

# Managing Depression in a Managed Care Environment

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## Summary

Major depressive disorder is a costly disease to patients, families, and society. The treatment approach in depression has evolved to focus on achieving remission. This is important for preventing relapse, and for preventing functional and structural changes to the brain from the effects of inappropriately treated depression. Several areas of the brain, including the hippocampus, are important in the pathophysiology, consequences, and treatment of depression.

## Key Points

- Depression is costly and has a large impact on patients, those around them, and society at large.
- Depression is frequently associated with many medical disorders and may have an impact upon them.
- Over time, untreated depression can cause both functional and structural changes in the brain.
- Antidepressants reverse these changes and restore function and structure.
- Damage to the hippocampus and levels of brain-derived neurotrophic factor likely play a key role in depression and its treatment.
- Successful and sustained remission will require that patients take their medications.

THE INCIDENCE RATE OF DEPRESSION is about 17 percent to 24 percent of the general population. In females, the rates are closer to 24 percent. Some degree of genetic predisposition is present. Recent research shows susceptibility to depression based on differences in a serotonin transporter gene. This can be a fatal disease. Approximately 10 percent to 15 percent of depressed patients will commit suicide.

Exhibit 1 illustrates the progression from euthymia to depression to recovery.<sup>1-6</sup> When patients get depressed, their mood decreases. Patients usually seek medical care when they are at the bottom of the mood curve. Treatment brings their mood back up to a symptom-free state (remission).

The treatment approach in depression has evolved over the years to focus on achieving remission. Untreated depression changes progression (Exhibit 2).<sup>7</sup> Inadequately treated depression may have a progressive course and may be associated with functional and structural changes in the brain.<sup>8,9</sup>

Treatment of depression can be divided into two phases – acute and continuation. Acute is to induce remission, and continuation is to prevent relapse. The acute phase of treatment typically lasts 10 to 12

weeks. The continuation or maintenance phase is another 12 weeks.

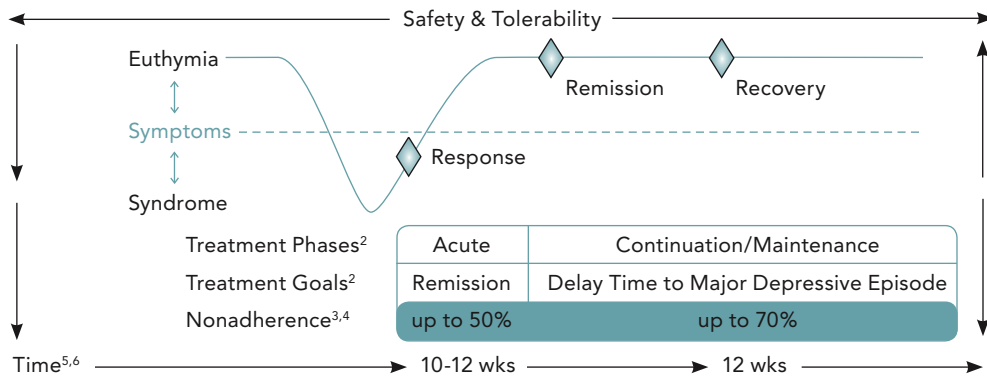
Major depressive disorder (MDD) is a costly, leading cause of disability affecting patients, families, and society.<sup>10</sup> Major depression is the fourth leading cause of disability and results in an estimated \$83.1 billion economic burden annually (Exhibit 3).<sup>10,11</sup> It is estimated that by 2020, MDD will be the second leading cause of disability. When patients are surveyed, 87 percent report moderate to very severe overall functional impairment.<sup>12</sup>

The functional impact of depression can be especially evident in the workplace. In one study, patients who suffered painful physical symptoms lost on average 3.6 days of work each month compared to 4.5 days lost in patients with MDD.<sup>13</sup> Patients with both pain and depression lost 9.4 days at work, approximately one-third of the month.<sup>13</sup>

Employees with depression have high rates of absenteeism, but they also have impaired presenteeism. This is a concept that reflects reduced productivity while at work.

It is not enough to merely ask a patient if he or she is missing work due to depression, as this question only

**Exhibit 1: Major Depressive Disorder (MDD):  
Progression to Disorder and Recovery<sup>1</sup>**



1. Kupfer DJ. J Clin Psychiatry. 1991; 52(5 suppl):28-34.  
2. APA. Am J Psychiatry. 2000; 157(4 suppl):1-45.  
3. Lin EH, et al. Med Care. 1995; 33(1):67-74.  
4. Simon GE, et al. Gen Hosp Psychiatry. 1993; 15:399-408.

