A Practice Assessment in Major Depressive Disorder: Closing the Treatment Gaps in the Management of Depression in Canada

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For many patients with major depressive disorder (MDD), the initial treatment with an antidepressant leads to the desired outcome: sustained remission from depressive symptoms. For others, a failure to respond to treatment leads to the disability and suboptimal quality of life that are the hallmarks of the disease. Research indicates that the proportion of patients who are not treated to remission is quite high. There is also research to suggest that untreated depression can lead to structural changes in the volume of the hippocampus (Figure 1),[1] with a separate study suggesting that a longer duration of untreated depression is correlated with lower total hippocampal volume.[2]

This review article will illustrate the treatment gap with a summary of relevant data from the literature, as well as the results of a recent practice assessment program conducted among primary-care physicians and psychiatrists across Canada in 2010.

In light of these observations—that suboptimal response (not achieving remission) is common in MDD—it is important for clinicians to develop a follow-up and monitoring strategy for MDD patients in their care. There are many potential methods that can be used to track response to therapy, some of which will be explored in this review.

While most physicians are aware of the recommended options for first-line pharmacotherapy for MDD, the recognition of this treatment gap and the relatively high rate of failure of first-line agents means that physicians need to be equally aware of the options for therapy beyond the first line. Clinical practice guidelines in Canada provide a detailed assessment and recommendations for second- and third-line therapies for MDD. These recommendations will also be summarized in this review.

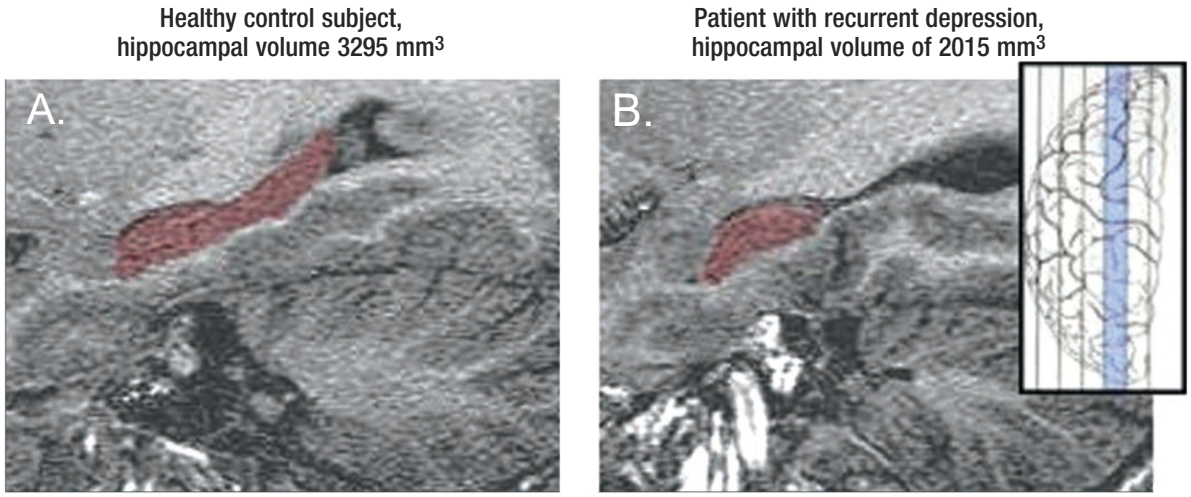
Impact of MDD

According to the Canadian Community Health Survey (CCHS), the lifetime prevalence of depression in Canada is 12.2%, with an annual prevalence of 4.8%.[3] Patients suffering from MDD can have a significantly reduced quality of life. In a study evaluating data from 11 clinical trials in depression and anxiety disorders, investigators found that 63% of people with MDD had severe impairment in quality of life (as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire Score).[4]

In a recently completed practice assessment program conducted among primary-care physicians and specialists in Canada, the Management of Unipolar Depression Practice Reflective (MOOD) Program, the participants were asked to assess the impact of MDD on their patients' quality of life.[5] The program involved 430 primary-care physicians across Canada (managing a total of 9,597 patients with depression) and 104 specialists (2,226 patients).

