It is well established that patients with major depressive disorder (MDD) typically present with an impairment in daily functioning.\(^1,2\) This can include functional disability at work and school, as well as impairment in roles at home and in social situations and interpersonal relationships. As part of recovery, the restoration of premorbid functioning is one of the goals of therapy in MDD.\(^3\)

This article summarizes the case for functioning as an important outcome in MDD management. Included is a review of the impact of MDD on patient function and an overview of medication treatment factors that can impact function in this patient population. This discussion focuses on the impact of antidepressant efficacy and tolerability as important contributors to functional outcomes, and suggests that one should keep both of these variables in mind when attempting to improve functioning with an antidepressant regimen. A brief discussion of the tools that can be used for assessment and monitoring of function is, therefore, also included.

**Impaired Function: A Significant Part of the Burden of MDD**

MDD is one of the world’s most significant causes of disability. The World Health Organization ranks it number one in terms of years lived with disability globally, with its impact most significant in developed economies. By 2020, MDD will be second only to ischemic heart disease in terms of global impact on disability (measured by disability-adjusted life years [DALYs]).\(^4\)

Researchers have reported that approximately two thirds of patients with MDD have severe impairment in quality of life.\(^5\) Perhaps most important on a practical basis, MDD impairs an individual’s ability to function normally in day-to-day life. For some individuals, it prevents them from going to work or school (i.e., absenteeism), while others who are able to go to work or school suffer an impairment in the quality of work they can do (i.e., presenteeism). A 2006 study compared workers with MDD to those with rheumatoid arthritis (RA)—a group that is known to be vulnerable to work disabilities—and healthy controls. The researchers found that, compared to healthy controls, subjects with depression fared significantly worse on mental-interpersonal, time management, output and physical tasks.\(^1\) Those with MDD had greater performance deficits in managing mental-interpersonal, time, and output tasks compared to those with RA, while those with RA fared significantly worse in managing physical job demands. The study’s authors suggested that physicians need to inquire about the impact of depression on work and monitor the impact of symptom reduction on recovery of work function.

The impact of depression on work function was also examined in a Statistics Canada report based on results from the 2002 Canadian Community Health Survey (CCHS) and the 1994/1995 to 2002/2003 National Population Health Surveys.\(^6\) One of the key findings of this analysis was that most workers (8 in 10) who had experienced depression in the
12 months prior to their survey interviews reported that their symptoms had interfered with their ability to work to some degree (Figure 1). Approximately one third of those surveyed reported that they had experienced moderate-to-very-severe interference with their ability to work. The average number of days—in the course of the previous year—on which respondents were totally unable to work or carry out normal activities was 32, and 40% of respondents lost at least six work days due to depression. This impact on work function was shown to be considerably greater for patients with MDD than for those with no such history. Figure 2 shows the relative impact on reduced work activities, mental health disability days and absenteeism for those with or without a history of MDD.

Other researchers have also used the CCHS database to quantify the impact of MDD on workplace function. McIntyre et al., for example, showed that the odds ratio for one or more mental health disability days in the past two weeks was 5.6 for those with MDD compared to those with no history of mood disorders.7 Patten et al. showed that MDD was significantly associated with an increased risk of transition to non-working status (hazard ratio of 2.6 compared to those with no history of mood disorders).8 American data also illustrate the considerable burden of MDD on workplace function. Data from the U.S. National Comorbidity Survey Replication show that MDD was associated with an average of 8.7 work days lost to illness per year (absenteeism) and an additional 18.2 days per year of “lost-day” equivalents due to presenteeism.9

The effects of MDD on job functioning, as shown in the above-mentioned studies, form an important part of the economic burden of MDD. A study by
Health Canada estimated that depression and distress cost Canadians approximately $14.4 billion annually—an estimate that is now 12 years old (1998 data were used in the analysis) and that even at the time of publication was indicated by the authors to be a conservative estimate. Of the total cited in this study, which encompassed costs of treatment, medication, lost productivity and premature death, indirect costs for lost productivity accounted for more than half the burden (approximately $7.7 billion annually). Recent measurements of the true economic burden of mental illness in Canada estimated annual costs of $51 billion, with approximately one third of the burden being due to short-term sick leaves and long-term disability, and more than one half due to reductions in health-related quality of life.

