more accurately honors the relationship between disease progression and therapy.[1] Logical next steps include examining treatment practices and clinical trial designs through the lens of this new understanding and ensuring philosophical agreement.

Among the challenges inherent in updating MDD therapeutic practices is the discordance between much of the existing trial data, which informs commonly used clinical interventions, and the realities of treating a chronic, often recurrent disease to a sustained asymptomatic state. One limitation is the aforementioned disparity in the volume of short- versus long-term treatment data in the published literature. Another factor is the scarcity of studies employing aggressive dosing strategies. Trial goals most often include obtaining a response (e.g., ≥ 50% reduction in HAM-D score) and minimizing adverse events, which leaves little incentive to treat patients aggressively. Without data that can help guide aggressive dosing in everyday clinical settings, patients who otherwise could benefit from such a strategy may instead suffer the effects of undertreatment. Availability of data regarding the use of pharmacologic and psychotherapeutic adjuncts to antidepressant therapy similarly is lacking.

Increasing the Likelihood of Remission in Clinical Studies

Raising the profile of sustained asymptomatic remission as the ideal therapeutic outcome requires a greater emphasis on prospective studies geared toward full remission. Several areas of trial design, discussed below, may be manipulated to help achieve this end.

Outcome measurement. Lack of a reliable physical marker of MDD leads to reliance on a variety of symptom measurement tools to gauge treatment outcomes. A more comprehensive sense of patient wellness in trials may be obtained via increased integration of psychosocial and functional impairment assessments.[1] Such efforts will help researchers more accurately separate the patients that may be considered fully remitted from the ones that would be likely to benefit from further intervention.

Dose, trial length optimization. If the ideal treatment goal is sustained asymptomatic remission, then study protocols must be configured to allow subjects to achieve it. The ability to vary study dosages according to individual needs typically is limited, and some patients may benefit from a more aggressive approach than seen in most trials. Furthermore, the desire to achieve sustained wellness indicates the need for a greater focus on long-term trials than we have seen to date.

Antidepressant selection. The drive toward longer trials and therapeutic time frames depends on medications that remain effective and tolerable over the long term, as the use of such agents helps minimize obstacles to achieving and maintaining remission. Adding value have been studies of antidepressant switches in nonresponsive or intolerant patients,[61–63] offering clinicians options to consider when a given treatment fails. Further attention in these areas may serve to boost the proportion of patients who complete trials in a state of asymptomatic remission.

Adherence. Central to achieving and maintaining asymptomatic remission is adherence to therapeutic regimens in the short and long terms. Additional research on the influence of treatment compliance on outcomes is warranted, both as a means of better understanding this relationship and to help raise the profile of adherence as a vital component of patient wellness.

Pharmacologic adjuncts. Combination therapy for MDD is not uncommon in clinical settings, although few studies are available to guide the practice. A variety of evidence suggests that MDD is a heterogeneous condition, perhaps with multiple etiologies, and some patients may respond better and/or more quickly with a combination of agents. Greater testing of these regimens therefore could lead to improved outcomes for patients who otherwise may not have been able to achieve asymptomatic remission.

Integration of psychotherapy. Psychotherapy has proven effective for the acute treatment of depressive episodes,[64] but few studies have assessed its prophylactic value over the long term. There is, however, compelling evidence[65–67] supporting the combination of psychotherapy and pharmacotherapy for depressed patients, including the elderly[67] and those with chronic depression,[65] both of whom face elevated recurrence risk. Although one of these trials tested combination treatment over a 3-year period,[67] few other studies have examined this approach in long-term recurrence prevention. Further trials are required to better characterize the role of psychotherapy in achieving and sustaining asymptomatic remission.

Increasing the Likelihood of Remission in Clinical Settings

Although an increase in research directed toward sustained asymptomatic remission ultimately will help improve treatment practices in clinical settings, there also are a number of strategies[4] clinicians may employ to enhance consistency between therapeutic regimens and current best thinking.

Acute, continuation, and maintenance phases. Conceptualization of the 3-phase approach to MDD treatment[68] occurred in concert with the work that led to the MacArthur Foundation task force recommendations,[3] although evidence regarding the undertreatment of depression[36] suggests that translation of theory into practice may be occurring at a rather conservative pace. Attention to acute, continuation, and maintenance phases of treatment honors the progression of therapeutic milestones (obtaining response, preventing relapse, preventing recurrence), lending structure to patient care and reinforcing the value of sustained patient wellness.

Antidepressant selection. As noted previously, the chronic, recurrent nature of MDD suggests that long-term treatment is indicated for many patients, and so tolerability over extended periods is a central consideration during antidepressant selection. At least as important is choosing medications that are safe in overdose.

Outcome measurement. Structured and consistent measurement of symptomatic and functional statuses allows clinicians to track patient progress with some degree of accuracy and provides meaningful data on which to base treatment decisions. Guiding patients to a symptom-free state is good; also attaining complete absence of functional impairment is better.[1]

Acute phase optimization. Previously cited evidence suggests that speed and completeness of response leads to more positive outcomes and that length of episode is positively associated with risk of recurrence. Accordingly, clinicians should strive to obtain complete symptom resolution during the acute phase. Using acute phase visits to address tactical issues (e.g., dosing, compliance, integration of psychotherapy) helps support a rigorous treatment approach and frees continuation and maintenance phases for consolidation of response.

Future Directions

Comprehensive assessment of patient wellness in the context of chronic disease requires consideration of symptoms, functional impairment, and pathophysiologic changes. Although we can guide most patients with MDD to a fully remitted state by focusing on the first two of these dimensions, our understanding of the latter remains in its infancy. As such, it is not entirely inaccurate to characterize treatment methodology as educated guesswork, albeit guesswork that relieves a great deal of suffering while continuing to evolve and improve.

A more scientific understanding of MDD is a primary target of neurobiological research into mood disorders, which continues to expand in step with advances in technology, theory, and practice. Attention has moved from neurotransmitter and receptor systems to gene expression and brain structure and function, a shift made possible with newer tools such as high-throughput genotyping via mass spectrometry, as well as a number of continually evolving neurologic imaging and modeling capabilities. Research on brain structure and function may yet be combined with genetic research to allow classification of genotypes by patterns of brain function.[69]

This fourth dimension of MDD assessment, genetic modifiers, would aid classification of patients into subgroups according to prognosis, ideal treatment approach, and/or any other factor that would assist the drive toward complete remission and recovery. Through the combination of targeted treatments with imaging and/or biological screens to scientifically assess the efficacy of interventions, a new standard of remission may emerge that surpasses the mere absence of symptoms and functional impairment to also encompass a truly disease-free state.[1]

CONCLUSION

Accurate definitions and optimal strategies associated with MDD treatment evolve with our understanding of disease etiology and progression, although the translation of these concepts into better clinical trials and therapeutic interventions is hampered by several factors. Evidence suggests that sustained asymptomatic remission is the ideal treatment outcome for depressed patients. The majority of published trial data, however, document acute response to antidepressant treatments. Increased emphasis on remission-focused trial design will facilitate popular acceptance of the conceptual shift. Clinicians can aid the transition by continuously working with patients toward a sustained remission that is defined by the absence of both symptoms and functional impairment. Such efforts will help reduce the burdens associated with depressive disorders.

Drug name: venlafaxine (Effexor).

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