

# The Burden of Disease for Treatment-Resistant Depression

John F. Greden, M.D.

Assessing the consequences of specific diseases on global, national, and individual levels is complex. The Global Burden of Disease Study was launched in 1992 to develop objective measures of the burden of disease. Two measures have become widely accepted: disability-adjusted life-years (DALYs) assesses years of life lost due to a disease plus years lived with the disability due to that disease, and years lived with disability (YLDs) is a related measure with greater relevance for diseases that do not routinely produce earlier mortality. When DALYs and YLDs were compared worldwide for 100 disorders, they revealed a huge burden of disease for depression. Indeed, the findings were startling. Neuropsychiatric conditions are by far the world's leader in YLDs, accounting for almost 30%. Unipolar major depressive disorder alone accounted for 11% of global YLDs. The disability of major depressive disorder produces its greatest burden upon women and starts early in life. No separate disability assessments have been compiled for treatment-resistant depression, but of individuals with major depressive disorder, the most severely disabled are those with treatment-resistant depression. The contributions to the morbidity associated with major depressive disorder and treatment-resistant depression include widespread prevalence; relatively early symptom onset; severe underdiagnosis and undertreatment; genetic vulnerabilities and precipitation or accentuation by relatively unavoidable stressors; a longitudinal pattern of frequent recurrences with increasing frequency, severity, and consequences unless treated with maintenance strategies; inadequate prioritization of recurrence prevention among clinicians; and possible suppression of brain neurogenesis, neuronal atrophy, cell death, hippocampal dysfunction, and magnetic resonance imaging changes for those with chronic treatment-resistant depression. Since the patterns of recurrences, cycle acceleration, and increasing severity of treatment-resistant depression are key reasons for its high burden, reducing the burden requires an entire paradigm shift, including emphasis on the prevention of recurrences. Only then will this prevalent, disabling yet treatable disorder lose its ignominious status as a world leader in disease burden. (J Clin Psychiatry 2001;62[suppl 16]:26-31)

The term *treatment-resistant depression* is used for a subgroup of individuals with major depressive disorder that presumably fail to respond to conventional treatment approaches. Treatment-resistant depression is receiving increasing attention despite the absence of a well-accepted definition,<sup>1-5</sup> perhaps because it is a major contributor to the immense burden associated with major depressive disorder. This article focuses on these burdens and disabilities. Topics addressed include operational definitions of disability and burden, key contributors to major depressive disorder's burdens of disability, the impact that treatment-resistant depression has on enhancing major de-

pressive disorder's burdens to the degree known, and a brief commentary about strategies to lessen the burden of disease for treatment-resistant depression (many of which are similar to those for lessening the burden of major depressive disorder). Other articles in this supplement address related causes of and approaches to treatment-resistant depression.

Investigators operationally define *treatment-resistant depression* in various ways.<sup>1</sup> To some, it might imply a posttreatment decrease in Hamilton Rating Scale for Depression (HAM-D) score of less than 50%; to others, a posttreatment HAM-D score that remains greater than a certain measure at a specified timepoint such as a HAM-D > 16 after 6 weeks; to still others, a failure to respond after 1, 2, or 3 "adequate" treatment trials.<sup>6</sup> Some clinical studies combine one or more of these definitions. Each definition unfortunately is confounded by innate variability, such as differences in the initial severity of the disorder, standardized rating scales used, versions of a specific rating scale (e.g., the 17-item vs. the 21-item HAM-D), length of time treatment is given, kinds of treatments, providers of treatments, and determinations of treatment

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From the Department of Psychiatry, the University of Michigan Depression Center, and the Mental Health Research Institute, University of Michigan, Ann Arbor.

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Reprint requests to: John F. Greden, M.D., University of Michigan Medical Center, Department of Psychiatry, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0704.

“adequacy.” Improved clarity for treatment-resistant depression is needed if we are to better understand and minimize its high burden.

