Depression is among the most disabling and costly illnesses in the world. Despite good short-term efficacy outcomes in the treatment of depression, long-term outcomes remain disappointing. Depression continues to be missed or underdiagnosed and undertreated, and comorbidities are frequently not identified. Of particular concern is the low rate of depression treated to full remission. Treating only to response leaves patients with residual depressive symptoms and an increased risk of a recurrent or chronic course. Anything less than full remission should be considered a treatment failure. This article examines the substantial psychiatric, medical, functional, and economic costs associated with not achieving remission. Available pharmacoeconomic data and randomized, controlled clinical trials published in the last 5 years identified through Medline searches with terms including burden, cost, economics, serotonin reuptake inhibitors (also, specific agents), venlafaxine, nefazadone, mirtazapine, psychotherapy, remission, and depression were reviewed. One of the limiting factors to this review is that few trials have compared the effects of various antidepressant strategies on clinically relevant outcomes such as depression-free days and patient productivity, making the full benefit of remission more difficult to measure. Patients who fail to achieve a full remission have a more recurrent and chronic course, increased medical and psychiatric comorbidities, greater functional burden, and increased social and economic costs. Cost-effective treatment for depression includes antidepressant therapies with higher remission rates. Antidepressants with a dual mechanism of action and combination therapies are associated with higher remission rates, more depression-free days, reduced pain-symptom morbidity, reduced health service utilization, and improved productivity.

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**Clinical Implications**

- Depression is among the most disabling and costly illnesses in the world, and greater effort should be made to diagnose and treat it.
- Patients should be treated to remission; response in the absence of full remission constitutes an adverse outcome and is associated with a more recurrent and chronic course, increased medical and psychiatric comorbidities, greater functional burden, and increased social and economic costs.
- Antidepressant strategies with higher remission rates, such as those with a dual mechanism of action and combination therapies, may provide more depression-free days, reduced pain symptom morbidity, reduced health service utilization, and improved productivity.

**Limitations**

- This is a narrative review.
- Few trials have compared the effects of various antidepressant strategies on clinically relevant outcomes such as depression-free days and patient productivity.
- Few data are available on combination and augmentation strategies to improve the rates of remission.

**Key Words:** major depressive disorder, remission, burden, cost, economic, functional, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors
Major depressive disorder (MDD) is a prevalent medical condition that is frequently recurrent or chronic and has a high risk for mortality and morbidity (1). Approximately 8% of adults will experience MDD at some time in their lives, and the 1-year prevalence rate is 4.1% to 4.6% in Canada (2). Depression is frequently recurrent or chronic and holds a high risk of morbidity and mortality. Among the most disabling illnesses in the world (3,4), the burden of depression includes psychiatric, medical, functional, and economic costs. Taken together, these may be more clearly defined as the “human cost.”

Depression Outcomes Are Disappointing
An apparent paradox has emerged in the management of depression. While short-term studies with antidepressants have demonstrated excellent efficacy outcomes, the long-term outcome for depression remains rather disappointing. Myriad modifiable deficiencies have been enumerated, including missed or underdiagnosis (5), ineffectual treatment paradigms (5,6), undertreatment (5,6), failure to identify comorbidity (7–10), and failure to treat to full remission (11–13).

The National Depressive and Manic-Depressive Association consensus statement found overwhelming evidence that individuals with depression were being undertreated (5). This undertreatment contributes to protracted suffering and impairments in work and interpersonal relationships and leaves patients with a heightened risk of suicide. Undertreatment may be related to patients not seeking care or being noncompliant or to physicians inadequately evaluating and treating these patients (5). More than 25% of patients with depression in primary care do not receive guideline-concordant therapy (6). In a recent trial involving 239 patients with 5 or more symptoms of depression, 27.6% were identified as failing to meet criteria for guideline-concordant treatment. Barriers to care that were identified included patient resistance, patient noncompliance, physician clinical judgement, patient psychosocial burden, and health care system problems. By contrast, there is evidence that more people in Canada with MDD are being treated appropriately, and this has been associated with an improvement in population health status (14).

When patients fail to achieve symptomatic remission, the diagnosis of unipolar MDD should be reassessed to determine whether it is indeed accurate. For example, it has frequently been noted that patients with bipolar disorder utilize health care services in the depressive phase 2 to 3 times more often than in the manic state (15,16). Therefore, it is not surprising that 35% to 45% of patients with bipolar disorder are initially diagnosed with unipolar depression (9,10). As in MDD, failure to achieve full remission of bipolar disorder leaves the patients with residual depressive symptoms (17,18) and a higher risk of a recurrent or chronic course.

