

Key Words: affective disorders, clinical protocols, depression, depressive disorder, drug therapy, mental disorders, mood disorders, pharmacotherapy, remission induction

# Remission as the Critical Outcome of Depression Treatment

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*ABSTRACT* ~ Major depressive disorder is currently the fourth largest contributor to the worldwide burden of disease. Direct and indirect costs associated with depression place a significant burden on the health care system and society. Despite the development of new antidepressant medications, the management of patients with depression remains a therapeutic challenge. Obtaining a response in antidepressant therapy—commonly defined in clinical trials as an improvement of >50% from baseline total score of the Hamilton Rating Scale for Depression (HAM-D)—ensures little beyond a reduction from baseline in signs and symptoms. For example, incompletely remitted patients still experience psychosocial dysfunction and are at increased risk of relapse and recurrence. As in other diseases, the goal of treatment should be full remission rather than response, with full remission entailing complete resolution of symptoms and a full return to premorbid levels of functioning. Achieving and maintaining remission is ultimately the best pathway toward sustained recovery. Within this context, the relative benefits of various psychotherapeutic and pharmacological approaches to treatment are reexamined, taking into account issues such as design sensitivity and statistical power. Although results of individual studies are inconsistent, the findings of pooled and meta-analyses suggest that combinations of psychotherapy and pharmacotherapy, and selection of antidepressants with potent effects on both serotonergic and noradrenergic neurotransmission, will increase the likelihood of remission. *Psychopharmacology Bulletin*. 2002;36(suppl 3):12-25

## INTRODUCTION

Major depressive disorder (MDD) is a common and often disabling condition. Depression not only adversely affects the lives of millions of Americans today; its effects can also span generations. Virtually everyone in the United States knows someone who suffers from a depressive disorder; those born after 1940 have at least a 10% lifetime risk of suffering from recurrent depressive episodes.<sup>1</sup> Once thought of as a self-limiting condition, depression is now known to increase mortality and worsen the course of numerous general medical disorders.<sup>2</sup> In fact, the

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World Health Organization<sup>3</sup> has ranked MDD as the fourth greatest cause of global illness burden, as well as the leading cause of health-related disability, accounting for approximately 12% of total years of life lost to disability among all diseases. In the United States alone, depression costs tens of billions of dollars each year,<sup>4</sup> a toll likely to increase in the future. The costs of depression are amplified by the fact that only a minority of depressed people ever receive definitive treatment.<sup>5</sup> As there are no effective means of primary or secondary prevention, the best hope to lessen such sobering losses in human and economic capital is in the hands of the health care professionals who care for depressed people. Prompt and vigorous treatment of each depressive episode recognized in primary and mental health care settings is a goal that is both timely and feasible. This manuscript reviews the concept of remission as it relates to the definition, course, and treatment of depressive disorders.

#### GAUGING ILLNESS ACTIVITY: ASSESSMENT OF TREATMENT OUTCOMES

MDD and dysthymia are as heterogeneous pathophysiologically as they are clinically diverse. The same diagnosis may be used to describe conditions as disparate as a hypersomnolent, mood reactive, acute syndrome in a 19-year-old, and a delusional, sleepless state affecting an emaciated elder. It is obvious that these conditions must differ substantially with respect to central nervous system dysfunction. Moreover, there are not yet any reliable, inexpensive biological markers that can be used in practice to gauge either global illness activity or relevant dimensions of central nervous system dysfunction. Therefore, measures of symptom severity such as the Hamilton Rating Scale for Depression (HAM-D)<sup>6</sup> and the Beck Depression Inventory (BDI)<sup>7</sup> provide the best method to quantify syndromal severity.

