Evaluating Antidepressant Therapies: Remission as the Optimal Outcome

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Depression is the fourth-largest contributor to the global burden of disease, and it causes profound suffering and extreme costs to health care systems and society. Although there have been many new antidepressants introduced, few depressed individuals receive the optimal treatment. One problem is that the traditional definition of response to antidepressant therapy, i.e., a 50% improvement in symptoms, ensures little beyond a reduction of syndromal intensity. Responders who have persistent depressive symptoms experience ongoing psychosocial dysfunction, poorer health, and an increased risk of relapse. The goal of the first or acute-phase treatment should be complete remission of symptoms *and* a full return to premorbid levels of functioning. Remission is also a necessary, transitional state toward sustained recovery. Within this context, evidence pertaining to various treatment approaches is reexamined, taking into account critical methodological issues such as design sensitivity and statistical power. Whereas results of individual studies are inconsistent, the findings of meta-analyses (i.e., quantitative and pooled) suggest that both psychotherapy-pharmacotherapy combinations and use of antidepressants that enhance serotonergic *and* noradrenergic neurotransmission increase the likelihood of remission. *(J Clin Psychiatry 2003;64[suppl 13]:18–25)*

Major depressive disorder is a common, potentially disabling condition that is ranked by the World Health Organization as the fourth-greatest cause of global illness burden.[1] In fact, depression is the leading cause of health-related disability among industrialized nations and accounts for about 12% of all years lost to disability.[1] Depression costs the economy of the United States tens of billions of dollars each year, largely due to absenteeism, prolonged disability, and premature loss of life.[2] Such dramatic costs and losses persist because only a minority of depressed individuals receive definitive treatment.[3] The best way to reduce the tragic consequences of depression is for health care professionals to recognize each time that someone suffering from a depressive episode presents to their clinics and to provide vigorous, definitive treatment whenever possible. These goals of timely and definitive treatment are both feasible and would result in dramatic improvements in patient outcomes. In this article, the impact of depression will be reviewed and the significant benefits that result from treatment to remission are highlighted.

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This work is supported by an educational grant from Eli Lilly and Company and by MH-30915 (Mental Health Intervention Research Center, Western Psychiatric Insititue and Clinic, Pittsburgh, Pa.; David J. Kupfer, M.D., Principal Investigator).

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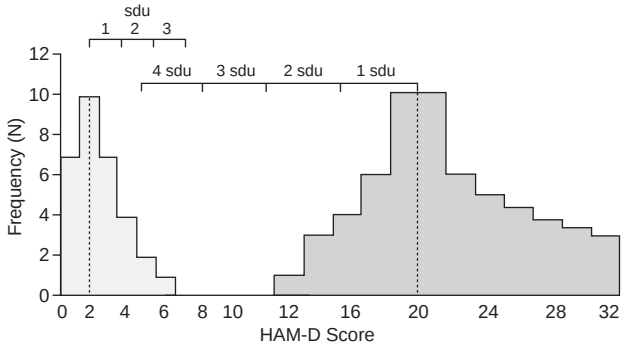
ASSESSING ILLNESS ACTIVITY AND MEASURING TREATMENT OUTCOMES

Depressive disorders are both clinically and pathophysiologically heterogeneous. The current DSM criteria are so broad that the same diagnosis can be used to describe conditions as diverse as a chronic hypersomnolent and mood reactive syndrome that complicates the college transition of a teenager and an elder's fulminant psychotic depressive state. Marked differences in central nervous system function must parallel such differences in clinical presentations.[4] Unfortunately, there are no valid yet inexpensive biological markers that can be used to gauge relevant dimensions of neurobiological disturbance associated with depression. Clinical evaluations such as the Hamilton Rating Scale for Depression (HAM-D)[5] or self-report measures such as the Beck Depression Inventory (BDI)[6] therefore continue to provide the most reliable methods to monitor syndromal activity.