Full Remission vs Response as the Goal of Therapy
The term “response” usually denotes a 50% reduction in depression scores, while the term “remission” refers to the virtual elimination of active depressive symptoms (for example, 17-item Hamilton Depression Rating Scale [HDRS17] scores ≤ 7 or 7-item HDRS [HDRS-7] scores ≤ 3) (19,20). It is becoming increasingly recognized that responding to therapy but failing to achieve full remission constitutes an adverse outcome (11–13). The typical rates of response across antidepressant trials are 60% to 70%, while remission rates are much lower (range 30% to 50%) (21,22). Antidepressant response rates in a tertiary, university-affiliated hospital database of 259 patients revealed that only 36% of patients achieved full remission with antidepressant treatment, implying that 64% of patients had no or only partial response (23).

Remission rates in primary care settings have been estimated at 45% over a 2-year period (24). In moderate-to-severe depression, lower remission rates (25,26) or a longer time to remission, compared with those achieved in specialist care, have been reported (27). The case is less clear for milder depressions (28,29). The implementation of interventional programs that include educational programs for physicians and that help to increase patient follow-up using nurses and other health care professionals has proven effective in diminishing depressive symptomatology (30,31). Despite the added cost of these programs, quality improvement initiatives, particularly those focused on pharmacotherapy, have shown decreases in the number of days with depressive burden and the number of days lost to work (32).

Evidence suggests that there is a window of opportunity for achieving full remission of depression. An increasing duration of depression has a negative impact on the probability of recovery (33,34). In a study of 431 patients with MDD, 50% of patients recovered within the first 6 months (34). The likelihood of recovery in subsequent months declined from 15% during the first 3 months of follow-up to 1% to 2% per month during years 3, 4, and 5. Chronic mood symptoms for 2 years or more have been associated with a doubling of the risk of relapse (33).

Clinical Impact of Not Achieving Full Remission

Psychiatric Burden
Failing to achieve full remission of MDD significantly impairs patient functioning and increases the risk of relapse (33,35–37). The presence of ongoing subthreshold symptoms...
after major depressive episodes (MDEs) suggests that the illness is still active (37). Patients with residual subthreshold depressive symptoms have significantly more severe and chronic courses, with shorter well intervals and fewer symptom-free weeks during follow-up, than asymptomatic patients (Table 1) (36). Several studies have reported that the risk of recurrence is 3 times that of patients without residual symptoms (33,35,37). In addition, patients with residual symptoms relapse to their next MDE more than 3 times faster than asymptomatic patients and to any depressive episode more than 5 times faster (37). Survival analysis of over 20,000 patients discharged with a diagnosis of an affective disorder revealed that the rate of recurrence increased with the number of previous episodes during over 15 years of follow-up (38). Continuing antidepressant therapy can significantly reduce the odds of relapse by 70% (39). Pooled data from 31 trials estimated a 41% relapse rate on placebo, compared with 8% on active treatment.

Over the long term, chronic or recurrent depression may be associated with morphometric changes in the brain. Using magnetic resonance imaging, Sheline and colleagues found that subjects with a history of depression had smaller hippocampal volumes bilaterally than did control subjects (40). In addition, subjects with depression scored lower in verbal memory, a measure of hippocampal function, suggesting that the volume loss was related to cognitive functioning. Other studies have found similar results, suggesting a deleterious effect of psychiatric symptoms on brain structure and function.

Mood disorders, especially MDD, are highly associated with suicide. Comorbidity with other disorders (such as anxiety, agitation, and rapid changes in the depressive state) increase suicide risk (41). Modelling data available as of 1994 place the risk of completed suicide in MDD patients at 3.4%, with a higher risk in men (7%) than women (1%) (42). Depressed males under age 25 years were found to be 10 times more likely to die from suicide than their female contemporaries. A metaanalysis of suicide studies in psychiatric patients estimated overall death from suicide to be 6% (43). The actual lifetime risk of suicide in MDD may be estimated as between 3.4% and 6% (42). The National Comorbidity Survey found that patients with MDD had an odds ratio (OR) of 11 for suicide ideation and an OR of 9.6 for suicide plans, compared with those without any disorder. (44,45).