5. AHCPR Depression Guideline Panel. 1993.  
6. VHA/DoD Major Depressive Disorder Working Group. 2000 (Module A). 1-35.  
References: 1-6

captures absenteeism. It also is critical to ask about the patient's level of functioning while at work, as presenteeism can be a significant workplace cost associated with depression.<sup>10,14</sup> Kessler and colleagues analyzed data from the National Comorbidity Survey Replication (NCS-R) to estimate the workplace costs of mood disorders and found that major depression was associated with substantial workplace costs, estimating that up to two-thirds of the total workplace costs of depression may be due to presenteeism.<sup>14</sup> The share of total workplace costs of presenteeism increased approximately 11 percent from 1990 to 2000.<sup>10</sup>

Inducing a remission is an important treatment goal for several reasons. Achieving remission can be extremely important to families. In the STAR\*D-Child Report, remission of maternal depression had a positive impact on children's well-being, and non-remission had a negative impact during a three-month acute treatment period.<sup>15</sup> Interestingly, 35 percent of the children of women with depression were diagnosable with depressive, anxiety, or conduct disorders at baseline. Overall, there was an 11 percent decrease in rates of diagnosis for children whose mothers remitted, versus an 8 percent increase shown for children whose mothers did not remit after three months of treatment ( $P=.01$ ).<sup>15</sup> Among children with no disorder symptoms at baseline, those with remitting mothers remained symptom-free, while 17 percent of children of non-remitting mothers acquired a disorder during the three-month study period.<sup>15</sup> The bottom line is that a mother's mental health affects the family.

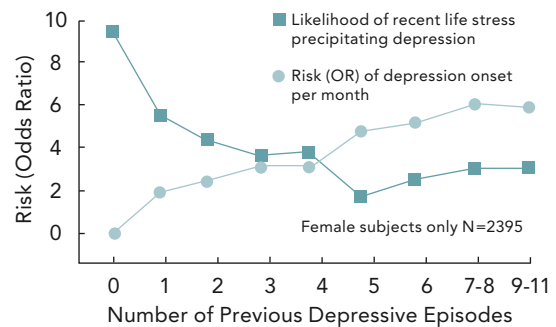
Unfortunately, studies show that few patients receive adequate treatment for MDD. Although 52 percent of patients with MDD in the previous 12 months received health care treatment for their depression,

treatment was at least minimally adequate in only 42 percent of these cases.<sup>12</sup> Overall, treatment was adequate in only 21.6 percent of all patients with MDD in the previous 12 months. Minimally adequate treatment for MDD was defined in this study as either receiving at least four outpatient visits with any type of physician for pharmacotherapy (including use of an antidepressant or mood stabilizer) for a minimum of 30 days, or at least eight outpatient visits with any professional in the specialty mental health sector for psychotherapy (mean 30-minute visit).<sup>12</sup>

Another reason to achieve an asymptomatic remission is to delay recurrence. If patients are treated to complete recovery, they will be symptom-free for a longer period (231 weeks in one study versus 68 weeks for patients who recovered with 1+ mild residual symptoms).<sup>16</sup>

Even the mildest residual symptoms, however, can negatively impact outcomes. Patients with residual

**Exhibit 2: Progression of Depression:  
Adverse Effects of Each Successive Episode**



Kendler KS, et al. Am J Psychiatry 2000; 157(8):1243-1251.  
Reference: 7

subthreshold depressive symptoms experienced on average a faster time to relapse than did asymptomatic patients. Targeting and treating pain symptoms also has a significant impact on the number of patients who enter remission (36 percent versus 18 percent).<sup>17</sup>

Depression is frequently associated with and may negatively impact other medical disorders.<sup>18-26</sup> Elderly patients with high depressive symptomatology have higher rates of stroke and are more likely to die of stroke compared to non-depressed patients.<sup>19-21</sup> Post-stroke patients are more likely to develop depression while post-stroke depression increases risk of death by 18 percent.<sup>20,22,23</sup>

There are associations between depression and heart disease. Depression increases the likelihood of patients developing various cardiovascular diseases, including coronary heart disease, congestive heart failure, ischemic heart disease (IHD), and especially acute myocardial infarction (MI).<sup>24</sup> For patients with cardiovascular diseases, developing depression is common and a predictor of mortality and morbidity. Depression has been shown to double the mortality rate after heart failure.<sup>25</sup> Post-MI depression is associated with a fourfold increase in the risk of mortality in the six months following an MI.<sup>26</sup>

A reason to treat patients early is that the rate of recovery from depression diminishes as the duration of a major depressive episode increases (Exhibit 5).<sup>27</sup> The longer the patient waits, the harder it is to get depressive symptoms under control.