A major depressive episode is defined in DSM-IV by the presence of either a depressed mood or pervasive loss of interest or pleasure and at least 4 other definite symptoms that occur "most every day." There are no truly cardinal symptoms of depression, and it is the syndromal quality of this constellation of signs and symptoms that helps to define the episode. In terms of assessing illness activity,

Figure 1. HAM-D Severity Distribution for Healthy Controls (lighter shade) and Depressed Outpatients (darker shade)[a]



[a]Reprinted from Thase et al.,[7] with permission.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, sdu = standard deviation unit.

any positive symptom criterion would qualify for a score of 2 or more on the corresponding HAM-D or BDI item. Thus, someone experiencing a major depressive episode should score a 10 or more on the HAM-D or BDI. Most depressed individuals have additional associated symptoms, such as anxiety and somatic symptoms, as well as a plethora of negative cognitions (about self, world, and future) that add to global severity. As a result, the average 17-item HAM-D score of a group of depressed patients seeking outpatient care typically ranges between 18 and 22 (Figure 1).[7] The relatively normal distribution of scores (with a standard deviation of about 4 points) illustrates that it is extremely unlikely that someone with a HAM-D score of 7 or less would meet criteria for a major depressive disorder. Specifically, a score of 7 is at least 3 standard deviation units below the mean, which conveys >99% certainty that the person does not "belong" to the depressed group. Scores on the BDI are typically about 10% to 20% higher than those observed on the HAM-D, but can be used for the same purpose.

Most nondepressed, "healthy" individuals score between 1 and 3 points on the HAM-D, resulting in both a mean and a standard deviation of about 2 points. Therefore, someone who scores 8 or more (i.e., 3 standard deviation units above the mean) has less than a 1% chance of being "well." Using the data displayed in Figure 1 to identify the optimal point of clarity between well and ill populations, HAM-D scores of 6, 7, or 8 provide the best "cutting points."

Symptom scoring patterns also are used to define categorical levels of illness activity. A score of 25 and higher on the HAM-D is, for example, used as an operational threshold of severe depression.[8] On the BDI, a score of 30 or above serves the same purpose.[8] HAM-D scores of 12 to 18 and 19 to 24 likewise could be used to define milder and moderately severe groups, respectively.

With respect to treatment outcomes, a 50% reduction in symptom severity on the HAM-D, BDI, or the Montgomery-Asberg Depression Rating Scale (MADRS) typically represents a decline of 2 to 3 standard deviation units. These are large and meaningful effects, and response (so defined) has proven satisfactory for distinguishing drug and placebo responses in antidepressant treatment trials.[9] However, a percentage change score does not ensure that a "responder" no longer meets criteria for a major depressive episode, particularly if the patient was severely depressed before treatment. A definition of a higher grade of response thus was needed to make the finer-grained distinction between "better" and "well." Depression researchers borrowed the term *remission* from oncology to describe this qualitatively different, more complete or higher grade of response.[10] Remission is when the responder has virtually no depressive symptoms (i.e., is now indistinguishable from someone who has never been depressed). Drawing again upon the data presented in Figure 1, a HAM-D score of ≤ 7 "fits" the remission construct. This empirically derived threshold almost perfectly matches the consensus recommendation of a panel of mood disorders experts.[11] Scores below the 10 to 12 range on the MADRS can be similarly used to define remission.[12]

ILLNESS ACTIVITY AND CENTRAL NERVOUS SYSTEM DYSFUNCTION

An oncologist uses the term *remission* to describe a complete absence of illness activity (i.e., no neoplastic cells). However, the pathophysiologic substrate of depression is not well characterized enough to permit use of such an "absence of disease activity" criterion. Yet, there is evidence of various neurobiological correlates of illness activity in depressive states, and these "markers" can be divided into 2 conceptually useful categories: state-dependent and state-independent.[4,13] As the name implies, state-independent markers are present whether or not the disease process is active. State-independent abnormalities may be either sequelae or scars of the illness, or they may occur before the onset of illness and among close biological relatives. The latter abnormalities, which are presumed to be under genetic control, are relevant to processes that convey illness and can be used to identify "at risk" groups.[13]

