

# The Burden of Recurrent Depression: Causes, Consequences, and Future Prospects

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Depression represents one of the most profound human problems currently facing the global health care system. It is a prevalent clinical condition and is estimated to rival virtually every other known medical illness in burden of disease morbidity early in this millennium. Understanding the chronic nature of this illness is key to the development of a more informed, longitudinal perspective on the diagnosis and treatment of depression. In this report, the morbid impact of depression is reviewed, from the perspectives of illness symptoms, societal impact, and emerging evidence of critical neurobiological consequences of the untreated condition. Reconceptualizing major depression from this longitudinal and multidimensional perspective is crucial to providing an effective response to this critical public health challenge. *(J Clin Psychiatry 2001;62[suppl 22]:5-9)*

## MAJOR DEPRESSION: AN OVERVIEW OF THE SCOPE OF THE PROBLEM

The World Health Organization has categorized depression as among the most disabling clinical diagnoses in the world, estimated to affect nearly 340 million people worldwide, and 18 million people in the United States at any one time.<sup>1</sup> The recent National Comorbidity Survey estimated the lifetime prevalence of major depression to be 17.1%,<sup>2</sup> with a disproportionate gender impact on women. A similar 6-month prevalence rate has been reported in a large European study.<sup>3</sup> These estimates underscore the nature of depression as a common clinical condition; however, they provide only a small perspective on

the devastating consequences of this illness. In an attempt to expand an appreciation of these consequences beyond an estimate of mortal risk alone, the World Health Organization in collaboration with the World Bank launched the Global Burden of Disease Study in 1992. A major thrust of this work was to objectively evaluate the burden of over 100 common medical conditions by developing measurements that incorporated non-fatal health outcomes. The metric Disability-Adjusted Life Years (DALYs) was developed as an indicator for this purpose.<sup>1</sup> The basic concept was that the years of life lost due to a disease would be added to the years lived with the disability due to the disease itself. In this work, a related measure, Years Lived With Disability (YLD), estimates disease burden for illnesses that do not commonly produce mortality.

The results of this work were provocative, and further clarified the profound impact of psychiatric disease worldwide. In terms of YLDs, psychiatric illnesses were the most important contributors, accounting for almost 30% of the total.<sup>1</sup> The authors summarized that "... the burdens of mental illnesses, such as depression, alcohol dependence and schizophrenia, have been seriously underestimated by traditional approaches that take into account only deaths and not disability. While unipolar depression is responsible for little more than one percent of deaths, they account for almost 11 percent of disease burden worldwide... In 1990, major depression is the fourth highest source of DALYs, and is projected to rise to number 2 by the year 2020. . . ." (Figure 1).<sup>1</sup>

Although most easily recognized as a disease of middle and later life, it is becoming increasingly evident that a proper conceptualization of major depression must view this illness as tending to develop at earlier points across the normal human lifespan. Nearly 1 in 8 adolescents<sup>4</sup> and as