### OPERATIONAL DEFINITIONS OF TREATMENT RESPONSE AND TREATMENT-RESISTANT DEPRESSION

Operational definitions of treatment response are a beginning. *Nonresponse* has been conceptualized to mean no clinically meaningful response. *Partial response* is more than 25% but less than 50% improvement. *Treatment response* denotes those with 50% or greater reduction on standardized rating scales. *Remission* implies no residual psychopathology or dysfunction associated with the original major depressive disorder. Assuming that remission is the optimal goal for treatment, the best definition of treatment-resistant depression would be “absence of remission.” That definition is not widely used, but it arguably should be, since it might help correct a misconception among clinicians who endorse the commonly held statement that approximately 30% of depressed individuals are nonresponders. This figure leads to the assumption that 70% are “responders.” In reality, many more patients do not experience timely remission with antidepressant treatment courses and perhaps as few as 30% to 40% achieve full-scale remission.<sup>7-10</sup> If absence of remission is used as the outcome measure, treatment “resistance” may be the most common outcome, perhaps affecting as many as 50% to 70% of those with major depressive disorder. This precise figure will certainly vary with all the confounds mentioned above, but one conclusion appears supportable: the prevalence of treatment-resistant depression is unacceptably large. A major public health challenge is to reduce this prevalence, a first step in ameliorating the immense burdens associated with major depressive disorder.

### OPERATIONAL DEFINITION OF DISABILITY AND BURDEN

Assessing the consequences of specific diseases on global, national, and individual levels is never simple. To address this challenge, the World Health Organization (WHO) in 1980 formulated the International Classification of Impairments, Disabilities, and Handicaps (ICIDH).<sup>11</sup> It classified 3 dimensions: impairment is any loss or abnormality of psychological, physiologic, or anatomic structure or function; disability is any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being; and handicap is a disadvantage for a given individual resulting from an impairment or a disability that limits or prevents the fulfillment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual. While ICIDH was help-

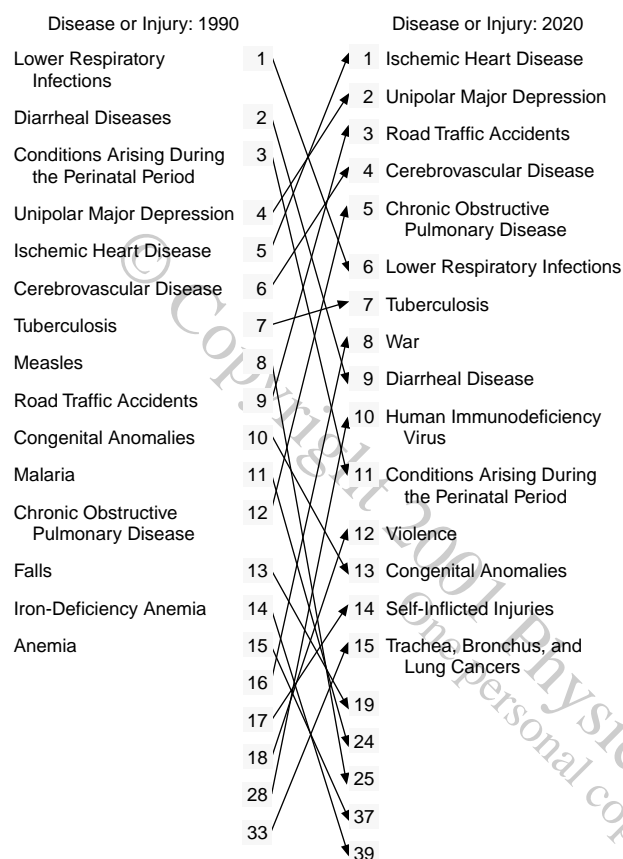
ful, a simpler concept was needed. The Global Burden of Disease Study was launched in 1992 with the objective of quantifying the burden of disease. It emphasized the inclusion of nonfatal health outcomes in debates on international health policy (all too often focused on mortality), the decoupling of epidemiologic assessments from advocacy so that disability estimates could become more objective, and the development of standardized measures that could be used to evaluate costs of disability. The measure of disability-adjusted life-years (DALYs) was developed as such an indicator for the consequences of specific diseases. The key principle was that the years of life lost due to a disease would be added to the years lived with the disability due to that disease. The new measure was applied to the estimation of both disability and mortality from over 100 diseases in all regions of the world. Years lived with disability (YLDs) is a related measure for those diseases that do not commonly produce mortality. Sponsored by the WHO and the World Bank, the “burden of disease” project is based at the Harvard School of Public Health.<sup>11</sup>

When DALYs and YLDs were compiled and compared for the selected 100 disorders, findings were revealing, even startling. First, neuropsychiatric conditions are the most important contributors to YLDs, accounting for almost 30%, by far the leader in the world. Second, unipolar major depressive disorder alone accounted for 11% of global YLDs.<sup>11</sup> When DALYs are compared, major depressive disorder ranked 4th among all diseases despite its relatively low mortality; by 2020, its estimated rank will be 2nd unless improvements in health delivery are implemented (Figure 1).