The best-studied examples of trait-like abnormalities associated with depression are a trio of interrelated disturbances that occur during the first 90 minutes of sleep: decreased slow wave (deep) sleep, blunted growth hormone secretion, and reduced latency to the onset of the first period of rapid eye movement (REM) sleep.[4,13] These well-replicated correlates of depressive vulnerability could result from either the premature loss of the inhibitory processes that facilitate restorative sleep (i.e., a "passive" pro-

cess) or excessive nocturnal arousal (i.e., an active phenomenon provoked by increased activity between pontine and limbic structures).[4]

State-dependent markers, in contrast, are present only during episodes of illness. They thus may reveal critical information about the pathophysiology of the depressive episode. The best-documented state-dependent correlate of depression is hypercortisolism, which results from increased activity of the hypothalamic-pituitary-adrenocortical (HPA) axis.[4,14–16] This abnormality may be viewed as an exaggerated and sustained variant of a normal mammalian response to severe stress. Increased HPA activity can be detected by measuring either cortisol concentrations in blood, urine, or saliva or corticotropin-releasing hormone (CRH) levels in cerebrospinal fluid.[4,14–16] Several tests of feedback inhibition, such as the dexamethasone suppression test (DST) and the combined CRH-DST challenge test, are used to study dynamic aspects of HPA axis regulation.

Depending on the measure used and the patient population studied, 20% to 60% of depressed patients have increased HPA activity.[4,14,15] Hypercortisolism is more common among older patients with recurrent depression, especially those with high symptom severity, marked psychomotor disturbance, or psychosis.[15] Sustained hypercortisolism also has been shown to have neurotoxic effects in animal studies and may be implicated in hippocampal atrophy associated with depression.[16] Although HPA hyperactivity usually normalizes with effective treatment, persistently elevated glucocorticoid levels have been associated with increased risk of relapse.[15]

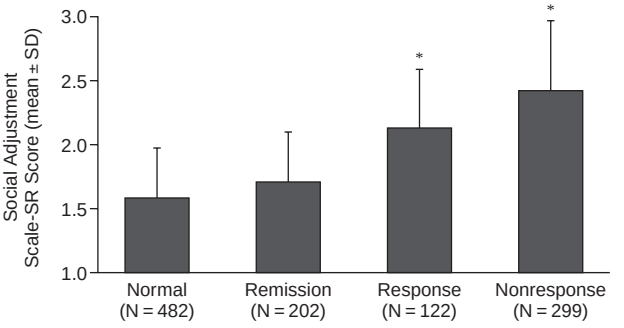
To date, no biological test has proven accurate enough to be used in clinical practice as a marker of depressive disorder. This partly reflects the heterogeneity of depressive disorders and the greater difficulty of studying functional abnormalities within the central nervous system as compared to cardiovascular, renal, or hematologic processes.

SOCIAL AND VOCATIONAL FUNCTIONING

Depression causes a greater negative impact on overall well-being than most general medical conditions, including hypertension, diabetes, rheumatoid arthritis, asthma, and osteoporosis.[17] Left untreated, depression ultimately causes pervasive psychosocial and occupational dysfunction.[18–23] Even patients who receive treatment continue to suffer impairment in these domains unless they achieve full remission of symptoms.[19] This underscores the importance of prompt, vigorous treatment.

As noted earlier, depression causes staggering losses in economic capital. For example, the annual economic loss in the United States alone in 1990 was estimated to be $40 billion.[2] Adjusting for inflation, the cost in 2002 approaches $60 billion. About 70% of these losses are attributable to early death (principally due to suicide), unemployment, absenteeism, and diminished productivity. Imagine the magnitude of the losses if underutilized human capital (i.e., incomplete education, underemployment, early retirement, or failure to advance in the workplace), suffering, and the "rippling" effects of depression within families[22,23] were taken into account.