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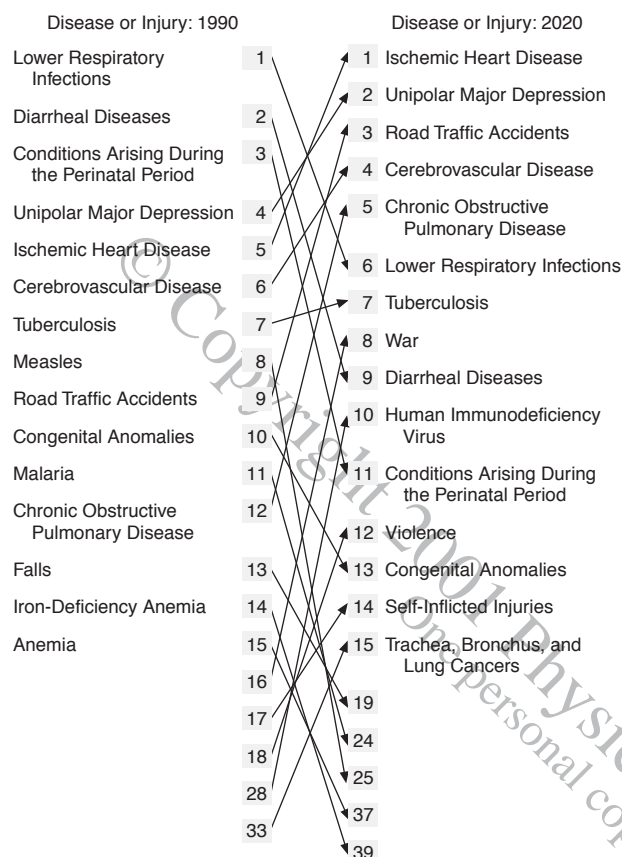
*The data summarized here are similar to material being published separately: Greden JF. Recurrent depression and mania: their overwhelming burden (In: Greden JF, ed. Treatment of Recurrent Depression, vol. 20. Washington, DC: APPI; 2001:1-18); Greden JF. Clinical prevention of recurrent depression: the need for paradigm shifts (In: Greden JF, ed. Treatment of Recurrent Depression, vol. 20. Washington, DC: APPI; 2001:143-170); Greden JF. The burden of disease for treatment-resistant depression (In: J Clin Psychiatry 2001;62[suppl 16]:26-31).*

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Figure 1. Change in Rank Order of DALYs for the 15 Leading Causes of Disease or Injury, World, 1990–2020<sup>a</sup>



<sup>a</sup>Adapted, with permission, from Murray and Lopez.<sup>1</sup>  
Abbreviation: DALY = Disability-Adjusted Life-Year.

many as 1 of every 33 children overall<sup>5</sup> experience depression. This is a critical observation since it has also been observed that subclinical symptoms or frank adolescent major depression strongly predicts a greater risk for adult recurrence of major depression, increasing the risk approximately 2- to 4-fold.<sup>6,7</sup> In many instances, the symptoms of major depression in adolescents may have differing presenting symptoms compared with adult forms of the disease, sometimes leading to misidentification of depression as substance use or abuse, attention-deficit/hyperactivity disorder, or simply “poor social adjustment.” A recent survey highlights the potentially alarming consequences of this underrecognition: 22% of adolescents with major depression reported a prior suicide attempt.<sup>4</sup> Sadly, the rate of teen suicides in the United States has risen from 2.3 per 100,000 in 1956 to 9.5 per 100,000 in 1997.<sup>8</sup>

The importance of identifying and proactively treating early-onset major depression is clear. Early-onset major depression has been associated with a number of important clinical consequences, beyond the fundamental observation of an increased likelihood of future episodes, as mentioned above. Two recent reports of clinical trial outcomes

have identified some of these consequences. In a comparison of patients with early-onset (i.e., before age 21 or 22 years) and late-onset (i.e., after age 21 or 22 years) depression,<sup>9,10</sup> it was observed that patients in the early-onset depression group tended to have a longer index first episode, sharply higher rates of recurrence, higher overall rates of comorbid personality disorders and lifetime substance use disorders, and a longer hospitalization. Further, there was a more extensive family history of mood disorders in the early-onset patient group, and lower educational attainment and lower annual earnings (12%–18%) for women.<sup>10</sup> The early-onset patient group also tended to include a predominance of females, more Caucasians, and more people who had never married.