The diagnostic criteria for a major depressive episode<sup>8</sup> specify that the syndrome involve the presence of at least five definite symptoms most every day (at least one of which must be either a depressed mood or pervasive loss of interest or pleasure). Each of these cardinal characteristics would warrant a score of 2 or more on the corresponding HAM-D or BDI item. Thus, a "floor" effect is observed on rating scales such that a score of 10 or more on the HAM-D or BDI should always be present with a positive diagnosis. In psychiatric practice, outpatients seeking treatment for depression typically manifest 6–8 signs or symptoms of at least moderate symptom intensity. As a result, the average score on the 17-item HAM-D at intake for a group of depressed outpatients generally ranges between 18 and 22 (Figure 1).<sup>9,10</sup> A standard deviation of about four points further defines this surprisingly normal distribution. Although not fully representative of the larger universe of depressed people (ie, our research projects did not include those with the mildest

episodes nor those suffering from significant medical or psychiatric comorbidity), the distribution of scores illustrates that it is improbable that someone with a HAM-D score of  $\leq 7$  would meet criteria for the diagnosis of MDD. Specifically, if the mean sample's HAM-D score was 20, there would be only a 1% chance that someone with a score of 7 (ie, three standard deviation units below the mean) would belong to this population.

Well-being is not synonymous with symptom-free. When we recruit healthy controls for research participation, for example, more than half have HAM-D scores greater than 0. The mean HAM-D score of a typical nondepressed control group ranges from 1 to 3, with a standard deviation of about 2. Because minor or subsyndromal depressive symptoms accompany most of the various emotional, situational, or physical problems that complicate human existence, even higher scores would be observed if the comparison group were broadened to include people with other psychiatric disorders, serious or chronic medical conditions, or substance abuse problems. Nevertheless, it is extremely unlikely for a nondepressed person to score more than 10 on the HAM-D.

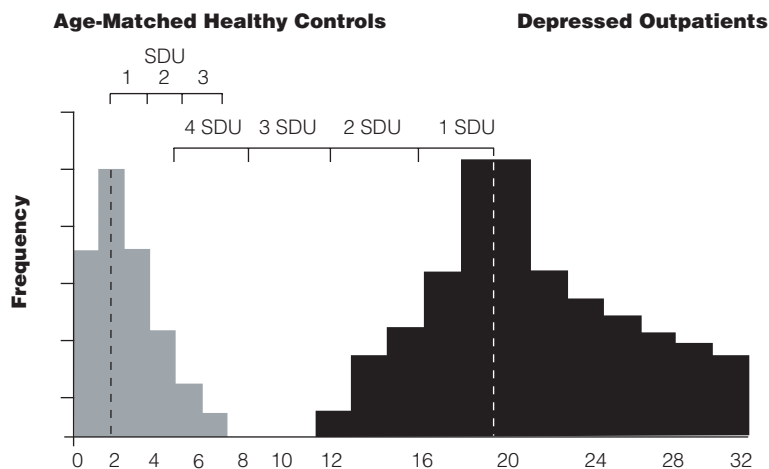
These typical symptom scoring patterns can be used as one means to gauge illness activity. For example, scores of  $\geq 25$  on the first 17 items of the HAM-D roughly correspond to the upper tertile of the score distribution for depressed outpatients and thus provide a useful operational

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FIGURE 1

HAM-D SEVERITY DISTRIBUTION FOR DEPRESSED OUTPATIENTS  
AND HEALTHY CONTROLS<sup>9,10</sup>



SDU=standard deviation unit.

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threshold of severe depression.<sup>9</sup> A score of  $\geq 30$  on the self-report BDI can be used for the same purpose. Alternatively, a 50% reduction of symptom severity on either measure approximates a 2–3 standard deviation unit decline. This, in statistical terms, is a large and meaningful effect and has evolved as a standard criterion for an adequate response in antidepressant treatment trials.<sup>11</sup> However, for patients scoring in the severe range on the BDI or HAM-D prior to treatment, a 50% symptom reduction as criterion for response may result in the designation of “responder” status among individuals who still manifest symptoms scoring in the range indicative of depression. The term *remission* was therefore chosen to define a higher grade of response (ie, a virtual absence of depressive symptoms).<sup>12</sup> Remission thus requires that the patient achieve a response and a low, absolute final score rather than merely a percentage change score. The data presented in Figure 1 can be used to empirically derive the point of greatest separation between the depressed and nondepressed score distributions; values of 6, 7, and 8 provide the best discrimination between depressed and well patients. This is consistent with the recommendation of a panel of mood disorders experts to define a clinically significant remission as a final HAM-D score of  $\leq 7$ .<sup>13</sup>

