MAJOR DEPRESSIVE DISORDER: BURDEN AND IMPACT BEYOND THE SUFFERER

Rajnish Mago, MD
Director of the Mood Disorders Program
Thomas Jefferson University, Philadelphia, PA
Associate Professor of Psychiatry and Human Behavior
Jefferson Medical College, Philadelphia, PA

Richard Weisler, MD, Distinguished Life Fellow of the APA
Adjunct Professor of Psychiatry
University of North Carolina (UNC) School of Medicine, Chapel Hill, NC
Adjunct Associate Professor of Psychiatry and Behavioral Sciences
Duke University Medical Center, Durham, NC
Private Practice, Raleigh, NC

© Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD
February 2016 MRC2.CORP.D.00092
Rajnish Mago, MD

**Position:** Dr. Mago is the Director of the Mood Disorders Program at Thomas Jefferson University (Philadelphia, PA) and an Associate Professor of Psychiatry and Human Behavior at Jefferson Medical College (Philadelphia, PA).

**Education:** Dr. Mago earned a Bachelor of Medicine and a Bachelor of Surgery degree (medical school degrees) and an MD in Psychiatry (post-graduate degree in Psychiatry) from King George’s Medical College, University of Lucknow (Lucknow, India). He was a Resident in Psychiatry at King George’s Medical College (Lucknow, India), Lady Hardinge Medical College (New Delhi, India), the Medical College of Pennsylvania / Eastern Pennsylvania Psychiatric Institute (Philadelphia, PA), and the University of Pennsylvania (Philadelphia, PA).

Richard Weisler, MD

**Position:** Dr. Weisler is an Adjunct Professor of Psychiatry at the University of North Carolina School of Medicine (Chapel Hill, NC) and an Adjunct Associate Professor of Psychiatry and Behavioral Sciences at Duke University Medical Center (Durham, NC).

**Education:** Dr. Weisler earned an MD degree from the University of North Carolina (Chapel Hill, NC). He was a Resident in Psychiatry at North Carolina and Dorothea Dix Hospital and the North Carolina Memorial Hospital (Chapel Hill, NC).
This program is paid for by Otsuka Pharmaceutical Development and Commercialization, Inc. and Lundbeck, LLC. The speakers are paid contractors of Otsuka Pharmaceutical Development and Commercialization, Inc.
PsychU Virtual Forum Rules of Engagement:

Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC) and Lundbeck, LLC. have entered into collaboration with Open Minds, LLC. to explore new ways of bringing/increasing awareness around serious mental illness.

OPDC/Lundbeck’s interaction with Open Minds is through PsychU, an online, non-branded portal dedicated to providing information and resources on important disease state and care delivery topics related to mental illness. One of the methods employed for the sharing of information will be the hosting of virtual fora. Virtual fora conducted by OPDC/Lundbeck are based on the following parameters:

When conducting medical dialogue, whether by presentation or debate, OPDC/Lundbeck and/or its paid consultants aim to provide the viewer with information that is accurate, not misleading, scientifically rigorous, and does not promote OPDC/Lundbeck products.

OPDC/Lundbeck and/or their paid consultants do not expect to be able to answer every question or comment during a PsychU Virtual Forum; however, they will do their best to address important topics and themes that arise.

OPDC/Lundbeck and/or their paid consultants are not able to provide clinical advice or answer questions relating to specific patient’s condition.

Otsuka and Lundbeck employees and contractors should not participate in this program (e.g., submit questions or comments) unless they have received express approval to do so from Otsuka Legal Affairs.

OPDC and Lundbeck operate in a highly regulated and scrutinized industry. Therefore, we may not be able to discuss every issue or topic that you are interested in, but we will do our best to communicate openly and directly. The lack of response to certain questions or comments should not be taken as an agreement with the view posed or an admission of any kind.
Objectives

• Understand the prevalence of major depressive disorder (MDD)
• Discuss the impact of MDD on patients, caregivers, and offspring
• Explore the impact of MDD on payers and employers
• Discuss the effect of residual symptoms and remission in MDD
The Prevalence of MDD Is Likely Underestimated and the Diagnosis Is Often Delayed

- Prevalence rates are likely underestimated due to:
  - Underdiagnosis:
    - Significant social stigma may prevent patients from seeking or accepting care for MDD
    - Certain providers may be uncomfortable discussing mental health with patients
  - Misdiagnosis:
    - Nonspecific symptoms
    - Significant heterogeneity and comorbid conditions
- Treatment of MDD is often delayed for years or even decades:
  - A nationally representative US sample (N = 9282) found a projected median of 8 years between MDD symptom onset and first contact with a care provider.