FIGURE 1.

Magnetic Resonance Spectroscopic Images of the Hippocampus: Healthy Control vs. Patient With History of Recurrent Depression[1]



As shown in Figure 2, a large proportion of patients, both in primary care and under care of a psychiatrist, reported an impact of MDD on important quality of life parameters.

Depression can also lead to much more devastating consequences: although the exact numbers are a matter of some debate,[6] depression dramatically increases the risk of suicide.

Depression is also the world's leading cause of disability in terms of years lost to disease (YLD),[7] and accounts for approximately 10% of all disability-adjusted life years.[8] Depression can significantly affect occupational functioning, which is particularly important given that most people with depression (approximately 7 in 10) are in the workforce.[9] These depressed employees may miss work altogether (absenteeism) or have decreased productivity on the job while unwell (presenteeism).

The impairment of functioning in depression is not restricted to the workplace. In the MOOD practice assessment program,[5] physicians were asked to rate how difficult depression has made it for patients to do their work, take care of things at home, or get along with other people. Among patients treated in primary care, the proportions of patients reporting that it was somewhat, very or extremely difficult were 43%, 31% and 8%, respectively. For those under the care of a psychiatrist, the respective percentages were 36%, 40% and 14%.

This decreased effectiveness in the workplace and in other situations can go on for extended periods of time for people who do not achieve remission. The duration of symptoms (*i.e.*, the duration of time that a patient will be functioning at a suboptimal level) is variable in MDD. The CCHS data showed that, among people who had a major depressive episode in the past year, more than half (57.1%) were depressed for more than 13 weeks of that year, and more than one-quarter (27.9%) were depressed for more than 27 weeks (Figure 3).[9] Taken together and applied to entire populations, the potential economic impact of depression is staggering.

Current State of Management of MDD: Identifying the Treatment Gap

Evidence demonstrating a distinct treatment gap in the management of MDD has been accumulating for some

FIGURE 2.

Proportion of Patients Reporting Impact of Depression on Quality-of-life Parameters: Canadian Practice Reflective Program[5]

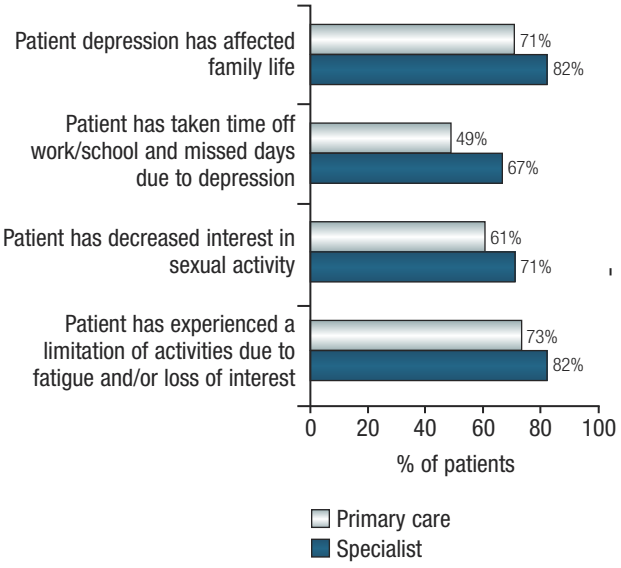
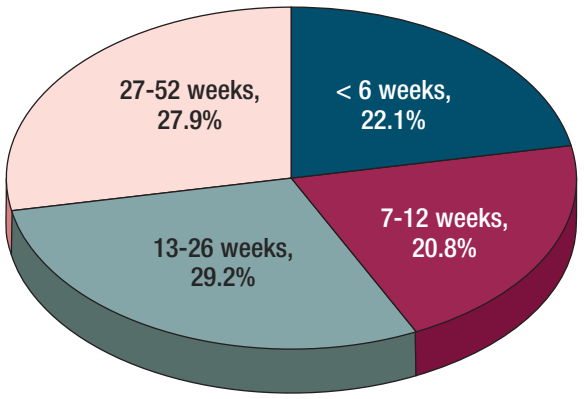


FIGURE 3.