Figure 2. Social Adjustment Normalizes With Remission of Chronic Depression[a]



[a]Data from Miller et al.[19]
*Statistically significant ($p \leq .05$) difference in Social Adjustment Scale-Self Report scores between response vs. nonresponse, remission vs. nonresponse, and remission vs. response.

Only about 30% of the total costs attributed to depression are tied to treatment.[2] Therefore, it is likely that effective treatment for patients currently untreated or receiving minimal care would largely offset the costs of medication and therapy. Mintz and colleagues[18] found that improvements in vocational functioning accompanied successful treatment, although better workplace performance typically lagged behind symptom reduction. They also found that treatment was usually needed to produce a marked degree of improvement in symptom status (i.e., remission) before vocational functioning fully normalized.

Miller et al.[19] examined the relationship between recovery of psychosocial functioning and quality of treatment response in a study of more than 500 patients with chronic depression. They found that, after 12 weeks of double-blind therapy with either imipramine or sertraline, only the subgroup of patients that achieved complete remission of depressive symptoms were functioning at a level comparable to healthy individuals. The social functioning of responders who did not obtain complete remission was actually closer to that of treatment nonresponders than to that of healthy individuals (Figure 2).

Hirschfeld and colleagues[21] recently reported on the effects of treatment with nefazodone and psychotherapy (both alone and in combination) on social functioning in a study of more than 600 outpatients with chronic forms of major depression. After 12 weeks of treatment, the group receiving both psychotherapy and pharmacotherapy experienced significantly greater improvements in social func-

tioning than either of the monotherapy groups. Moreover, this advantage was not just an epiphenomenon of the higher remission rate resulting from combined treatment. In other words, cognitive-behavioral therapy and nefazodone appeared to have complementary effects on functioning at home and at work over and above a greater probability of remission. As observed by Miller et al.,[19] only the subgroup of fully remitted patients achieved "normal" levels of social functioning at the end of the acute phase of treatment.

The impact of these findings from controlled treatment studies is further expanded by data from the longer-term study by Judd and colleagues.[20] Psychosocial function and disability related to employment or social relationships were assessed prospectively across 10 years. Treatment was not controlled and, generally, participants received low levels of care despite their enrollment in a prestigious study funded by the National Institute of Mental Health. The presence of even a few persistent "minor" depressive symptoms was associated with significant periods of psychosocial disability.

GENERAL MEDICAL CONDITIONS

Depression adversely affects health and the impact of health care. Depressed patients, on average, use health care services 3 times as often and make 7 times more emergency room visits than nondepressed patients.[24,25] On average, depressed individuals spend twice as much on medical care as nondepressed people.[26,27] Depression actually worsens the course of general medical disorders such as heart disease and diabetes.[7] Persistent depressive symptoms also increase the mortality of life-threatening conditions such as stroke and heart attack.[23–32]

Depression increases mortality for at least 6 months after myocardial infarction.[28] Penninx and colleagues[29] demonstrated that even minor depressive symptoms increase the mortality rate of patients with heart disease. Several recent studies have shown that depression similarly increases morbidity and mortality in patients with congestive heart failure.[30,31] Depression worsens outcomes after stroke[32] and following confinement to a nursing home.[33]

Depression and diabetes seem to be subtly intertwined. For example, people with diabetes (both insulin-dependent and noninsulin-dependent forms) are more likely to be depressed than nondiabetic individuals.[34,35] Depression may even predispose an individual to the development of diabetes.[35,36] There is also increasing evidence that depression may worsen glycemic control[36] and diminish adherence to treatment.[37–39] Not surprisingly, depression increases the health care costs of people with diabetes[37,38] and may even increase the likelihood of development of long-term complications (e.g., retinopathy or kidney disease).[36]

It is widely believed that effective treatment of depression will improve health care outcomes.[10,40] However, data supporting this simple hypothesis are surprisingly scant.