Overall lifetime prevalence of MDD across all ages was 16.6%

IMPACT OF MDD ON PATIENTS, CAREGIVERS, AND OFFSPRING
Burden of Disease to the Individual

In a 2012 review of the societal costs of MDD to the individual:

• Physical:
  – From meta-analyses of longitudinal studies (mostly from the United States [US]), MDD was a consistent predictor of the subsequent first onset of a variety of chronic physical disorders (ie, coronary artery disease, stroke, diabetes, heart attacks, and certain types of cancer).

• Financial:
  – Personal earnings and household incomes of people with MDD were found to be substantially lower than those of people without depression (though it was unclear whether depression was primarily a cause, a consequence, or both).

• Education:
  – Several studies showed that MDD was associated with an approximate 60% elevated risk of failure to complete secondary school than otherwise comparable youth in high-income countries.

Impact on Patient QoL: Disability

• In a systematic review of epidemiology data, depressive disorders were\(^1\):
  – A leading cause of disability-adjusted life years (DALYs) in 2010
  – The second-leading cause of years lived with a disability in 2010.

• Unipolar major depression is predicted to be the second-leading worldwide cause of DALYs in 2020 (after ischemic heart disease), compared with being the fourth-leading cause in 1990.\(^2\)

Link Between Depression and Other Illnesses

- A 2008–2009 survey was completed by means of a live interview in a noninstitutionalized sample of 92,264 adults living in the US. The data showed chronic health conditions among persons aged 18 or older who experienced a major depressive episode in the past year (2008 and 2009 data).

![Diagram showing the link between depression and other illnesses]

- When these 2008/2009 rates in adults (aged ≥ 18 years) were compared with adults without reported mental illness in the past year, the differences in all chronic health conditions were statistically significantly different at the 0.05 level.

Suicide Risk in MDD

- In a Finnish study of 269 patients diagnosed with MDD:¹
  - Significant differences between those attempting suicide and those not attempting suicide were seen in terms of:
    - Severity of index episode of depression (p = 0.02)
    - Amount of suicidal ideation and anxiety (p = 0.008 and 0.026, respectively)
    - Prevalence of suicide attempts during the index episode of MDD (p = 0.003)
    - Time to full remission (p = 0.002)
    - Total time in depression (p = 0.002).

Over 5 years follow-up in this Finnish study, the risk of suicide attempts was nearly 21-fold greater during a major depressive episode compared with full remission (N = 332 vs 16 per 1000 patient-years).²

---

Impact of Being a Caregiver

• A 2004 US report estimated that more than 44 million Americans were caregivers of people with a wide range of disabilities, including mental health issues¹,²:
  – Most caregivers said they experienced few adverse issues but those who provided the most hours and the most intense care experienced the most strain.

• The well-being of caregivers was noted as a public health concern due to the associated psychological and physical problems¹,³:
  – Specific psychological problems included depression and anxiety¹
  – Specific physical problems included decreased immunity, greater cardiovascular reactivity, slow wound healing, and increased risk for serious illness³
  – Risk of mortality was also increased in caregivers who experienced caregiver strain⁴:
    • Mortality risks were 63% higher than among noncaregiving controls.

Mean total annual child health expenditure*
$282 vs $214
(p = 0.0006)

Mean total annual child mental health expenditure*
$513 vs $338
(p = 0.0006)

*For children of parents with depression compared with children of parents without depression in the US
Study used data from a 1997 Medical Expenditure Panel Survey; values then inflated to 2001 US dollars.
IMPACT OF MDD ON PAYERS AND EMPLOYERS
Impact on Payers: Commercial Plan Performance on HEDIS (Healthcare Effectiveness Data and Information Set)

Follow-up rates for the HEDIS antidepressant measures have improved minimally over time