Duration of Depressive Symptoms During the Past Year: Canadian Community Health Survey[9]



time. Published clinical trials and observational studies have identified a large proportion of patients who do not achieve response or remission. Furthermore, a recent real-life Canadian practice assessment program has also revealed shortcomings of therapy in a large proportion of patients in both primary care and, to a lesser extent, among patients of psychiatrists.

Published evidence. There is a wealth of published data showing the large proportion of patients with MDD who do not achieve remission with first-line antidepressants (*e.g.*, selective serotonin reuptake inhibitors [SSRIs] or serotonin-norepinephrine reuptake inhibitors [SNRIs]). The authors of a meta-analysis published in 2010 reported that the rates of remission (defined as a Hamilton Depression Rating Scale–17 [HAMD-17] score < 7-8, or a Montgomery-Åsberg Depression Rating Scale [MADRS] score < 10-12) in clinical trials using SSRIs or SNRIs were 41.9% and 48.5%, respectively.[10]

Another large study in MDD examined the likelihood of remission not only with a first antidepressant, but also with subsequent treatment strategies. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study enrolled 3,671 patients with MDD.[11] The goal for these patients was remission, defined as a score of 5 or less on the Quick Inventory of Depressive Symptomatology–Self Report (QIDS–SR). The first step for pharmacotherapy was monotherapy with the SSRI citalopram. Patients who did not achieve remission with this first step were subsequently randomized to a second treatment step. The possible treatments at this level were

Depression is the world's leading cause of disability in terms of years lost to disease, and accounts for approximately 10% of all disability-adjusted life years.

TABLE 1.
Questions in the Nine-item Patient Health Questionnaire (PHQ-9)[12]

In the past two weeks has the patient experienced the following:

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling/staying asleep, sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself or that you are a failure, or have let yourself or your family down
7. Trouble concentrating on things such as reading the newspaper or watching TV
8. Moving or speaking so slowly that other people could have noticed, or the opposite: being so fidgety or restless that you have been moving around more than usual
9. Patient feels they would be better off dead or of hurting themselves in some way

four switch treatments (citalopram was stopped and new treatment initiated with sustained-release bupropion, cognitive therapy, sertraline, or extended-release venlafaxine) and three augmentation options (citalopram plus bupropion, buspirone, or cognitive therapy). Those who still did not achieve remission moved on to a third or fourth option, each involving another antidepressant, augmentation therapy, or combination antidepressant therapy.

The investigators reported that two-thirds (63%) of patients failed to achieve remission with a first-line antidepressant.[11] In fact, when one considers the theoretical cumulative remission rate of all four therapy steps, only then does the rate of successful treatment approach that of failed first-line treatment in the study. According to the study authors, the cumulative remission rate (67%) is based on the assumption that there were no study dropouts and that those who exited the study would have had the same remission rates as those who continued to follow study protocol.

One of the key learning points from this trial was the fact that three out of 10 patients did not achieve remission, even in this closely regulated and monitored clinical trial, even after four different interventions. This result illustrates the considerable treatment gap that remains to be filled.

Canadian practice assessment program. The MOOD program was designed to improve awareness regarding patient outcomes among Canadian physicians, to reinforce outcome-based treatment, and to compare patient outcomes to national peer outcomes and to guidelines.[5]

The physicians were asked to rate their patients' depression using the nine-item Patient Health Questionnaire (PHQ-9[12]) (available online at: *www.cqaimh.org/pdf/tool_phq9.pdf*). For each of the nine questions (shown in Table 1), the patients assessed the frequency over the past two weeks, answering "not at all", "several days", "more than half the days" or "nearly every day".

The patients are assigned a score of 1-3 for each answer, for a total possible score of 1 to 27. Based on the total score, the patient can be classified as having "minimal depression" (score of 1 to 4), "mild depression" (5 to 9), moderate depression (10 to 14), moderately severe depression (15 to 19), or severe depression (20 to 27).