There are three key brain areas involved in regulation of mood: the ventromedial prefrontal cortex,

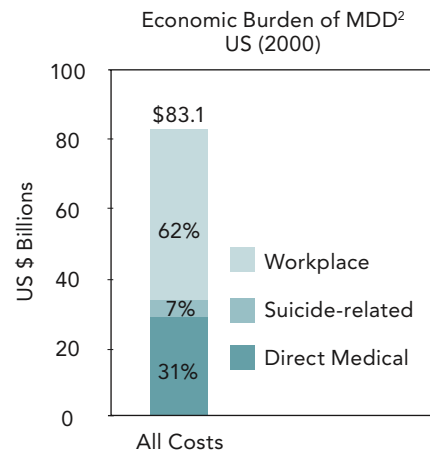
lateral orbital prefrontal cortex, and dorsolateral prefrontal cortex.<sup>28</sup> The ventromedial prefrontal cortex modulates pain, aggression, and sexual and eating behaviors. This area is hyperactive in depression. A hyperactive ventromedial prefrontal cortex may result in injury to the hippocampus. The lateral orbital prefrontal cortex corrects and inhibits maladaptive, perseverative, and emotional responses. Activity in this area is increased in depression, obsessive-compulsive disorder, posttraumatic stress disorder, and panic disorder. The dorsolateral prefrontal cortex provides cognitive control, solving complex tasks, and manipulation of information in working memory. This area is hypoactive in depression, which has been associated with neuropsychological manifestations of depression.

Two additional areas involved in mood regulation are the amygdala and the hippocampus.<sup>29</sup> The amygdala is involved in emotional learning and memory. Abnormal activation of the amygdala correlates with the severity of the depression. The amygdala also may be implicated in the tendency of depressed patients to ruminate. The hippocampus is involved in contextual learning and memory, and provides regulatory feedback to the hypothalamic pituitary axis. Dysfunction in the hippocampus may be responsible for inappropriate emotional responses.

The key areas of the brain communicate through gamma-aminobutyric acid (GABA) and glutamate. Serotonin and norepinephrine influence the balance between excitatory (glutamergic) and inhibitory

**Exhibit 3: MDD is Disabling and an Economic Burden**

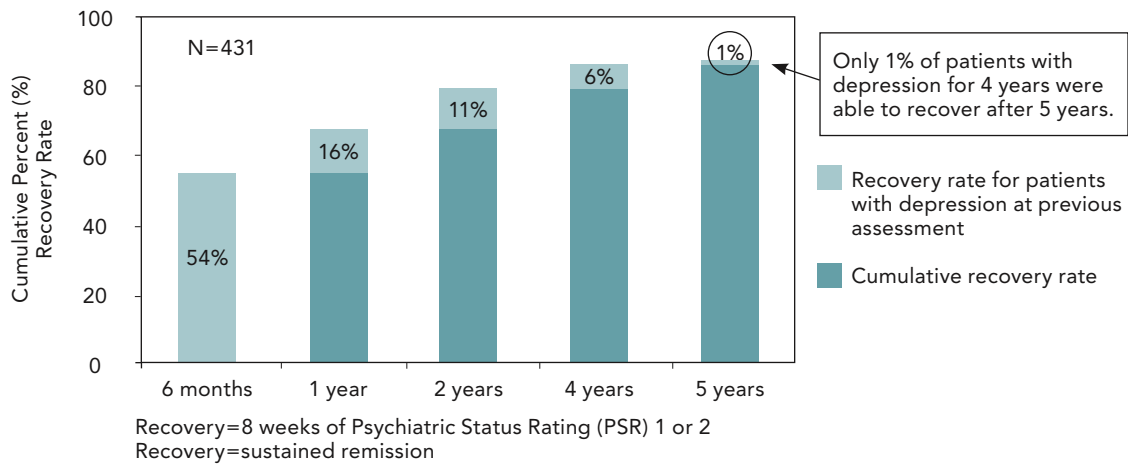
Disability <sup>1</sup>		
Rank	1990	2020 (est)
1	Lower respiratory infections	Ischemic heart disease
2	Perinatal conditions	Major depressive disorder
3	HIV/AIDS	Road traffic accidents
4	Major depressive disorder	Cerebrovascular disease
5	Diarrheal diseases	Chronic obstructive pulmonary disease



\*Rank based on a composite measure of Disability - Adjusted Life Year (DALY) in 15-44 year olds

1. Murray CJ, et al. *Science*. 1996;274:740-743  
 2. Greenberg PE, et al. *J Clin Psychiatry*. 2003;64:1465-1475.

Exhibit 4: Rates of Recovery Diminish with Duration of Major Depressive Episode



Keller MB, et al. Arch Gen Psychiatry. 1992; 49:809-816.  
Reference: 8

(gabanergic) activity in the prefrontal cortex and the limbic system. Excitatory neurons from the prefrontal cortex have regulatory influence on the locus coeruleus and dorsal nuclei raphe.