## NEUROBIOLOGY

When oncologists use the term remission, they are referring to a complete absence of illness activity (ie, no neoplastic cells) in addition to relief from the signs and symptoms of the malignancy. The pathophysiologic substrate of depression, however, is neither as well understood nor as readily characterized as that of various cancers, which renders the absence of disease activity criterion inapplicable (at least for the moment) to define remission of depression. There are, nevertheless, a number of neurobiological correlates of syndromal activity that have been associated with depressive states. These markers of depression can be divided into two conceptually useful categories: disturbances that manifest primarily during symptomatic exacerbations (ie, state-dependent markers) and abnormalities that persist long after remission (ie, state-independent markers).<sup>14</sup>

If one of the latter abnormalities is subsequently found to be present before the first lifetime depressive episode and among close biological relatives, it can be considered a trait marker. Trait markers, which are in all likelihood under genetic control, appear to be most relevant to vulnerability to the onset of illness and identifying at-risk populations.<sup>14</sup> One example of a trait-like abnormality is reduced latency to the onset of the first rapid eye movement period following sleep onset.<sup>14</sup> This well-replicated correlate of depressive vulnerability could result from

either the premature loss of deep, restorative sleep during the first 90 minutes of the night (ie, a passive process), or abnormally increased “pressure” to dream (ie, an active consequence of a disinhibited circuit between pontine and limbic structures).<sup>15</sup>

State-dependent markers are more likely to convey information about the pathophysiology of the acute depressive episode. The best-studied state-dependent biological correlate of severe depressive states is hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis.<sup>15,16</sup> Elevated HPA activity, which reflects either a dysregulation or disinhibition of one of the most basic mammalian stress response systems, can be indexed by measurement of cortisol concentrations in blood, urine, or saliva, by corticotropin-releasing hormone levels in cerebrospinal fluid, or by responses to a dynamic test of feedback inhibition such as the dexamethasone suppression test. Regardless of the parameter studied, between 20% and 60% of depressed patients manifest one or more signs of increased HPA activity.<sup>15,16</sup> Hypercortisolism is associated with high symptom severity, recurrent episodes, older age, marked psychomotor disturbance, and psychosis.<sup>15</sup> Consistent with the expected behavior of an index of state-dependent abnormality, HPA hyperactivity generally normalizes with effective treatment. Longitudinal studies indicate that persistently elevated HPA activity despite symptomatic improvement conveys an increased risk of relapse, even when there is ongoing treatment.<sup>15</sup>

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**SOCIAL AND VOCATIONAL FUNCTIONING**

The consequences of untreated or inadequately treated depression extend beyond the individual. The direct and indirect costs of depression are staggering, with a societal burden that is greater than that imposed by other chronic medical conditions, including hypertension, rheumatoid arthritis, asthma, and osteoporosis.<sup>17</sup> As stated, depression is often a disabling condition associated with chronic and pervasive psychosocial and occupational dysfunction.<sup>18-21</sup> Moreover, patients who fail to achieve full remission of symptoms continue to suffer impairment in these domains, underscoring the importance of prompt and aggressive treatment.

Extrapolating from the work of Greenberg and colleagues,<sup>4</sup> depression affects the United States economy at a cost of about \$50 billion per year (adjusted to 2002 dollars). Most of this loss in economic capital is attributable to early death, absenteeism, and diminished productivity in the workplace. This does not take into account the measurable costs of underutilized human capital (eg, incomplete education, underemployment, early retirement, or failure to advance in the workplace), the immeasurable costs of suffering, and the “rippling” effect of depression within families and across generations. For example, the impact of a

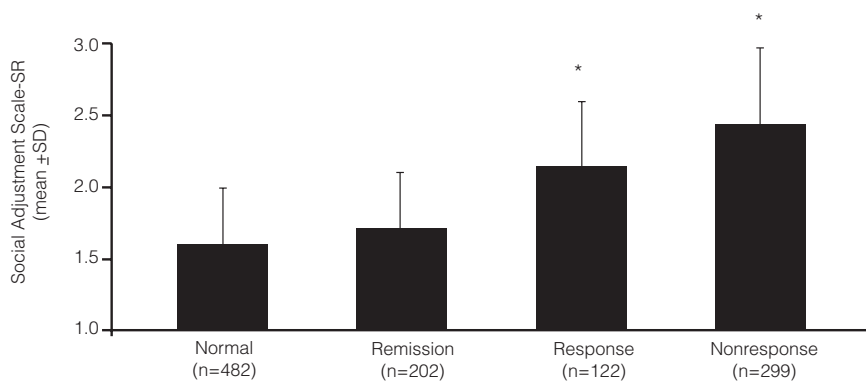
depressed parent can be seen on the well-being of his or her children,<sup>21</sup> as well as on the spouse.<sup>23</sup> As treatment represented only about 30% of the costs calculated by Greenberg and colleagues,<sup>4</sup> it is highly plausible that provision of “high-quality” therapy to those who currently receive either minimal or no care would virtually pay for itself.