Note: These data are for HMO Commercial plans.
Impact of MDD on Employers

1 Employee with depression/sadness/ mental illness costs an employer:

- $4700/year for absenteeism
- $250/year for presenteeism

Direct 2-year costs:
- Likely treatment resistant: $22,784
- MDD controls: $11,733

Indirect 2-year costs:
- Likely treatment resistant: $12,765
- MDD controls: $6885

*On-the-job productivity losses.
†Costs are in 2007 US dollars. Direct 2-year costs are "all-cause direct costs."
## Reasons for Lost Productive Time (LPT) Between Workers With and Without Depression

<table>
<thead>
<tr>
<th>Type of LPT</th>
<th>MDD population: mean (SE) LPT (hours / worker / week)</th>
<th>Expected mean LPT in absence of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absenteeism</td>
<td>1.2 (0.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>7.2 (1.3)</td>
<td>1.1</td>
</tr>
<tr>
<td>Total LPT</td>
<td>8.4 (1.3)</td>
<td>1.5</td>
</tr>
<tr>
<td>Pain/weakness/fatigue</td>
<td>10.0 (1.2)</td>
<td>5.1</td>
</tr>
<tr>
<td>Gastrointestinal complaints</td>
<td>10.7 (1.5)</td>
<td>2.0</td>
</tr>
<tr>
<td>Panic/anxiety</td>
<td>9.3 (1.7)</td>
<td>4.1</td>
</tr>
<tr>
<td>Faintness/dizziness</td>
<td>8.9 (2.4)</td>
<td>4.5</td>
</tr>
<tr>
<td>Autonomic instability</td>
<td>9.5 (1.9)</td>
<td>6.5</td>
</tr>
<tr>
<td>Ears ringing/head or nose fullness</td>
<td>8.1 (1.2)</td>
<td>2.8</td>
</tr>
<tr>
<td>Sensory or nerve impairment</td>
<td>10.0 (1.4)</td>
<td>3.2</td>
</tr>
<tr>
<td>None</td>
<td>5.8 (3.7)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

SE, standard error.

Unemployment and Disability

• In a nationally representative US survey, over 4000 US workforce respondents (English speaking, ≥ 18 years of age) were classified by clinical severity of depression (from “severe” to “not depressed”).

• For those 539 employees reported as having depression, prevalence rates of unemployment or disability increased significantly with MDD severity, as did the monthly salary-equivalent of lost performance.

<table>
<thead>
<tr>
<th>MDD Severity</th>
<th>Unemployment/disability (%)</th>
<th>(Estimated) Monthly cost of reduced work and performance ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Moderate</td>
<td>23</td>
<td>188</td>
</tr>
<tr>
<td>Severe</td>
<td>31</td>
<td>199</td>
</tr>
</tbody>
</table>

## Total Societal Costs (2000)\(^1\)

<table>
<thead>
<tr>
<th>Type of cost</th>
<th>Dollars (in billions)</th>
<th>Percentage of Total</th>
<th>Cost/Case (in dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs*</td>
<td>83.08</td>
<td>100.0</td>
<td>8118</td>
</tr>
<tr>
<td>Direct cost(^†)</td>
<td>26.09</td>
<td>31.4</td>
<td>3309</td>
</tr>
<tr>
<td>Inpatient</td>
<td>8.88</td>
<td>10.7</td>
<td>1127</td>
</tr>
<tr>
<td>Outpatient</td>
<td>6.80</td>
<td>8.2</td>
<td>863</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>10.40</td>
<td>12.5</td>
<td>1319</td>
</tr>
<tr>
<td>Suicide-related costs(^‡)</td>
<td>5.45</td>
<td>6.6</td>
<td>302</td>
</tr>
<tr>
<td>Workplace costs(^§)</td>
<td>51.54</td>
<td>62.0</td>
<td>4507</td>
</tr>
<tr>
<td>Absenteeism</td>
<td>36.25</td>
<td>43.6</td>
<td>3169</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>15.30</td>
<td>18.4</td>
<td>1337</td>
</tr>
</tbody>
</table>

\(^*\)Total costs = direct, suicide-related, and workplace costs.
\(^†\)Direct treatment costs were estimated based on published utilization data for individuals recorded as receiving any medical treatment for depression in 2000.
\(^‡\)Suicide-related costs were estimated using a human capital framework based on the total number of suicides by age and gender cohort in 2000, as reported by the Centers for Disease Control.
\(^§\)Workplace costs were estimated as the wage-based value of both absenteeism (ie, days missed from work due to depression) and presenteeism (ie, reduced productivity while at work due to depression).