Figure 4 shows the results of the PHQ-9 among the patients treated by Canadian primary-care physicians and

specialists who took part in the MOOD program. The proportion of patients with severity that was mild or greater was 76% for primary care and 86% for patients treated by specialists.

These findings help to illustrate the substantial numbers of patients with MDD who are not adequately managed in Canada. There are several possible explanations for this, as Ghaemi has pointed out.[13]

One part of the problem may be that not enough patients with MDD are being assessed with validated tools. Structured tools like the PHQ-9 can be very helpful not only for establishing a criteria-based diagnosis, but also as a reliable means of charting patient progress, response and remission (or lack thereof) to the selected treatment regimen, assessing severity and using the findings to help make treatment decisions.

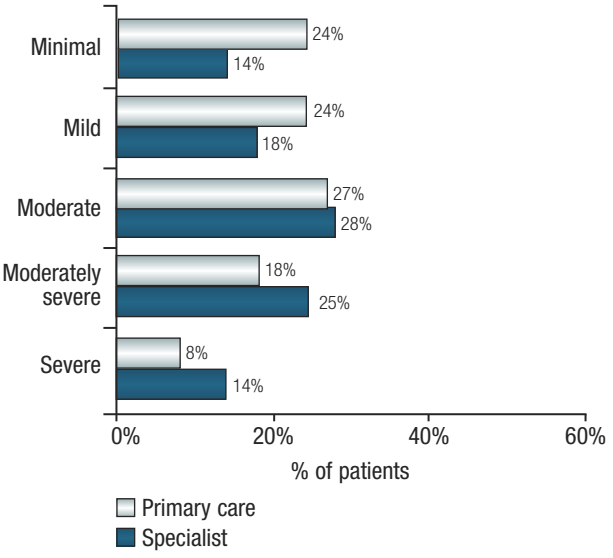
One of the striking findings of this practice assessment program was that approximately two-thirds of the patients in primary care (5,700 of 8,736: 65%) and almost three-quarters of those in specialty care (1,539 of 2,100: 73%) had not been assessed with a depression scale.[5] Of those who had been assessed, the most commonly used instruments were the HAM-D and the PHQ-9 in primary care, and the HAM-D and the Beck Depression Inventory in psychiatric practices.

The importance of assessment is illustrated by the finding that most assessments led to changes in care. As shown in Figure 5, among patients treated in primary care, 67% had a change in treatment as a result of depression assessment, including a change in medication (20%), increase in the dose of current medication (30%), and addition of other medication (22%).[5] Among patients under specialist care, 25% changed medication as the result of assessment, 38% had a dose increase of their current medication, and 23% had another therapy added on (total proportion of patients with a change in treatment: 77%).

While conducting a quantitative assessment may not always be possible due to time constraints, it is important to ask patients a minimal number of questions to establish a baseline and to monitor their progress or failure to progress. In this respect, Arroll *et al* have reported on the diagnostic accuracy of two questions to detect cases of depression.[14] Asked verbally, the two questions in Table 2 offer a rapid and effective solution to help physicians diagnose and treat depression.

FIGURE 4.

Results of the 9-item Patient Health Questionnaire (PHQ-9) in the Canadian Practice Reflective Program[5]



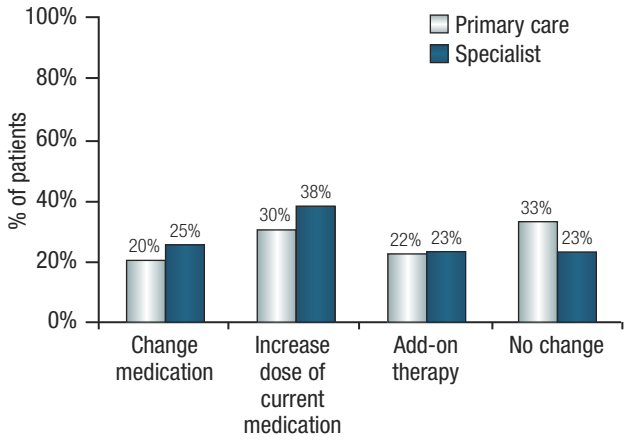
Improving Outcomes in MDD: Getting the Most Out of the Therapeutic Options

The 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of MDD in adults provide extensive evidence-based recommendations for the treatment of MDD,[15-18] noting that there are antidepressant options beyond SSRI and SNRI agents.