The hippocampus appears to be the weak link in the brain. The hippocampus is at a “vulnerable intersection” of cognitive, emotional, and neuro-endocrine regulation.<sup>30</sup> It is rich in glucocorticoid receptors and is a recipient of significant input from excitatory glutaminergic neurons. Approximately half of persons with severe depression exhibit high levels of the stress hormone cortisol, which is thought to be toxic to neurons. Excessive excitatory input from the ventromedial prefrontal cortex and increased levels of glucocorticoids also may have a toxic effect in the hippocampus.<sup>31</sup> Hippocampal dysfunction may contribute to cognitive impairment, and emotional and neuro-endocrine dysregulation, observed in MDD.

During depressive episodes, normal mechanisms may malfunction and lead to hippocampal damage. Hippocampal dysfunction then leads to increased glucocorticoids via the HPA axis. The increase in glucocorticoids continues to damage the hippocampus, resulting in a “runaway” system and even more neuronal damage.<sup>31</sup> Some studies have shown that the hippocampus atrophies with depression. The duration of time that depression is untreated is inversely related to hippocampal volume, with longer periods of untreated depression correlated with lower total hippocampal volume.<sup>42</sup>

MDD may be more than just a psychiatric disease, as there is evidence of widespread systemic consequences (Exhibit 5).<sup>24</sup> Neuroendocrine dysregulation and elevated sympathetic tone may result in cardiovascular

morbidity and increased risk of metabolic syndrome. Immune response may be compromised in MDD.

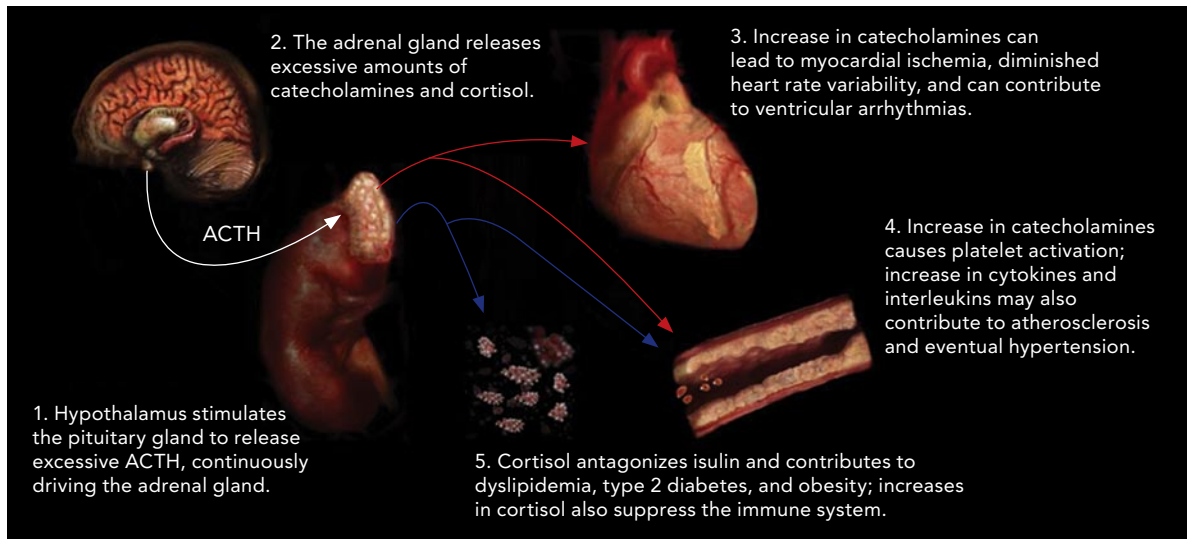
The neurotrophic hypothesis of depression states that a deficiency in neurotrophic support may contribute to hippocampal pathology during the development of depression, and that reversal of this deficiency by antidepressant treatments may contribute to the resolution of depressive symptoms. Neurogenesis (the birth of new neurons) continues postnatally and into adulthood in the brains of many animal species, including humans. One specific area where neurons continue to be born throughout life is in the hippocampus.