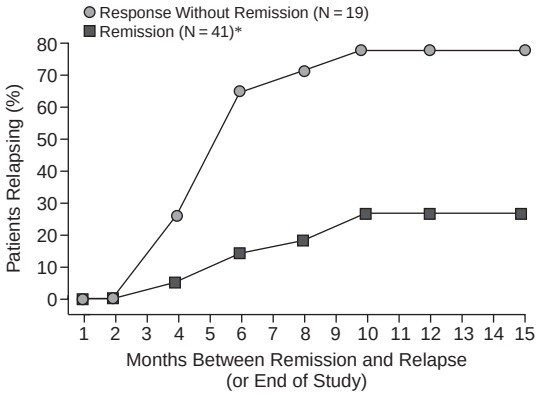
LONGITUDINAL COURSE

Incomplete remission of a depressive episode has important prognostic implications, whether observed following psychotherapy,[41] during continuation pharmacotherapy,[42] or across a decade of naturalistic follow-up.[43] In every case, incompletely remitted patients were significantly more likely to relapse than fully remitted patients. Thase and colleagues[41] followed 50 patients who had responded to a 16-week course of cognitive-behavioral therapy, a form of psychotherapy that has been proposed to have durable long-term effects. Outcomes across a 1-year prospective follow-up period differed dramatically depending on whether or not patients had achieved remission before completion of the 4-month therapy protocol. In fact, patients who had achieved a HAM-D score of ≤ 7 by week 10 of therapy were at a remarkably lower risk than the remainder of the group (9% vs. 52%). Studies by Simons et al.,[44] Evans et al.,[45] and Jarrett et al.[46] have similarly observed a strong association between incomplete remission and increased risk of relapse following time-limited cognitive-behavioral therapy.

Paykel and colleagues[42] evaluated the impact of residual symptoms on relapse in a prospective 15-month follow-up study of continuation-phase pharmacotherapy. Participants had responded to treatment (doctor's choice) with tricyclic antidepressants (TCAs) or with selective serotonin reuptake inhibitors (SSRIs). Those who were not remitted (i.e., a HAM-D-17 score of ≤ 7) at the start of follow-up had a 3-fold greater risk of relapse when compared with fully remitted patients (Figure 3). The speed of relapse was also 3 times faster for those with residual symptoms compared with those without residual symptoms.

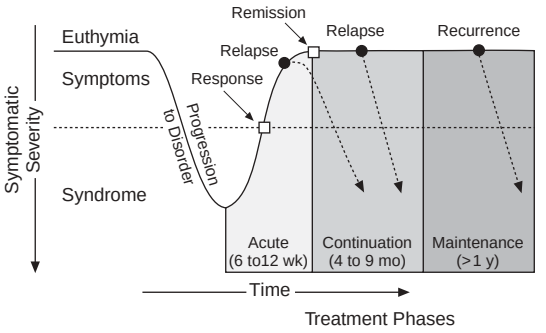
Judd and colleagues[43] recently published compelling evidence that treatment to remission early in the course of a major depressive episode has long-lasting consequences. Patients were evaluated in a prospective, yet naturalistic, 10-year follow-up study. Those who achieved full remission of symptoms following treatment of their first lifetime depressive episode were compared with patients who responded but had residual depressive symptoms. The fully remitted group had a significantly lower risk of relapse or recurrence and was almost 3 times more likely to be illness-free across the decade-long follow-up. By contrast, the incompletely remitted group had more depressive episodes, a greater risk of chronicity (i.e., a subsequent episode with a duration of more than 2 years), significantly shorter durations of wellness between episodes, and fewer depression-free weeks. These are indeed sobering findings given the relatively small proportion of patients with depressive episodes who receive treatment to remission.