Third, when considered globally, nearly half of all disability due to disease or injury occurs in young adults, aged 15 to 44 years, and almost one fifth (18%) stems from conditions arising in early childhood before the age of 4 years, illustrating that to reduce the burdens of disease, we need to conceptualize disorders across the life spectrum, seeking to prevent deterioration prior to the appearance of disability. That lesson is integral to reducing treatment-resistant depression’s burden. Fourth, major depressive disorder’s disability produces its greatest burden upon women. Indeed, for women (Table 1), no disorder produces greater burden whether one considers developed regions, developing regions (not shown in Table 1), or the entire world.

It should be noted that these disabilities are for unipolar major depressive disorder and encompass all types and severities. No separate disability assessments have been compiled for treatment-resistant depression, but indirect evidence for disability is strong and the prevailing impression is that those with treatment-resistant depression are the most disabled of those with major depressive disorder. The DALY data were summarized above, but how much of this disability is linked to treatment resistance or is found in individuals with treatment-responsive major depressive

**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>11</sup>  
Abbreviation: DALY= disability-adjusted life-year.

disorder that is simply undiagnosed or untreated is unspecified. DALYs also include suicide, a small but tragic part of the problem. Teen suicides in America have increased from 2.3 per 100,000 in 1956 to 9.5 per 100,000 in 1997,<sup>12</sup> but it is unknown how many are attributable to untreated depression or treatment-resistant depression. Health expenditures are several-fold higher for depressed patients, not counting psychiatric costs,<sup>13,14</sup> but it is unknown how these expenses might be linked to treatment-resistant depression.

Major depressive disorder is grossly disabling. Undoubtedly, treatment-resistant depression is the most disabling type of major depressive disorder, but the relative disability associated with different types of depression remains to be studied. Recurrence is a major contributor.<sup>15</sup>

### CONTRIBUTORS TO THE HIGH MORBIDITY OF TREATMENT-RESISTANT DEPRESSION

Figure 2 is a schematic illustration of contributors to the morbidity of major depressive disorder. Since treatment-resistant depression is a subsegment of major depressive

disorder, these are also contributors to the burden of treatment-resistant depression.

This figure is based on the assumption that any disorder is almost certain to produce huge burdens if characterized by a constellation that includes widespread prevalence, relatively early symptom onset, severe underdiagnosis and undertreatment, genetic vulnerabilities and precipitation or accentuation by relatively unavoidable stressors, and a longitudinal pattern of frequent recurrences with increasing frequency, severity, and consequences unless treated, yet inadequate prioritization of recurrence prevention among clinicians. These parameters sadly characterize major depressive disorder as we enter the 21st century. Together, they form the foundation of major depressive disorder's huge disability. They also likely contribute to the development of treatment-resistant depression, and they continually enhance major depressive disorder's disability. Because of their importance, these parameters warrant commentary.

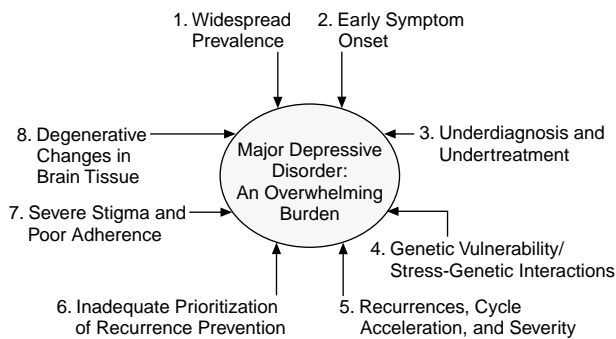
Few major disorders are as widely prevalent as major depressive disorder. Its widespread prevalence has been documented in studies by Kessler et al.,<sup>16</sup> which reveal that more than 15% of the population are at lifetime risk for major depressive disorder, with risk approximately 1.7 times greater among women than among men. Extrapolating to the world, this means that approximately 340 million individuals have major depressive disorder at any given time, 18 million in the United States alone. What a powerful starting point for major depressive disorder's large negative health impact!