Depression is frequently comorbid with other psychiatric diagnoses. Comorbid conditions have implications for assessment, management, prognosis, course, and outcome of both associated conditions (7,46). Depression is particularly prevalent in association with anxiety disorders, substance use disorders, and eating disorders, but it is also seen in patients with schizophrenia, attention-deficit hyperactivity disorder (ADHD), and dementia (7). The National Comorbidity Study of individuals with MDD reported a lifetime prevalence of at least 1 comorbid disorder in 74% of patients, including both anxiety disorders (58%) and substance use disorders (39%) (8).

Medical Burden

Depression is also highly comorbid with medical illnesses, which can contribute to poor outcomes (46–48). A more comprehensive discussion of the topic can be found in recent review articles (7,49–52). Patients with bipolar and unipolar disorder have been shown to have mortality rates 1.5 to 2 times greater than those of the general population (53). Excess deaths were the result of suicide and natural causes, especially cardiovascular, cancer, cerebrovascular, and respiratory causes. A national survey of 2058 community-dwelling persons aged 60 years or over found that persons with a medical condition tended to have higher depressive symptom scores than those without a medical condition and that the number of comorbid medical conditions showed a significant linear association with depression (47). The use of general medical services by depression patients is 30% to 50% higher than that of patients without depression and is associated with significant increases in the cost of general medical services (54,55). Moreover, primary care patients described as “high utilizers” of health services often have a cryptic mood disorder (56,57). The average length of stay on medical or surgical units was increased by 10 days when medical patients were depressed and by 26 days if patients were not receiving treatment for their depression (58).

| Table 1 Incomplete recovery from first episode of MDD increases the risk of a chronic course |
|-----------------------------------------------|-----------------------------------------------|
| Duration of follow-up, mean (SD) years        | Residual subthreshold symptoms, n = 24         |
|                                               | Asymptomatic patients, n = 70                   |
| Time to major depressive episode, weeks       | 9 (4.3)                                       |
| Free of any depressive episodes during follow-up, % (n) | 8 (2)                                      |
| % of weeks in subthreshold or threshold depression | 68                                           |
| Data are from Judd and others (38).           |                                               |
Somatic symptoms at presentation are reported by 69% to 76% of patients with depression, with one-half of the depression patients reporting multiple unexplained somatic symptoms (59,60). Somatic presentation decreased the likelihood of physician recognition and diagnosis of depression from 77% in patients with a psychosocial presentation to 22% in those with a somatic presentation (60). Depression is frequently associated with unexplained somatic symptoms (51), pain (51,61,62), coronary disease (63–66), cerebrovascular disease (67), osteoporosis (68,69), and diabetes (70). Further, recent data suggest that depression may accelerate the onset of perimenopause (71), which is already an at-risk period for metabolic bone disease.

As many as 76% of patients suffering from depression were found to report pain symptoms, including headache, stomach pain, vague and poorly localized pain, and back pain (51,61). Patients with MDD were 4 times more likely to report a painful physical condition, compared with those without depression (62). Data show that patients who have achieved remission have significantly fewer somatic complaints, compared with those who have only a partial response (51). It is a provocative hypothesis, which requires empirical confirmation, that antidepressants that offer higher remission rates also offer greater symptom relief in the treatment of painful physical symptoms.

Depression after acute myocardial infarction (MI) was associated with a significantly higher risk of cardiac events (63–66). Depression increased the risk for cardiac mortality by up to 4 times in subjects both with and without cardiovascular disease at baseline (66). In a cohort of patients with cardiovascular disease, the relative risk (RR) of cardiovascular mortality was 1.6 for patients with minor depression and 3.0 for patients with major depression, compared with patients without depression. Similar increased cardiovascular mortality risks were associated with minor depression (RR 1.5) and major depression (RR 3.9) among subjects without cardiovascular disease at baseline. Similarly, the RR of a cardiac event in patients with unstable angina was 4.68 times higher in patients with depression, compared with those without (72). During the 13-year follow-up, patients with a history of MDD were 2.6 times more likely to report stroke than those without (67).

Major depression may increase the risk of bone loss among both men and women (68,69). In a study in 24 women, the mean bone density in the women with depression was 14% lower at the femoral neck, 11% lower at the trochanter, and 6% lower at the spine (69). It is not known whether this bone loss will result in increased fractures or whether treatment of depression can prevent or reverse decreases in bone density.

These data support the concept of medically toxic effects of depressive symptoms. It stands to reason that treating to full remission may improve symptoms and prevent medical morbidity.