The observation that MDD causes lost productivity is understandable, given the demographic that this disorder affects. A study published in 2007, using data from Ontario, showed that approximately 75% of people with depression are between the ages of 20 and 64 years (Figure 3), the peak years of employment and of workplace productivity. Other statistics suggest that the majority of people of working age who suffer from depression are indeed employed. Data from the 2002 CCHS showed that 71% of 25- to 64-year-old Canadians who reported having experienced a major depressive episode in the previous 12 months were employed.

The effects of MDD on patient functioning also extend beyond the workplace. In fact, research has shown that more than half of MDD patients report impairments rated as moderate or worse in home, relationship and social domains of functioning (Figure 4).

The above-mentioned observations clearly illustrate that MDD has a considerable impact on function in the workplace and beyond. As such, improving function should be one of the goals of treatment.

Improving Function in MDD: A Recognized Goal of Therapy

The 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults list the goals for treatment of the acute and maintenance phases of MDD (Table 1). In recognition of the importance of restoring function as a component of overall treatment success, the authors included (for the first time in Canadian treatment guidelines) restoration of function and return to full functioning and quality of life as goals for the acute and maintenance phases of treatment, respectively. These recommendations reflect the potential for incremental functional improvements all along the path to recovery.

That resolution of symptoms and restoration of function are listed as separate treatment goals reflects a common observation made by many practicing clinicians: resolution of symptoms does not necessarily equate to restoration of premorbid function. In a recent assessment of educational needs in Continuing Health Education (CHE) in Canada, more than 40% of physicians reported that, among their MDD patients in symptomatic remission, more than 30% were still not functioning as optimally as possible. Of note, the recognition of function as a treatment goal by physicians and guideline authors is in line with observations from patients. A separate national survey, conducted in 2009, showed that the vast majority (approximately 90%) of MDD patients were concerned about the functional impact of depression; 62% indicated that they were “very concerned.”

In addition to its importance as a treatment goal, patient function has also been recognized as an important variable to be included in clinical-trial protocols. Some authors have pointed out that, although
a diagnosis of depression is made based on the presence of symptoms and functional impairment, most clinical trials do not include function in their definitions of response or remission. In 2009, McKnight and Kashdan published an article documenting the disconnect between traditional efficacy outcomes and functional status. In this “call to arms” paper for the psychiatric specialty, the authors stated that “functional outcomes might offer depression researchers more critical feedback and better guidance when studying depression treatment outcomes.”

The separation of symptom resolution and functional improvement in the guidelines, and the call to include more functional outcome measures in clinical trials, illustrate the important concept that improvements in symptoms does not necessarily translate into improved function in MDD. Functional improvement may involve improvements in symptoms, but is influenced by other variables as well, including tolerability of the treatment regimen. For example, a patient’s ability to function normally at work may be negatively affected by some of the core symptoms of depression (e.g., tearfulness, irritability, poor concentration), with successful treatment leading to resolution of these symptoms and functional restoration. However, some antidepressant side effects may counteract these benefits. If the treatment regimen also causes insomnia, daytime sedation or other undesirable effects, for example, then overall function is not likely to be restored.

This concept is illustrated in Table 2. The column on the left shows the impact of the symptoms of depression, while the column on the right shows the potential side effects of antidepressant medications (these include the top symptoms identified by patients as having an impact on work function in a survey conducted by CANMAT). The corresponding entries in the middle column are the potential im-
pairments in function in the workplace related to the entries in the left and right columns. The goal of treatment selection is to choose a regimen that is most effective at alleviating the symptoms on the left side, while having the lowest propensity to cause the side effects on the right. Using this approach when choosing agents improves the chances of restoring the patient’s function as quickly and completely as possible.

Impact of Antidepressants on Patient Function

To reduce the impact of MDD, experts recommend pharmacotherapy (e.g., selective serotonin reuptake inhibitors [SSRIs]) as part of the treatment strategy. With respect to function, each agent’s profile of efficacy and tolerability can help clinicians predict which will have the most favourable impact.

While many effective antidepressants are available, none of these is 100% effective in resolving all symptoms in all patients with MDD. Similarly, while the newer antidepressants (e.g., SSRIs and serotonin-norepinephrine reuptake inhibitors [SNRIs]) are generally well tolerated, no single agent is completely free of side effects. When selecting a therapy, one therefore needs to analyze the risk:benefit profile of each agent and determine which is best for the individual patient.

Such an analysis has been carried out in a systematic fashion using clinical-trial data for the various antidepressant medications. Cipriani et al. compiled data from randomized controlled trials in MDD involving 12 different newer antidepressants: the SSRIs citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; the SNRIs duloxetine and venlafaxine; as well as bupropion, milnacipran, mirtazapine and reboxetine. A total of 117 studies met the authors’ standards for inclusion into their analysis, which collectively included a total of 25,928 patients.