The burden of high prevalence is accentuated by the onset of symptoms of major depressive disorder at a relatively young age. Pine et al.<sup>17</sup> noted that many individuals later shown to have major depressive disorder experience symptom onset during the late adolescent years. Characteristically, depressive symptoms that do not quite qualify for a diagnosis of major depressive disorder are often ignored among teens or attributed to causes such as substance use or abuse, attention-deficit/hyperactivity disorder, or the unhelpfully termed "adjustment disorder of adolescence." If untreated—the most common scenario—the lifetime progression of major depressive disorder probably gains momentum. Subclinical depressive symptoms during teenage years strongly predict subsequent adult major depressive disorder, resulting in a 2- to 3-fold increased risk.<sup>17</sup> Untreated teens that meet DSM-IV criteria for major depressive disorder also have eventual higher rates of comorbid diagnoses and higher recurrences of major depressive disorder episodes.<sup>18</sup> The reported brain morphologic changes and cycle acceleration patterns that start into motion<sup>19,20</sup> hypothetically contribute to a greater prevalence of treatment-resistant depression and even higher disabilities in untreated teens than in those whose major depressive disorder is recognized early and treated successfully. For disorders with early onset of symptoms, early detection and

Table 1. Leading Causes of Years Lived With Disability (YLDs) by Sex, 1990<sup>a</sup>

Both Sexes			Males			Females		
Disease or Injury	YLDs	Cumulative %	Disease or Injury	YLDs	Cumulative %	Disease or Injury	YLDs	Cumulative %
<b>I. World</b>			<b>I. World</b>			<b>I. World</b>		
All causes	472,736		All causes	235,096		All causes	237,641	
1. Unipolar major depression	50,810	10.7	1. Unipolar major depression	18,070	7.7	1. Unipolar major depression	32,740	13.8
2. Iron-deficiency anemia	21,987	15.4	2. Alcohol use	13,935	13.6	2. Iron-deficiency anemia	12,239	18.9
3. Falls	21,949	20.0	3. Falls	13,474	19.3	3. Falls	8,475	22.5
4. Alcohol use	15,770	23.4	4. Iron-deficiency anemia	9,748	23.5	4. Osteoarthritis	7,934	25.8
5. Chronic obstructive pulmonary disease	14,692	26.5	5. Chronic obstructive pulmonary disease	8,357	27.0	5. Bipolar disorder	6,938	28.8
6. Bipolar disorder	14,141	29.5	6. Bipolar disorder	7,203	30.1	6. Congenital anomalies	6,767	31.6
<b>II. Developed regions</b>			<b>II. Developed regions</b>			<b>II. Developed regions</b>		
All causes	75,389		All causes	38,242		All causes	37,147	
1. Unipolar major depression	9,780	13.0	1. Alcohol use	5,231	13.7	1. Unipolar major depression	6,392	17.2
2. Alcohol use	6,112	21.1	2. Unipolar major depression	3,388	22.5	2. Osteoarthritis	2,811	24.8
3. Osteoarthritis	4,681	27.3	3. Osteoarthritis	1,870	27.4	3. Dementia and other degenerative and hereditary CNS disorders	2,054	30.3
4. Dementia and other degenerative and hereditary CNS disorders	3,264	31.6	4. Schizophrenia	1,557	31.5	4. Schizophrenia	1,443	34.2
5. Schizophrenia	2,999	35.6	5. Drug use	1,484	35.4	5. Bipolar disorder	1,248	37.5
6. Bipolar disorder	2,505	38.9	6. Road traffic accidents	1,446	39.2	6. Cerebrovascular disease	1,216	40.8

<sup>a</sup>Adapted, with permission, from Murray and Lopez.<sup>11</sup> Abbreviation: CNS = central nervous system.