Despite the enormous worldwide prevalence of depression, the majority of affected individuals still do not receive adequate treatment. It has been repeatedly estimated that from 40% to 80% of persons suffering with depression do not seek treatment for their illness.<sup>2–4,11</sup> Even when patients do seek professional advice and intervention, most often in a primary care setting, a considerable degree of underrecognition still prevails,<sup>12</sup> with some studies reporting that rates of missed diagnoses of depression and other psychosocial disorders can be as high as 50%.<sup>3,12,13</sup> Even among those who are diagnosed, treatment is characteristically incomplete or inadequate from a number of perspectives. In a recent survey of depressed patients, only 31% were prescribed specific medication for their illness, and of those, only 25% were given the appropriate pharmacologic intervention, an antidepressant.<sup>3</sup> It may be commonly assumed that the introduction of selective serotonin reuptake inhibitors (SSRIs) has led to a remarkable simplicity of depression treatment, eliminating or reducing the complexity of dosing and enhancing overall compliance. Unfortunately, this is not entirely true. Though the advent of SSRIs was a notable event in the evolution of modern pharmacotherapy for patients with depression, it is still noted that among those who are taking antidepressant therapy, reports of inadequate dosing, particularly of the older tricyclic antidepressants, and inadequate duration of therapy, with all classes of antidepressants, are persistent problems.<sup>14–18</sup> Recent estimates have suggested that less than 10% of patients with depression are likely to receive adequate treatment.<sup>12,14</sup>

Early identification of illness, aggressive intervention with appropriate therapies when needed, and thoughtful follow-up to enhance long-term compliance with needed treatment are a cost-effective process. An emerging body of data supports this view. The long-term functional effects of major depression are devastating and at least as serious as chronic medical disorders such as diabetes and cardiovascular disease.<sup>19,20</sup> These functional effects are wide-ranging and include disruptions in physical, social, and role functioning.<sup>21</sup> Major depression may also have a profound impact on the course and outcome of other comor-

**Table 1. The Global Burden of Major Depression**

Contributing factors
Large worldwide prevalence
Early-onset forms of illness
Genetic vulnerability
Unavoidability of stress
Stigma and poor detection and treatment
Functional consequences
Recognized limitations in current treatment options
Failure to treat results in recurrent, treatment-refractory forms
Exacerbation of other comorbid medical conditions
Failure of long-term compliance
Alteration in stress-sensitive brain adaptive circuits

bid medical conditions. For example, it has been observed that depression may adversely affect the long-term course of illnesses such as breast cancer,<sup>22,23</sup> malignant melanoma,<sup>24</sup> and cardiovascular disease.<sup>25-27</sup>

Even before mental health care costs are considered, patients with major depression have a several-fold higher amount of health care expenses than nondepressed patients.<sup>28-30</sup> In addition, depressed patients seek treatment for medical complaints from their family physician at a rate 3 times higher than patients without depression.<sup>3</sup>

Beyond the impact on health care utilization, depression interferes with daily activities, with an impact on both family and work life. The cost in the workplace is staggering, with loss due to absenteeism, reductions in worker productivity, medical visits, hospitalizations, and disabilities. For instance, adults suffering from major depression reported a 4-fold higher rate of working days lost over a 6-month period compared with nonsufferers.<sup>3</sup> In another report, an annual 150 million impaired work days were estimated among 15- to 24-year olds due to depression.<sup>4</sup>

Table 1 summarizes some of the contributing factors and functional consequences that define the global burden of depression. In the following section, a focus is placed on emerging evidence of the biological ramifications of these issues and their importance in understanding issues of disease persistence, as well as delineating potential new targets for therapeutic intervention.

### NEUROBIOLOGICAL CONSEQUENCES OF RECURRENT DEPRESSION

Much of the burden of major depression can be linked to the characteristic recurrent nature of the disorder. This hallmark recurrent pattern is typically accompanied by cycle acceleration and increasing severity with each subsequent episode, particularly in the absence of treatment intervention. It has been estimated that 75% to 90% of patients with depression will have multiple episodes.<sup>31,32</sup> In a large prospective study, a recurrence rate of 85% was reported over 15 years of follow-up and was high even among those who had recovered and remained well for at least 5 years.<sup>33</sup> As mentioned earlier, a high recurrence rate