Figure 3. Longitudinal Follow-Up Study of Patients Treated With Usual Care by Their Physicians[a]



[a]Reprinted with permission from Paykel et al.[42] Incomplete remission (HAM-D-17 > 7) associated with an increased risk of relapse during continuation pharmacotherapy.
*p < .001.

Figure 4. Matching Outcomes to Phases of Depression Treatment: The 5 "Rs"[a]



[a]Adapted from Kupfer,[47] with permission.

THERAPEUTIC IMPLICATIONS

Kupfer[47] illustrated how the course of a prototypic depressive episode could be matched with corresponding phases of treatment (Figure 4). It is increasingly clear that this approach, although initially intended for pharmacotherapy, is also relevant to psychotherapy.[41,46] An acute or initial phase of treatment was proposed to correspond to the weeks or months needed to achieve an acceptable level of improvement. It is now recommended that remission, not response, be used as the goal for acute-phase therapy.[7] Thereafter, a finite period of continuation-phase therapy was recommended to prevent relapse. As approximately 40% to 60% of antidepressant responders relapse within 4 to 6 months of stopping medication,[10,48] the continuation phase of pharmacotherapy was proposed to extend for at least 6 months for virtually all antidepressant responders. A third or maintenance phase of therapy was recommended to prevent recurrent depressive episodes. Maintenance-phase therapy has an indefinite duration and may extend for a lifetime. It is recommended for most people who have suffered 3 or more episodes of depression, as well as those who have had 2 episodes in close proximity.[10,48] Antidepressant doses are typically held consistent in continuation- and maintenance-phase pharmacotherapy whereas the frequency of psychotherapy diminishes to every other week or once a month.

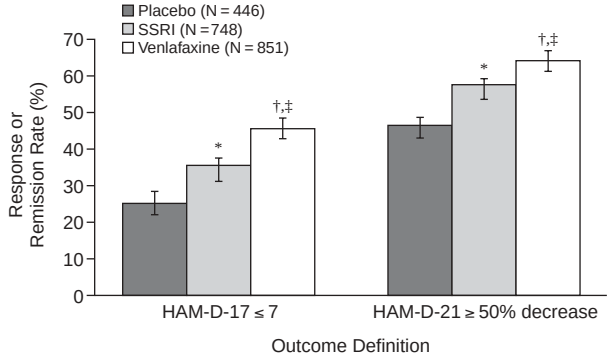
A symptomatic flare-up should be addressed vigorously regardless of the phase of treatment. The treatment regimen must be adjusted or revised as necessary until full remission is regained. Various considerations include side effects, the cost and feasibility of treatment alternatives, and a careful reappraisal of therapeutic goals. If the initial strategy is pharmacotherapy alone, ensuring full adherence and increasing the dose of medication are common responses. Another possibility is to add a form of psychotherapy that explicitly targets residual depressive symptoms. Fava and colleagues[49] demonstrated the value of adding a time-limited course of cognitive-behavioral therapy to ongoing antidepressant therapy. Ten sessions (20 weeks) of symptom-focused therapy produced a sustained benefit (i.e., reduced relapse risk) that was still apparent 6 years later. Paykel et al.[50] partially replicated this study in a larger, 2-center clinical trial. They randomly assigned 158 incompletely remitted patients taking antidepressants to receive continuation-phase pharmacotherapy either alone or in combination with 16 sessions (20 weeks) of individual cognitive-behavioral therapy. Among the patients treated with antidepressants alone, 45% relapsed within 1 year despite ongoing antidepressant pharmacotherapy. The relapse rate was only 29% in the group that received psychotherapy in addition to medication management.