Note: Cost/case may not equal total cost divided by population estimates due to rounding.

RESIDUAL SYMPTOMS AND REMISSION IN MDD
Remission Is the Goal

% Reduction in Score

Remission
MADRS: total score \( \leq 8 \)\(^1\)

Response
MADRS: \( \geq 50\% \)\(^1\)

Partial Response
HAM-D: 50\%\(^2\)

Nonresponse
HAM-D: < 50\%\(^2\)

Remission has also been defined as attainment of a virtually asymptomatic status (17-item Hamilton Depression Rating Scale [HDRS]* score \( \leq 7 \)).\(^3\)

* Also abbreviated as HAM-D Rating Scale

MADRS, Montgomery-Asberg Depression Rating Scale

## Residual Symptoms After Remission: STAR*D
### Proportion of Remitters With at Least Mild or Moderate Levels of Residual Symptoms (n = 943)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>At least mild symptoms* (% of patients)</th>
<th>At least moderate symptoms† (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increase</td>
<td>71.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Mid-nocturnal insomnia</td>
<td>54.9</td>
<td>40.5</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>50.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Sleep-onset insomnia</td>
<td>29.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Sad mood</td>
<td>27.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>24.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Energy</td>
<td>22.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Concentration/decision making</td>
<td>20.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>16.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Early morning insomnia</td>
<td>16.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Restless</td>
<td>15.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Involvement</td>
<td>9.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Outlook self</td>
<td>6.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Slowed down</td>
<td>5.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Defined as any 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR<sub>16</sub>) item ≥ 1; †Defined as any QIDS-SR<sub>16</sub> item ≥ 2.

QIDS-SR, Quick Inventory of Depressive Symptomatology; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Reported Predictors of Poor Response to Treatment

- **Medical comorbidity**¹:
  - Hypercholesterolemia
  - Greater body weight
  - Hypofolatemia
  - MRI white matter hyperintensities

- **Depressive symptoms**¹:
  - Hopelessness
  - Cognitive impairment (executive dysfunction)
  - Somatic symptoms
  - Psychomotor retardation

- **Anxiety symptoms**²-⁴:
  - Anxiety
  - Anxious distress
  - Subthreshold anxiety

In addition, lack of an early treatment response has been reported to be predictive of a poor treatment response.⁵

---

Residual Symptoms

• From a meta-analysis of randomized, double-blind, placebo-controlled trials published between 1980 and mid-2007, pooled results noted that about approximately half of patients receiving antidepressants experienced a ≥ 50% reduction in symptoms.1

• Among patients with MDD treated in one of two academically affiliated, depression-specialty clinics, only 50% achieved full remission.2

• Compared with patients who achieved full remission, those with residual symptoms had1:
  – A greater risk of relapse and recurrence
  – More chronic depressive episodes
  – Shorter duration between episodes
  – Continued impairment in work and relationships.

Early Improvement and Remission

- Results from 2 publications (a German study of 795 patients with major depression\textsuperscript{1} and a systematic review of 41 trials in MDD [N = 6562]\textsuperscript{2}) found that earlier onset of response before 2 weeks of treatment was common and highly predictive of better later outcomes.

- Based on results from these and other studies, Möller et al recommended that, if no improvement was observed after 2 weeks, then treatment should be adjusted or changed immediately.\textsuperscript{3}

MAJOR DEPRESSIVE DISORDER: BURDEN AND IMPACT BEYOND THE SUFFERER

Rajnish Mago, MD
Director of the Mood Disorders Program
Thomas Jefferson University, Philadelphia, PA
Associate Professor of Psychiatry and Human Behavior
Jefferson Medical College, Philadelphia, PA

Richard Weisler, MD, Distinguished Life Fellow of the APA
Adjunct Professor of Psychiatry
University of North Carolina (UNC) School of Medicine, Chapel Hill, NC
Adjunct Associate Professor of Psychiatry and Behavioral Sciences
Duke University Medical Center, Durham, NC
Private Practice, Raleigh, NC