is evident even among depressed adolescents.<sup>4</sup> With each new episode of depression, the next episode tends to occur sooner and have a more severe, treatment-resistant course than the preceding episode,<sup>21,34</sup> a phenomenon termed *cycle acceleration*. It is precisely because of this recurrent pattern, with the potential for gradually worsening cycle acceleration, that an effective clinical approach should consider major depression to be a lifetime disorder, with a complex, multidimensional character. Indeed, these descriptive observations highlight the progressive and deleterious effect of each episode upon the next and underlie the critical importance of early and sustained treatment intervention. As a clinical rule, more than 2 lifetime episodes, even if individually treated to full clinical resolution, should incline the treating clinician toward institution of lifelong medication in the interest of forestalling future recurrence.

A growing body of evidence examining functional and structural alterations of the brain is consistent with these clinical observations and supports the view that chronic, recurrent depression is both predisposed by and perpetuated because of alterations in neuronal function. Recent neuroimaging and histopathologic studies have provided evidence of these pathophysiologic events. Hippocampal volume reductions have been reported in patients with severe recurrent depression,<sup>35,36</sup> with current depression,<sup>37</sup> and with posttraumatic stress disorder.<sup>38</sup> Additionally, reduced hippocampal gray matter density has been reported in patients with chronic depression.<sup>39</sup> In some reports, these alterations in hippocampal structure were positively correlated with total duration of depression,<sup>35</sup> impairment of short-term verbal memory,<sup>38</sup> and verbal recognition,<sup>39</sup> although other reports have not found similar correlations.<sup>36,37</sup> Changes in the prefrontal cortex of patients with depression have also been described, including reductions in cortical thickness<sup>40</sup> and volume<sup>41,42</sup> and in the number, density, and size of glial cells and neurons.<sup>40-42</sup> Finally, decreased cerebral metabolism and cerebral blood flow have been reported in patients with a family history of major depression.<sup>41</sup>

Neurodegenerative changes in brain structures, particularly hippocampal neurons, have been documented in animal and human studies of chronic stress. These changes are thought to be mediated by the destructive effects of the sustained glucocorticoid tone that occurs in the setting of chronic stress and are accentuated by alterations in neurotrophins, toxins, alcohol, or vascular conditions or through all such mechanisms.<sup>43</sup> Stress has been shown to reduce hippocampal neurogenesis,<sup>44-47</sup> with chronic stress down-regulating 5-HT<sub>1A</sub> receptor binding and gene expression.<sup>48</sup> It is well documented that during stress, similar to well-established observations in the melancholic form of major depression, levels of glucocorticoids are increased in a sustained fashion.<sup>43,46,47</sup> The increase in glucocorticoid levels acts to decrease neurogenesis of dentate gyrus granule neurons in the hippocampus,<sup>45-47</sup> with additional changes in

cellular glucose uptake and metabolism and activation of glutamatergic neural circuits, which eventually may lead to neurotoxicity.<sup>46</sup> In addition to these stress-sensitive glucocorticoid-dependent events, it has recently been shown that levels and expression of brain-derived neurotrophic factor (BDNF), a growth factor involved in the maintenance and survival of neurons in the mature brain, are reduced during stress.<sup>43,46</sup> Pyramidal neurons in the CA3 region of the hippocampus are particularly susceptible to these neurochemical consequences of chronic stress, as atrophy and death of these cells has been documented in response to stress. It has been suggested that neurons in these regions that had previously been damaged by other insults such as vascular compromise, hypoglycemia or other metabolic events, or infectious stressors such as acute viral infections may be at heightened susceptibility to additional atrophy.<sup>43,46</sup>