The analysis examined two separate variables: efficacy and acceptability. For efficacy, the authors used response as their variable, defined as a reduction of at least 50% from baseline on the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS), or a rating of “improved” or “very much improved” on the Clinical Global Impression (CGI) scale. Acceptability was simply measured by the number of patients who dropped out of the studies for any reason during the first eight weeks. For both analyses, the authors used fluoxetine as the reference compound.

Table 2. How Do Depressive Symptoms and Medication Side-effects Impact Function?

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>FUNCTION</th>
<th>SIDE EFFECTS</th>
</tr>
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<tbody>
<tr>
<td>Clinical</td>
<td>Workplace</td>
<td>Clinical</td>
</tr>
<tr>
<td>Irritability</td>
<td>Conflict</td>
<td>Sweating</td>
</tr>
<tr>
<td>Sadness</td>
<td>Unexpected emotions</td>
<td>Agitation/anxiety</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Withdrawal</td>
<td>Apathy</td>
</tr>
<tr>
<td>Loss of enjoyment</td>
<td>Poor motivation</td>
<td>Nausea and GI effects</td>
</tr>
<tr>
<td>Helplessness</td>
<td>Decreased task efficiency</td>
<td>Intoxication/feeling “buzzed”</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Increased errors</td>
<td>Daytime sedation</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>Poor decision making</td>
<td>Headaches</td>
</tr>
<tr>
<td>Memory problems</td>
<td>Reduced task vigilance</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Indecisiveness</td>
<td>Limited range of activities</td>
<td>Constipation/dry mouth</td>
</tr>
<tr>
<td>Sleep changes</td>
<td>Neglect</td>
<td>Dizziness</td>
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</tbody>
</table>
Four agents were found to have significantly better efficacy than fluoxetine: mirtazapine, escitalopram, venlafaxine and sertraline. Reboxetine was found to be significantly less effective, while the other six agents were not significantly different from fluoxetine in terms of efficacy. The authors also calculated the likelihood of each agent being ranked in the top four positions in terms of efficacy. The rank order in this analysis was: mirtazapine > escitalopram > venlafaxine > sertraline > citalopram > milnacipran > bupropion > duloxetine > fluvoxamine > paroxetine > fluoxetine > reboxetine.

The only agent found to be significantly different from fluoxetine in terms of acceptability was reboxetine (found to be significantly less acceptable than the reference agent). The rank order for the cumulative probability of being among the four most acceptable agents was: escitalopram > sertraline > citalopram > milnacipran > bupropion > duloxetine > fluvoxamine > paroxetine > fluoxetine > reboxetine.

Figure 5 shows these two analyses plotted in a scatter graph, with the odds ratios for acceptability on the y axis and those for efficacy on the x axis. Agents to the right and above fluoxetine were more efficacious and more acceptable in the analysis. These included bupropion, citalopram, escitalopram and sertraline. These latter two agents in particular stood out as being the most desirable in this analysis, ranking among the top four in terms of efficacy and acceptability. The authors concluded that these two agents should be considered as the best options when starting treatment for moderate to severe MDD.

Considering these results in the context of the three-column table on function in MDD (Table 2), one might expect that escitalopram and sertraline would offer the best chance at alleviating the symptoms on the left, while minimizing the risk of causing the side effects on the right. As such, these agents might be expected to have a favourable impact on patient functioning.

Although functional outcome measures have been underused in clinical trials of antidepressant therapy, there are some data available. In an open-label, three-month, surveillance study of 5,175 patients with MDD, the investigators used the patient-rated Sheehan Disability Scale (SDS) as one efficacy measurement. At baseline, a considerable proportion of patients reported marked or extreme disability for work (38%), social life (41%) and family life (37%). After three months of treatment with escitalopram, 80.6%, 79.5% and 83.5% of patients indicated either no or mild disability for those variables, respectively.

A recent trial comparing venlafaxine to bupropion in 591 patients with MDD also included the SDS as a secondary outcome measure. In this study, both active treatments led to significantly greater improvements in the SDS compared to placebo (-5.8 for placebo, -7.8 for bupropion and -9.2 for venlafaxine).

Investigators have also examined the impact of treatment on the SDS in a post-hoc pooled analysis of trials comparing duloxetine to paroxetine and placebo. In this analysis, the differences between antidepressant treatment and placebo in terms of SDS total and sub-domains were all significant.