Neurogenesis is regulated by growth factors, including brain-derived neurotrophic factor (BDNF), which can lead to the development of new cells and help keep them alive.<sup>33</sup> Neurotrophic factors such as BDNF are critical for growth and guidance of the developing nervous system, and the survival and function of the adult learning system, learning, and memory.

BDNF has been shown to be associated with regulation of mood, and in preclinical studies, to be influenced by stress and perception of pain. In one study, patients with MDD had significantly lower levels of BDNF compared to control subjects. Antidepressant treatment was shown to raise BDNF levels back to normal levels. Both 5-HT and NE are believed to play roles in the modulation of BDNF. Antidepressants act in part by inducing neurotrophic effects that reverse the structural changes that may have occurred.<sup>34</sup> Antidepressants increase the synaptic levels of NE and 5-HT during the course of weeks or months, suggesting that adaptation or plasticity is necessary for therapeutic response. BDNF also helps the hippocampal cells stay healthy.

Severe stress can cause several changes in the

### Exhibit 5: Major Depressive Disorder May Have Systemic Consequences



Musselman DL, et al. Arch Gen Psychiatry 1998; 55(7):580-592.  
Reference: 24

hippocampal neurons, including a reduction in their dendritic branching, and a reduction in BDNF expression, which could be one of the factors mediating the dendritic effects. Antidepressants are thought to produce the opposite effects; they increase dendritic branching and BDNF expression of the hippocampal neurons. By these actions, antidepressants may reverse and prevent the actions of stress on the hippocampus, and therefore may ameliorate certain symptoms of depression. Early and sustained treatment with antidepressants may be necessary to reverse or prevent damage to the hippocampus.

The best way to optimize the chance of a remission is to initiate therapy early and make sure the patient takes his or her medication. One challenge of depression treatment is nonadherence. There can be a 50 percent nonadherence rate during the acute phase of treatment and up to a 70 percent nonadherence rate during the continuation phase of treatment. Seventy-five percent of antidepressants are discontinued by four months of therapy.

There are several interventions that can help improve medication compliance. Patients need to be educated about the disease and treatment options, and the common side effects of the prescribed antidepressant medication, and need to be reassured that other medication options will be explored in the event of side effects. The most important education point is to emphasize that these medications need to be taken on a daily basis to be effective. Patients need to know that antidepressant medications are not addictive; do take several weeks to begin working; and do not cause end organ damage. Another

point to emphasize is that continued treatment with medication has a neuro-protective effect.

In order to maximize the chance of a remission, there are some important issues to address when treating depressed patients with comorbid anxiety disorder, substance abuse and dependence, or chronic pain. In patients with comorbid anxiety disorder, high anxiety is associated with higher suicide risk and reduced remission rates. Patients with high levels of anxiety are frequent utilizers of medical services. The patient's anxiety should be addressed and treated aggressively. Short-term use of benzodiazepines along with the antidepressant medication is recommended for these patients. These patients also should be referred for cognitive behavioral therapy.

Substance abuse and dependence is commonly missed in the clinical interview, but is easily detected by conducting a urine drug screen and checking liver function tests. The CAGE questionnaire also is a good tool to detect alcohol abuse. Patients with substance issues should be referred to a treatment program. Because addiction is a chronic disease and requires lifelong treatment, health care providers need to avoid getting frustrated with patients who repeatedly relapse. These patients need to be educated that treating depression without treating the underlying substance abuse is minimally effective, and at times dangerous.

Chronic pain by itself frequently results in depression, but it also exacerbates depressive symptoms. Depressive symptoms lower pain threshold and result in exaggerated pain response. Improving a patient's pain symptoms increases the

odds for depression remission. Aggressive treatment of depressive symptoms will allow for better pain management and reduce utilization of medical services. Tricyclic and serotonin-norepinephrine uptake inhibitor (SNRI) antidepressants are most effective for these patients. The SNRIs are preferred due to their safety and tolerability profile.

Interventions to treat MDD include biological (antidepressant medications), psychological (cognitive behavioral therapy), and social (change in living situation). The use of multiple interventions increases the likelihood of achieving remission.

If a patient does not get better, the diagnosis should be reconsidered. The patient may have bipolar or another psychiatric disorder. If the patient is not responding to the treatment, he or she can be referred to a psychiatrist. Case management and involvement of pharmacists can be beneficial in keeping patients on therapy.

## Conclusion

Major depressive disorder is a costly disease in terms of morbidity, mortality, and economics. Patients need to be treated appropriately to remission to prevent relapse. Medication may be necessary for long periods of time to prevent the long-term consequences to the brain and other body systems of inadequately treated depression. **JMCM**

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