Consistent with these observations, a recent hypothesis has proposed that the action of antidepressants is, in fact, mediated by alterations in certain key postreceptor intracellular targets.<sup>43</sup> Neurotransmitters, such as serotonin and norepinephrine, activate postsynaptic receptors, which in turn activate second messenger systems such as the cAMP pathway. These signaling events then converge at a gene expression level to stimulate specific gene targets, such as cAMP-response element binding protein, or CREB.<sup>43</sup> Elevated CREB levels have been found with long-term antidepressant treatment and are proposed to influence the increased expression of BDNF.<sup>43</sup> In this model, antidepressants exert their therapeutic benefit by reversing neuronal degeneration through the increased availability of neurotransmitters, which then ultimately increase BDNF levels and perhaps other brain neurotrophic factors, and thereby mitigate the long-term deleterious effects of elevated glucocorticoids, with a subsequent increase in the survival and growth of specific, stress-sensitive neurons.<sup>43</sup> Consistent with this model, recent data have shown that administration of antidepressants can block stress-induced neurodegeneration of CA3 pyramidal neurons and down-regulation of BDNF expression.<sup>46</sup>

Although these are recent emerging areas of investigation, they provide neurochemical evidence that is consistent with the clinical and epidemiologic observations noted earlier. They lend further importance to the view that early, aggressive treatment can play a crucial role in recovery and future prevention by exerting effects at a tissue level. In the following section, some of the challenges to intervention in the complex clinical setting of major depression are reviewed.

### **A WAY FORWARD: NEW OPPORTUNITIES FOR THE TREATMENT OF DEPRESSION**

Data reviewed here have underscored the fact that depression is a chronic, recurrent disease and is a grossly disabling clinical condition that affects an enormous number

of people around the world. The burden of the illness is substantial and is greater in impact than most other major diseases. A growing body of evidence suggests that depression is also associated with pathophysiologic changes in brain structure and function. It is also true that there are a number of available treatment options, pharmacologic and psychotherapeutic, with proven efficacy in patients with major depression. Indeed, antidepressants are clearly superior to placebo in controlled clinical trial settings, and many recent studies have demonstrated their equally superior advantage in the prevention of relapse in remitted patients in long-term treatment. Despite having the tools to combat major depression and the evidence to support their effectiveness, we do not, unfortunately, have a pleasant story to tell about the treatment of depression in actual practice. A substantial reason for this failure to translate research success into practical success hinges on our continued struggle with some of the fundamental difficulties in the management of depression: proper early identification of patients with the disease, continued shortfalls in the transition to and compliance with extended duration therapies that will sustain the acute change and prevent future occurrences, and the continuing struggle to overcome our society's stigmatized view of patients with depression.

Nevertheless, recent studies point to genuine areas of optimism and are beginning to shape a new way forward, one that considers major depression as a complex disease, one that requires a sustained, multidisciplinary investment. These data also provide hope that such a sustained effort will pay substantial dividends to offset the long-term social, clinical, and biological consequences of this disease. In a recent study in primary care patients, Katon and colleagues<sup>49</sup> have demonstrated that improvement in treatment adherence is possible, even during long-term treatment. Control patients, provided usual care, were found to have diminishing treatment adherence over 6 months. Patients in the collaborative intervention group, which included patient education combined with targeted psychiatric consultation, had better adherence than controls over those 6 months. The intervention patients were also more likely to rate their quality of care as good or excellent, to have a greater decrease in the severity of their depression, and to be fully recovered by 6 months.<sup>49</sup>

Beyond the development of more sophisticated patient education methods and the further refinement of practically useful collaborative, generalist/specialty care treatment models, the advent of newer electronic technologies holds promise for enhancing patient compliance and long-term treatment adherence. Major depression, in its active phase, is an isolating disease. Contemporary Internet-based communication methods are being pursued to provide novel methods of clinician-patient and patient-patient based interactions. There is also increasing development of telephone-based interactive voice response systems. These newer technologies may assist in bringing patients closer

to the expert diagnostic system, assist in maintaining continued compliance with appropriate treatment regimens, make it easier for patients to access their medication source, and provide expanded communication of the nature of depression and its treatment to society at large. The opportunities for change have never been greater.

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