Importantly, the authors of the guidelines emphasized the importance of including psychotherapy (*e.g.*, cognitive behavioural therapy, interpersonal therapy) in the treatment strategy, as these modalities have evidence of efficacy and have been studied in conjunction with antidepressant therapy.[16]

FIGURE 5.

Actions as a Result of Assessment: Canadian Practice Reflective Program[5]



With respect to pharmacotherapy, the guidelines include a simple algorithm illustrating the recommended approach.[16] In short, the authors recommend that patients who do not demonstrate any improvement after four to six weeks should have their treatment regimen adjusted. For those who exhibit more than minimal improvement (*e.g.*, ≥ 20% improvement in scores on a depression rating scale) after four to six weeks, the guidelines suggest waiting an additional two to four weeks before considering a change in regimen.

Based on available evidence, the guideline authors recommended a number of pharmacologic agents from different classes (Table 3). For first-line monotherapy, traditional antidepressants (*e.g.*, SSRIs, SNRIs) and other agents (*e.g.*, bupropion, a norepinephrine dopamine reuptake inhibitor [NDRI], and mirtazapine, an alpha$_2$-adrenergic antagonist) are recommended. For second-line therapy, the recommended options are extended-release quetiapine (quetiapine XR, an antidepressant/ atypical antipsychotic), and tricyclic antidepressants (TCA). Monoamine oxidase inhibitors are reserved for third-line therapy. Although the recommended agents come from differing pharmacologic classes (*e.g.*, atypical antipsychotic, SSRI, non-SSRI, etc.), the commonality is their antidepressant activity. The authors acknowledge that the distinction between these therapies has been blurred, as some medications that were previously considered augmentation agents (*e.g.*, quetiapine) may be effective antidepressants in monotherapy.[16]

TABLE 2.

Screening for Depression in Primary Care: Two Verbally Asked Questions[14]

Question 1:	During the past month have you often been bothered by feeling down, depressed, or hopeless?
Question 2:	During the past month have you often been bothered by little interest or pleasure in doing things?

Since the publication of the guidelines, quetiapine XR has been approved in Canada for the symptomatic relief of MDD when traditional antidepressants have failed due to lack of efficacy and/or lack of tolerability. This agent is the only antidepressant/ atypical antipsychotic that currently has this indication, the approval for which was given based on the positive results of randomized controlled studies in MDD.[19-20]

In one of these studies, 612 patients with MDD were randomly assigned to quetiapine XR 150 mg/day or 300 mg/day, duloxetine 60 mg/day (active control), or placebo.[19] For the primary endpoint of change from baseline to Week 6 in MADRS total score, the investigators observed significant reductions for quetiapine XR and duloxetine compared to placebo (Figure 6). Response and remission rates were also significantly better with active therapies compared to placebo.

The particular option selected in the case of suboptimal response to an initial antidepressant is primarily a clinical decision. The appealing aspects of a switch from one monotherapy to another are the lack of potential for drug interactions, no additive side effects, cost, and simplicity of dosing. The appealing aspects of using an add-on strategy include a faster onset of response, the ability to address specific residual symptoms or side effects and continued coverage with the index agent for late responders.

TABLE 3.

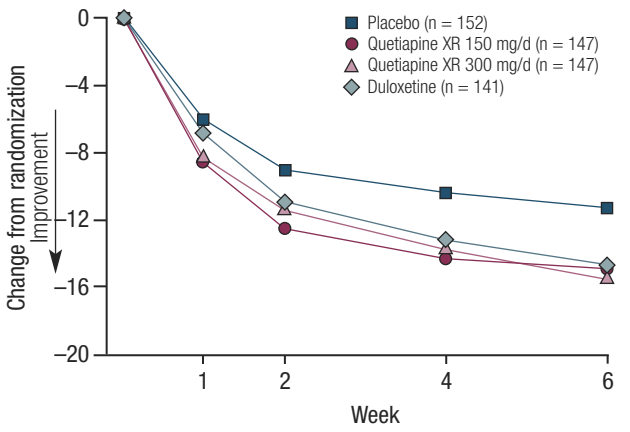
2009 CANMAT Pharmacotherapy Recommendations for MDD: Initial Therapy[16]