Mintz and colleagues<sup>18</sup> examined the effects of treatment on vocational functioning. They found that improvements in vocational functioning lagged behind symptom reduction. Moreover, unless there was a marked degree of improvement in symptom status (ie, remission), vocational functioning did not normalize.

Miller and colleagues<sup>19</sup> examined the relationship between the quality of treatment response and the magnitude of recovery of psychosocial functioning. This study involved a large group of people with long-standing depressive syndromes treated in a standardized protocol across 12 weeks with either imipramine or sertraline. Miller and colleagues<sup>19</sup> found that only patients who had achieved a complete remission of depressive symptoms experienced a virtual normalization of social functioning (Figure 2). By contrast, incompletely remitted patients were much closer in functioning to the treatment nonresponders than to the healthy comparison group.

These findings are further supported by recent data from a study by Judd and colleagues,<sup>20</sup> who examined social and occupational disability during the long-term course of MDD. Functional impairment (ie, disability related to work/employment, social relationships, and overall

FIGURE 2

SOCIAL ADJUSTMENT NORMALIZES WITH REMISSION<sup>19</sup>

\* Significantly different from normal controls and remission groups.

SR=self report.

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psychosocial function) among patients from the National Institute of Mental Health Collaborative Depression Study was assessed monthly during an average of 10 years of follow-up. Results showed that the presence of even a few depressive symptoms was associated with significantly greater psychosocial disability compared with time periods when the same patients were in full remission.

Hirschfeld and colleagues<sup>21</sup> subsequently studied the effects of treatment with nefazodone or a form of cognitive-behavioral therapy, both singly and in combination, in a randomized 12-week treatment trial involving more than 600 chronically depressed outpatients. They found that not only did the group receiving both psychotherapy and pharmacotherapy experience significantly greater improvements in social functioning, but the benefits of combined treatment were not fully explained by a greater degree of symptomatic measures. Again, social functioning in fully remitted patients had essentially normalized after only 12 weeks of treatment, whereas partially remitted patients continued to experience significant psychosocial impairment.

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### GENERAL MEDICAL CONDITIONS

On average, depressed patients use health care services three times as often and make seven times more emergency room visits than nondepressed patients.<sup>24,25</sup> Medical costs for the average depressed patient are double those for the average nondepressed person.<sup>26,27</sup> Moreover, when depression is accompanied by certain nonpsychiatric medical conditions, the outcome of these concurrent medical disorders is likely to be worsened. The presence of depression—and, by extrapolation, sustained depressive symptoms in patients who do not achieve remission—is associated with increased morbidity and mortality of many general medical conditions.

Major depression has been shown to increase 6-month mortality after myocardial infarction.<sup>28</sup> A subsequent study by Penninx and colleagues<sup>29</sup> demonstrated that the presence of major or minor depression increased the risk of cardiac mortality, even among subjects without preexisting cardiac disease. Similarly, recent studies have confirmed that the presence of major depression or depressive symptoms is associated with increased morbidity and mortality in patients with congestive heart failure.<sup>30,31</sup>

The odds and prevalence of depression are substantially greater in patients with type 1 or type 2 diabetes than in nondiabetic individuals<sup>32</sup> and may even be a risk factor for its onset.<sup>33</sup> Not surprisingly, there is a growing body of evidence demonstrating that the presence of depression or depressive symptoms is linked to poor glycemic control,<sup>34</sup> diminished adherence to dietary and medication regimens,<sup>35</sup> and long-

term diabetic complications.<sup>36</sup> Comorbid depression also has been associated with increased health care use and expenditures among patients with diabetes.<sup>37</sup>

The presence of depression at admission has been shown to increase the risk of 1-year mortality by approximately 60% among nursing home residents,<sup>38</sup> and it may worsen outcomes after stroke<sup>39</sup> and among patients with cancer and acquired immunodeficiency syndrome.<sup>40</sup> Given the association of depressive symptoms with the outcomes of these conditions, it is not unreasonable to presume that improved treatment of depression might result in improvements in their overall prognosis.