**Functional Burden**

Depression is associated with a substantial functional burden. Employees with depression are absent from work about twice as much as other employees (73). Among employees reporting any work loss in the previous 30 days, those with depression (n = 200) were absent 7.6 days, compared with 4.7 days for all other employees (n = 6448) (P < 0.05). The salary-equivalent productivity loss averaged between $182 and $395, similar to the direct costs of successful depression treatment (73). In addition, workers with persistent depression are 7 times more likely to be less effective on the job (74). Depression has a significant economic impact on employers, in terms of disability, recidivism, and medical plan costs (75,76).

The severe impairments in psychosocial functioning seen in chronic depression patients are improved with antidepressant therapy (77). However, only patients who reached full remission achieved levels of psychosocial functioning that approached or equalled those of community samples. Analysis of data from a randomized trial found that patients in remission were more likely to maintain paid employment and report fewer days missed from work due to illness, compared with those with partial or no response (Figure 1) (78). Pooled data from 8 clinical studies of patients with moderate-to-severe MDD found that venlafaxine was associated with earlier achievement of sustained full work function, compared with treatment with either selective serotonin reuptake inhibitors (SSRIs) or placebo (79).

**Economic Burden**

In the US, the total annual cost of depression in 1990 was estimated to be US$44 billion, with absenteeism and productivity costs accounting for US$24 billion (80). A comprehensive Canadian analysis in 1998 estimated the total mental health burden at $14.4 billion, placing mental health problems among the costliest conditions in Canada (81). Reduced productivity associated with depression and distress over the short term was estimated at $6 billion (81).

Depression is among the most disabling illnesses in the world (3,4). The Global Burden of Disease study found that neuropsychiatric conditions account for almost 30% of the world’s years of life lived with disability (YLDs), and unipolar MDD alone accounted for 11% (82). Depression ranked fourth in disability-adjusted life years (DALYs; a measure of years of healthy life lost to either premature death or disability) in 2000, and it is estimated that depression will rank second by 2020 (3,4). It stands to reason that this disquieting trend can be modified if improvements are made in the detection, diagnosis, and treatment of depression.
Evidence supports the idea that the dual-mechanism antidepressants and combination therapy, which may have higher rates of remission, may also yield lower health care and societal costs. Several analyses have demonstrated that venlafaxine as first-line therapy is a cost-effective option, providing more symptom-free days at a lower cost, compared with SSRIs and tricyclic antidepressants (83–89). Cost advantages have been related to fewer total and psychiatric outpatient visits (85), more symptom-free days, and fewer hospitalizations (88).

In economic studies conducted in North America and the UK using decision modelling, nefazodone has been shown to be cost-effective in the treatment of depression when compared with imipramine and perhaps fluoxetine (90–93). Compared with psychotherapy, nefazodone monotherapy was less costly per acute responder than the cognitive behavioral analysis system of psychotherapy (CBASP) used alone or in combination with nefazodone in patients with chronic depression (94).

Decision modelling using costs from 4 European countries determined that mirtazapine was more effective and less costly overall in Austria, France, Sweden, and the UK, compared with amitriptyline or fluoxetine (95–97). Mirtazapine was less costly in terms of productivity in all except the UK analysis (95).

Despite higher acquisition costs, combination therapy can be more cost-effective than monotherapy for MDD. A prospective estimate of cost-effectiveness found that the combination of fluoxetine and pindolol incurred lower direct medical costs than treatment with fluoxetine alone over 6 weeks of treatment (98). In addition, the combination of SSRI and psychotherapy improved response rates and was less costly than SSRI therapy alone (99).

**Summary**

Depression is a significant clinical and economic burden throughout the world. Currently, outcomes remain disappointing but could be improved by striving to achieve and sustain full remission. Better outcomes are associated with early and aggressive treatment and the choice of initial antidepressant medication, which maximize the chances of attaining full remission. The cost of not achieving remission is a more recurrent and chronic course as well as increased medical and psychiatric comorbidities, including increased somatic complaints of pain and a greater cost to human capital.
Antidepressant therapies with a dual mechanism of action and combination therapies, which are associated with higher remission rates, have been shown to be cost-effective in the treatment of depression. Benefits include higher remission rates, more depression-free days, greater breadth of somatic symptom improvement (including pain syndromes), improved psychosocial functioning, reduced health service utilization, fewer psychiatric outpatient visits, fewer hospitalizations, and improved productivity.

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