Figure 2. Contributors to the High Morbidity of Major Depressive Disorder and Treatment-Resistant Depression<sup>a</sup>

<sup>a</sup>Adapted, with permission, from Greden.<sup>15</sup>

intervention are the likely foundation for preventing many cases of treatment-resistant depression.

The severe underdiagnosis and undertreatment associated with major depressive disorder have been addressed in various reports. Details will not be resummized other than to reiterate that a distressingly small minority of patients receive accurate diagnosis and adequate treatment and that the pattern is worldwide and has persisted over decades.<sup>21-26</sup> It also is prudent to point out that if an accu-

rate diagnosis is not made, or appropriate treatment not provided, the term *treatment resistance* may be a misnomer.

Genetic vulnerability coupled with precipitation or accentuation of clinical features by unavoidable stressful life events is a potent combination. That is the case for major depressive disorder. Many episodes are catalyzed or worsened by events such as deaths, divorces, financial upheaval, or trauma and assault.<sup>27</sup> When such stressors cannot be prevented and no preventive antidepressant maintenance treatments are in place, new flare-ups are even more likely, treatment resistance begins to develop, and the burden of disease grows with each passing month and year. As we enhance our genetic knowledge base and integrate a constellation of various physical, chemical, optical, and electronic systems,<sup>28</sup> we anticipate being able to learn who is most vulnerable and when, and how to better predict and prevent the progression of major depressive disorder into a chronic and treatment-resistant state. Meanwhile, the only well-demonstrated effective step is to employ antidepressant maintenance strategies<sup>29</sup> and to buttress coping skills with cognitive-behavioral therapy<sup>30</sup> and/or interpersonal therapy.<sup>31</sup>

The progression of untreated depression with its pattern of recurrences, cycle acceleration, and increasing severity is a key reason for the high burden of treatment-resistant

depression.<sup>15,32–34</sup> Inadequate or ineffective use of recurrence prevention, often accentuated by stigma and poor adherence, is a gateway to continued progression. While brain morphological assessments of chronic, severe depression, often labeled as treatment-resistant depression, are still in an early stage, as illustrated in Figure 2, the entire sequence may culminate in suppression of brain neurogenesis, neuronal atrophy, cell death,<sup>20</sup> hippocampal dysfunction,<sup>35</sup> and magnetic resonance imaging changes.<sup>36</sup> The sequence and mechanisms contributing to these processes have been summarized elsewhere.<sup>29</sup> Whether and how such changes contribute to the development or disability of major depressive disorder and treatment-resistant depression again remain to be investigated more thoroughly, but there are suggested linkages. Recent studies of cognitive function in late-life depression illustrate that nondemented elderly depressive individuals with cognitive impairment may experience some improvement after 12 weeks of antidepressant treatment but may not necessarily reach normal levels of performance, particularly in memory and executive functions.<sup>37</sup> While they are unproved, it is reasonable to hypothesize that these gains could be linked in some manner to gradual repair of neuronal loss via changes in brain neurotrophins and neurogenesis associated with antidepressant and mood-stabilizing treatments.<sup>20,38</sup> If confirmed, such neurogenesis would further dramatize the need to continue treatments that sustain these processes in those with treatment-resistant depression who have responded to treatment, recognizing that progressive normalization of brain morphology may be underway.

### STRATEGIES TO LESSEN THE DISEASE BURDEN OF TREATMENT-RESISTANT DEPRESSION

Counteracting the burdens of treatment-resistant depression is inextricably intertwined with comprehensive research and better public health approaches to major depressive disorder. We need to clarify and standardize operational definitions of treatment-resistant depression, promote earlier recognition and intervention, develop better evidence-based strategies to help depressed patients who respond but do not remit with their initial antidepressant treatment, and refocus our attentions on prevention of progression. A National Institute of Mental Health study known as the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) aims to catalyze this effort.

In essence, we need an entire paradigm shift. A 12-step approach to such a shift was recently described.<sup>29</sup> Preventing and attacking the progression of major depressive disorder will reduce the unacceptably high prevalence of treatment-resistant depression. Only then will this prevalent, disabling yet treatable disorder lose its ignominious status as a world leader in burden of disease.

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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