### LONGITUDINAL COURSE

It is now certain that incomplete remission of a depressive episode has ominous prognostic implications. Whether observed following psychotherapy,<sup>41</sup> during continuation pharmacotherapy,<sup>42</sup> or across 10 years of prospective naturalistic follow-up,<sup>43</sup> incompletely remitted patients are at significantly greater risk of relapse and recurrence. As illustrated in Figure 3, incompletely remitted patients generally have two to three times higher relapse/recurrence rates than patients who are fully remitted, regardless of the duration of follow-up.

In a prospective follow-up study of patients who had responded to cognitive behavior therapy, Thase and colleagues<sup>41</sup> found that outcome at the end of 1 year after termination of therapy differed dramatically (ie, a minimal risk of relapse versus no better than a 50:50 chance of staying well), depending on the duration and quality of remission. Specifically, patients who had not achieved a HAM-D score of  $\leq 7$  by week 10 of therapy were at significantly higher risk for relapse compared with patients who had remitted (52% versus 9%, respectively). Increased risk of relapse following cognitive therapy also was associated with high levels of dysfunctional attitudes,<sup>41</sup> a self-report measure of negative reactivity that may reflect the process by which an incompletely remitted patient may amplify cognitive and affective responses to new adversities.

Paykel and colleagues<sup>42</sup> subsequently evaluated the impact of residual symptoms on relapse in a longitudinal, naturalistic follow-up study of depressed inpatients and outpatients. Patients were selected consecutively from treatment facilities in the United Kingdom, treated with usual care by their physicians, and followed for up to 15 months. Failure to achieve remission (ie, score of  $\leq 7$  on the 17-item HAM-D) was a strong predictor of subsequent early relapse: patients with residual symptoms (score of  $\geq 8$  on the 17-item HAM-D) had a threefold greater risk of relapse compared with patients classified as full remitters.



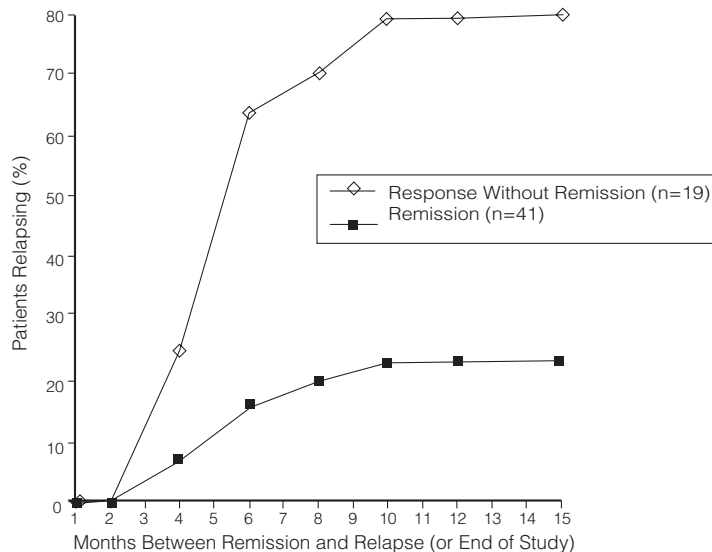
Recent data from Judd and colleagues<sup>42</sup> has provided compelling evidence suggesting that treatment to remission early in the course of MDD is imperative. The long-term course following a first lifetime major depressive episode was evaluated in a prospective, naturalistic follow-up study (mean duration of follow-up was approximately 10 years). Compared with patients who achieved full remission of symptoms following their first depressive episode, patients with residual depressive symptoms had a significantly greater risk of relapse or recurrence and experienced the onset of the next major depressive episode more than three times faster. Moreover, failure to achieve remission of the first depressive episode appeared to herald a more serious and chronic course of disease. Specifically, patients with residual symptoms experienced more depressive episodes, a greater number of chronic depressive episodes (ie, duration of more than 2 years), significantly shorter durations of wellness between episodes, and fewer weeks free of depressive symptoms. This finding that long-term chronicity can be predicted from the outcome of even the first depressive episode underscores the validity of remission as the critical endpoint of treatment.