First-line monotherapy	• Bupropion (Wellbutrin®) • Citalopram (Celexa®) • Desvenlafaxine (Pristiq®) • Duloxetine (Cymbalta®) • Escitalopram (Cipralex®) • Fluoxetine (Prozac®) • Fluvoxamine (Luvox®) • Mirtazapine (Remeron®) • Moclobemide (Manerix®) • Paroxetine (Paxil®) • Sertraline (Zoloft®) • Venlafaxine (Effexor®)
Second-line monotherapy	• Quetiapine XR (Seroquel XR®) • Tricyclic antidepressant
Third-line monotherapy	• Monoamine oxidase inhibitors

Note: all agents listed are available in Canada; not all are approved for MDD.

FIGURE 6.

Quetiapine XR or Duloxetine vs. Placebo in MDD: Change in MADRS Scores from Baseline to Week 6[19]



P Value vs. Placebo.

Quetiapine XR 150 mg/d	< 0.01	< 0.001	< 0.001	< 0.001
Quetiapine XR 300 mg/d	< 0.01	< 0.01	< 0.001	< 0.001
Duloxetine	0.301	< 0.05	< 0.01	< 0.01

When a change in therapy is indicated, there are a number of potential strategies than can be used. These include switching to another agent or adding another agent to the existing regimen. It is important for clinicians to realize that there are many choices beyond those agents normally considered to be first-line antidepressants (*e.g.*, SSRIs and SNRIs). Some of these agents—such as the antidepressant/atypical antipsychotic quetiapine XR, and bupropion and mirtazapine—have markedly different mechanisms of action and may prove to be helpful in patients who were previously unresponsive to SSRI or SNRI therapy, or both, either as monotherapy or as add-on therapy. (See Table 4 for CANMAT recommendations regarding add-on strategies for non-responders.)

Conclusions

MDD is associated with a substantial burden on individual patients, their families and on the health-care system in general. Evidence shows that treating to remission, the goal of therapy, is problematic both for primary-care providers and specialists. To achieve remission, therapeutic adjustments (*e.g.*, dose increase, switching, add-on therapy) are necessary in at least half of all patients with MDD.

For patients receiving therapy for MDD, regular follow-up and assessment is required to determine response to therapy and to make treatment decisions based on this assessment. Standardized tools such as the PHQ-9 can be very helpful in this regard.

Regardless of the therapy chosen, clinicians and their patients should never lose sight of the goal: remission of depressive symptoms. It may require one or more changes of therapy before an effective treatment is found, but given the significant impact of the disease, this persistence is certainly appropriate. Robust treatment trials, paired with best practices to treat depression—including carefully drawing out the history and context of symptoms, and monitoring response to treatment—are essential to helping patients achieve a full functional recovery. Dx

TABLE 4.
Recommendations for Non-response and Incomplete Response to Initial Antidepressant

First-line	• Switch to an agent with evidence for superiority	• Duloxetine, escitalopram, mirtazapine, sertraline, venlafaxine
	• Add-on another agent	• Aripiprazole, lithium, olanzapine, quetiapine XR*, risperidone
Second-line	• Add-on another agent	• Bupropion, mirtazapine, quetiapine, triiodothyronine, other antidepressant
	• Switch to an agent with evidence for superiority, but with side-effect limitations	• Amitriptyline, clomipramine, monoamine oxidase inhibitors
Third-line	• Add-on another agent	• Buspirone, modafinil, stimulants, ziprasidone

*Supported by clinical trial data[21,22] published after the release of the 2009 CANMAT guidelines).
Note: all agents listed are available in Canada; not all are approved for MDD.

Adapted from Lam RW *et al.* J Affect Disord 2009; 117 Suppl 1:S26-43.

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