Acute-Phase Strategies

Many psychiatrists favor combining psychotherapy and pharmacotherapy from the outset to increase the likelihood of remission.[51] Most early studies did not demonstrate a clear-cut advantage for combined therapy over well-executed monotherapies, although these studies were too small (i.e., underpowered) and typically did not focus on higher-risk patient groups.[52,53] Significant additive effects have been documented in studies of patients with severe episodes of recurrent depression[54] and chronic forms of major depression.[55] If the greater cost of providing both forms of therapy is a consideration, patients with such difficult-to-treat depressions should be prioritized to receive the combination first.

Until recently, it was assumed that all U.S. Food and Drug Administration–approved antidepressants were comparably effective in unselected groups of depressed patients.[10,51] The ascendance of the several SSRIs as the

Figure 5. Final On-Therapy Outcomes (Mean, 95% CI) With Strict (Remission) and Liberal (Response) Criteria[a]



[a]Adapted from Thase et al.,[62] with permission. The relative advantage was 1.28 to 1 using the remission redefinition, but only 1.12 to 1 using the response definition.
*p < .001 SSRI vs. placebo; †p < .001 venlafaxine vs. SSRI; ‡p < .001 venlafaxine vs. placebo.
Abbreviations: CI = confidence interval, HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

leading antidepressant medications in the United States has more to do with tolerability, ease of prescription, and safety. There is now evidence of modest, yet clinically significant, differences in responsivity to TCAs and SSRIs.[56,57] The former compounds, particularly amitriptyline and clomipramine, have been shown to be more effective than SSRIs in a meta-analysis of 25 studies of depressed in-patients.[56] The SSRIs, on the other hand, appear to be significantly more effective than TCAs for depressed premenopausal women.[56] The older monoamine oxidase inhibitors, in retrospect, may have had a similar efficacy advantage relative to the TCAs.[58] It is presumed that higher circulating estrogen levels may account for the better response of younger women to serotonergic medications. In contrast, the advantage for the tertiary amine TCAs (when compared with the SSRIs among severely depressed patients) is presumed to result from potentiation of noradrenergic neurotransmission in addition to serotonin reuptake inhibition.[59]

The latter observation motivated the search for safer "dual" reuptake inhibitors. The first of these newer compounds, venlafaxine, has a tolerability profile generally similar to the SSRIs yet (at least at higher doses) has the ability to inhibit reuptake of both serotonin and norepinephrine.[60] There is evidence that venlafaxine may have stronger antidepressant effects than the SSRIs (Figure 5).[61,62] This advantage is not seen consistently across trials, although the studies are all too small to detect such modest effects reliably. This illustrates the need to conduct large trials when comparing active antidepressants.[63]

There is some evidence that treatment with either of the 2 other newer "dual" reuptake inhibitors, milnacipran[64,65] and duloxetine (Eli Lilly and Company, Indianapolis, Ind.),[66,67] also yields significantly greater response and remission rates. A study evaluating duloxetine, 60 mg once daily versus placebo, showed a 31% remission rate relative to 15% for placebo, which is more than a 2-fold advantage over placebo.[66] In controlled trials, duloxetine therapy has not been associated with an increased risk of hypertension (i.e., sustained elevations of systolic or diastolic blood pressure). By contrast, therapy with various TCAs, milnacipran, or venlafaxine is associated with high blood pressure.[68] Further research is needed to clarify this apparent discrepancy between mechanisms of action and potential untoward effects.

CONCLUSION

The tragic personal and economic costs and consequences of depression can be mitigated by prompt recognition and vigorous treatment. Complete symptomatic remission is increasingly recommended as the goal of acute-phase therapy to both reduce relapse risks and optimize psychosocial outcomes. A wide range of treatment options are available, and several strategies have been shown to increase the likelihood of remission.

Drug names: amitriptyline (Elavil, Endep, and others), clomipramine (Anafranil and others), imipramine (Tofranil and others), nefazodone (Serzone), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined, to the best of his knowledge, that milnacipran and duloxetine have not been approved by the U.S. Food and Drug Administration for treatment of major depressive disorder.

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