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FIGURE 3

#### INCREASE IN RISK OF RELAPSE DURING CONTINUATION PHARMACOTHERAPY DUE TO INCOMPLETE REMISSION\*



\* Incomplete remission was defined as a score  $\geq 7$  on the Hamilton Rating Scale for Depression.

Source: Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med.* 1995;25:1171-1180.

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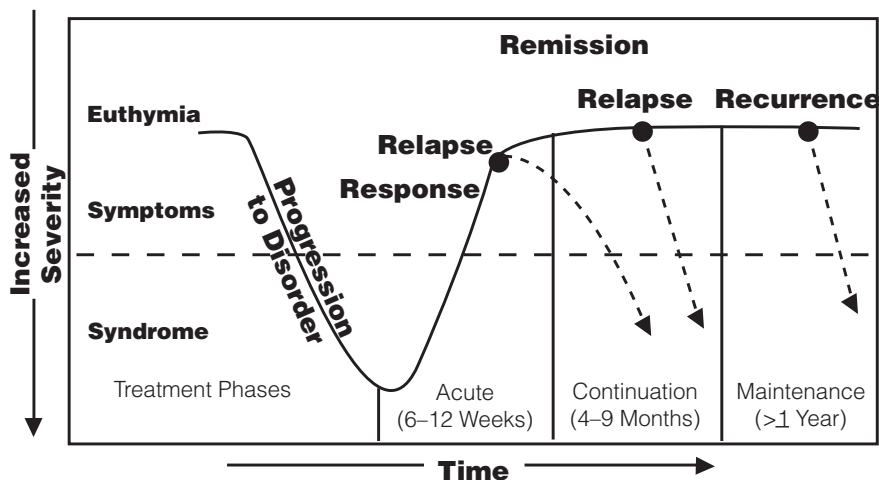
## THERAPEUTIC IMPLICATIONS

Kupfer<sup>44</sup> has proposed matching the course of a prototypic depressive episode with corresponding phases of antidepressant treatment (Figure 4). An initial or acute phase of treatment was suggested to correspond to the weeks or months of therapy needed to obtain an acceptable treatment response. A second or continuation phase was recommended to cover the transition from response to remission and the consolidation of remission into recovery. The continuation phase usually lasts 4–9 months. As approximately 40% to 60% of responders have been shown to relapse following premature discontinuation of antidepressants, continuation-phase pharmacotherapy is now recommended for virtually all patients.<sup>12,45</sup> Given recent evidence that incompletely remitted patients have a higher risk of relapse despite continued antidepressant therapy,<sup>46,47</sup> it has been suggested that the start of the continuation phase be delayed until full remission is obtained. A third indefinite, and perhaps even lifelong, course of maintenance-phase therapy was recommended to prevent recurrences in those who had already experienced three or more episodes of depression.

Incomplete remission should be viewed as a “red flag” during any of the phases of treatment. The treatment regimen should be adjusted, revised, or modified until full remission is achieved, with consideration

FIGURE 4

### MATCHING OUTCOMES TO PHASES OF DEPRESSION TREATMENT: THE FIVE RS



Source: Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry*. 1991;52(suppl 5):28-34.