While these studies are informative, with the growing recognition of function as an important outcome in MDD, designs of future randomized, controlled trials should incorporate a validated instrument like the SDS, or more rigorous instruments such as the World Health Organization Health and Work Per-
formance Questionnaire (HPQ), as a primary treatment outcome measure.\(^{23}\)

Data from such trials may also help to rationalize the separation of symptom- and function-related treatment goals in depression, as mentioned earlier, and illustrate that antidepressants with similar effects on symptoms can have differential effects on function. In a randomized, double-blind trial comparing escitalopram to duloxetine in patients with MDD, the primary efficacy endpoint was mean change in MADRS total score, while the SDS was included among secondary assessments. In this study, both treatments were associated with similar reductions in total MADRS score at study end (week 24), but SDS total scores were significantly better with escitalopram vs. duloxetine (both baseline scores 20.5: reduced to 7.58 with escitalopram and to 9.95 with duloxetine at week 24; \(p < 0.05\)).\(^{24}\) These data suggest that functional gains must be considered when evaluating the effectiveness of medications and their impact on recovery.

### Other Factors Contributing to Functional Outcomes

Beyond pharmacotherapy, researchers have also identified other variables that can have an impact on a patient’s ability to return to premorbid functioning. One group of researchers, for example, attempted to determine the factors that impact function in MDD and quantify their relative importance.\(^{25}\) This was a small, single-centre study of 97 adults with MDD, but the results are nonetheless informative.

While the investigators reported that change in severity of depression symptoms was the main factor behind change in patient functioning, it accounted for only 32% of the variance in functioning over time. Several environmental and personal variables were identified as also being important contributors to changes in function. Collectively, gender, work status, societal attitudes, health satisfaction and quality of life accounted for 20% of the variance in functioning. These findings also highlight the importance of incorporating adaptive cognitive and behavioural interventions into any function-focused treatment plan.

### Assessing Function in MDD

Given that restoration of function is a goal of therapy in MDD, it is important that clinicians be able to measure a particular patient’s function at presentation and to monitor the effects of treatment on function over time. In a busy primary-care practice, such a tool should be concise and easy to use. Unfortunately, the Global Assessment of Functioning (GAF) is one of the most commonly used tools to assess functioning despite being minimally associated with treatment outcomes. Moos et al. found patients’ clinical diagnoses and symptoms were stronger predictors of GAF ratings than was their social or occupational functioning.\(^{26}\)

A number of validated tools have been used in this regard, some of which are more cumbersome than others. Recently, Langlieb et al. searched the literature to compile a list of these tools and to document the effects of MDD on functioning and quality of life as captured by these tools in clinical trials.\(^{27}\) The authors identified the SDS, the 36-item Short-Form Health Survey, and the Work Limitations Questionnaire as the most commonly used validated scales for assessing function in clinical trials in MDD. These and other less commonly used tools are listed in Table 3. Of the three most commonly used tools, the SDS is the least cumbersome and, therefore, perhaps the most useful for clinical practice.
Another recently validated tool—and one which provides a more complete assessment of work-related function than the SDS and, unlike the SDS and other tools mentioned above, is specific to depression—is the Lam Employment Absence and Productivity Scale (LEAPS).\(^2\) The short and simple tool is a self-rated questionnaire which first assesses work hours scheduled/missed and then seven items rated on a 5-point Likert scale (including energy/motivation, concentration/memory, anxiety/irritability, and items related to work productivity and quality).

Regardless of the tool chosen, the authors of the above-mentioned review concluded that clinicians should assess function in their patients with MDD as part of routine follow-up.

Conclusions

MDD has a considerable impact on patients and on the healthcare system. To minimize this impact, clinical practice guidelines recommend that clinicians treating patients with MDD include restoration of function among their treatment goals. As such, the ideal therapeutic regimen is one that balances optimal efficacy in resolving symptoms of MDD, while minimizing potentially impairing antidepressant-associated side effects. A systematic analysis suggests that, among the newer antidepressants, escitalopram and sertraline may offer the best balance of efficacy and acceptability, though only escitalopram has been shown to lead to significantly better functional improvements in a head-to-head trial. Further evaluation is also needed to determine if antidepressants can be discerned on the basis of “functional effectiveness.”

Regardless of the regimen chosen, functioning needs to be assessed on a regular basis to ascertain the baseline level of disability, define goals, and monitor the response to treatment until recovery is achieved.

References