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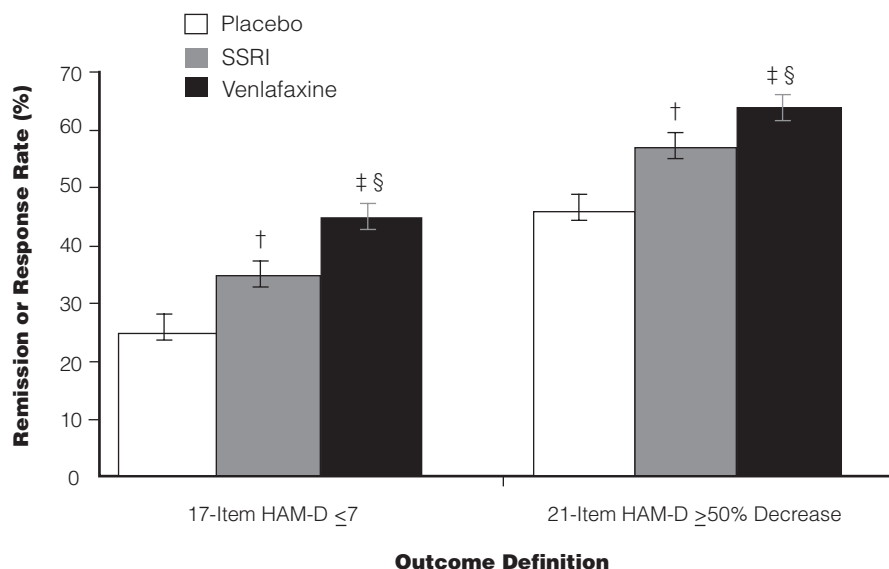
given to side effects, cost and feasibility of various treatment options, and careful reappraisal of therapeutic goals. One possibility is to add psychotherapy to ongoing antidepressant treatment, explicitly targeting the unremitted or residual symptoms. Fava and colleagues,<sup>46</sup> for example, used a time-limited course of cognitive behavior therapy to convert partially remitted antidepressant responders to full remission and observed a sustained benefit across 6 years of follow-up. Paykel and colleagues<sup>47</sup> subsequently replicated this finding in a larger two-center study of incompletely remitted antidepressant responders. In this study, 45% of the patients who did not receive psychotherapy fully relapsed within 1 year despite continuation-phase pharmacotherapy, as compared with only 29% in the group receiving combination therapy.

One of the most favored up-front strategies to increase the likelihood of remission is combining psychotherapy and pharmacotherapy.<sup>48</sup>

FIGURE 5

#### FINAL ON-THERAPY OUTCOMES (MEAN 95% CI) WITH REMISSION AND RESPONSE CRITERIA\*

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\*The relative advantage was 1.28 to 1.00 using the remission (strict) definition, but only 1.12 to 1.00 using the response (liberal) definition.

†  $P < .001$  SSRI versus placebo.

‡  $P < .001$  venlafaxine versus SSRI.

§  $P < .001$  venlafaxine versus placebo.

SSRI=selective serotonin reuptake inhibitor; HAM-D=Hamilton Rating Scale for Depression.

Adapted from: Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.

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Although many early studies failed to detect a significant advantage when compared with well-executed monotherapies,<sup>49</sup> several recent reports have demonstrated large additive effects among patients with severe recurrent<sup>50</sup> or chronic<sup>51</sup> forms of depression. When cost containment is a consideration, the combination can be reserved for patients most likely to show additive benefit.

Another strategy to increase the likelihood of remission concerns the initial choice of antidepressant medications. Traditionally, antidepressants approved by the Food and Drug Administration were considered to be equally effective across unselected groups of patients.<sup>12,48</sup> However, more recent data suggest that when compared with tricyclic antidepressants, the selective serotonin reuptake inhibitors (SSRIs) may have a modest yet significant advantage for depressed premenopausal women,<sup>52</sup> whereas amitriptyline and clomipramine may be more effective than the SSRIs, in severely depressed inpatients.<sup>53</sup>

In other recent studies, venlafaxine, a dual-acting agent that inhibits both serotonin and norepinephrine at moderate doses, has been shown to have an advantage over SSRIs in terms of symptomatic response<sup>54</sup> and remission rates.<sup>55</sup> These findings illustrate the utility of meta-analytic strategies to make finely calibrated distinctions between good and potentially better treatments.<sup>56</sup> Moreover, as illustrated in Figure 5, use of the more stringent remission criteria permitted a more reliable (ie, powerful) separation between venlafaxine, the SSRIs, and placebo.

## CONCLUSION

The manifold and potentially tragic consequences of depression are only mitigated when patients are treated to full and sustained remission. For this reason alone, remission is the unambiguously certain goal of acute-phase therapy whenever possible. Prompt recognition and vigorous treatment of all depressive episodes are thus among the highest public health priorities. Several different treatment strategies may increase the likelihood of achieving or sustaining remission. ❖

## ACKNOWLEDGMENT

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