Comparative Efficacy of Newer Antidepressants for Major Depression: A Canadian Perspective

By Sidney H. Kennedy, MD, FRCPC, and Sakina J. Rizvi, HBSc

Sidney H. Kennedy, MD, FRCPC
Psychiatrist-in-Chief,
Department of Psychiatry,
University Health Network
University of Toronto

Sakina J. Rizvi, HBSc
Department of Psychiatry,
University of Toronto
Departments of Pharmaceutical Sciences and Neuroscience,
University of Toronto

Introduction

Major Depressive Disorder (MDD) is a common disorder; Canadian statistics from 2002 (the Mental Health and Well-being Survey) indicated that 4.8% of Canadians aged 15 years or older met the criteria for MDD in the previous 12 months.[1] The same survey found that 12.2% of adults met the criteria for depression at some point during their lifetime.[1]

Over the past several decades, pharmacologic management of MDD has evolved substantially. Despite the introduction of many new antidepressant medications and a continually advancing understanding of their individual strengths and weaknesses, selecting the best possible treatment for each individual patient remains a significant challenge for general practitioners and psychiatrists. Response and remission are key goals in the management of MDD. Acceptability is also an important step towards achieving these goals, since patients require long-term (often life-long) pharmacotherapy.

First-line pharmacotherapy for MDD is typically chosen from among the "newer antidepressants"— either a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI).[2] Which of these agents should be preferred over the others has been a topic of considerable research and debate over the years.[3-20] To date, no consensus has emerged.

One of the latest attempts to answer this question and provide clinicians with evidence-based guidance on the relative effectiveness and acceptability of the various newer antidepressants was published in *The Lancet* in February of 2009.[17] This independently funded meta-analysis, by Cipriani et al, reviewed clinical-trial data for 12 newer antidepressants used to treat MDD, in an

MULTIPLE TREATMENT META-ANALYSES

Multiple-treatment meta-analysis is a technique used to synthesize data from several independent studies and analyze the outcomes.

This method allows the integration of data from direct comparisons (when treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are compared with a common comparator treatment).

The multiple-treatment meta-analysis thereby allows for comparisons between treatments which have not been compared in a prospective, head-to-head trial. The results can be more informative than a traditional meta-analysis, going beyond simple pairwise comparisons to rank many different treatments.

Because the indirect comparisons of the agents in question are not randomized, investigators using this method need to account for potentially confounding variables, as was done in the multiple-treatment meta-analysis of antidepressants for MDD, by Cipriani et al.[17]

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effort to provide a clinically useful tool to assist physicians in selecting antidepressant medications for their patients.

The aim of this review is to present the highlights of the meta-analysis and provide an interpretation of these data in the context of other recent meta-analyses. Finally, the results are considered from a Canadian perspective.

Overview of the Cipriani Meta-analysis[17]

Study design and methodology. This analysis (a multiple-treatment meta-analysis; see description in sidebar) included randomized controlled trials (RCTs) involving patients with unipolar MDD, treated with one of 12 newer antidepressants: the SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline); the SNRIs (duloxetine, milnacipran and venlafaxine); and three other newer agents (bupropion, mirtazapine and reboxetine). The trials were published between 1991 and 2007.

The primary outcome measures assessed were response and acceptability. Response could be defined by any one of the following criteria at eight weeks: reduction of at least 50% from baseline on the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS), or a rating of "improved" or "very much improved" on the Clinical Global Impression (CGI) scale. Acceptability was quantified by the number of patients who terminated the study early for any reason during the first eight weeks. Fluoxetine, the prototypical SSRI and the agent with the largest body of clinical-trial evidence, was used as the reference agent.

Results. The authors identified 117 studies that met the criteria for inclusion in their meta-analysis. The total number of subjects included in these studies was 25,928. Figure 1, based on Patrick et al,[18] captures the relative balance between efficacy and acceptability in comparison with fluoxetine.

With respect to efficacy, the investigators found that four antidepressants had significantly greater response rates than fluoxetine: mirtazapine, escitalopram, venlafaxine and sertraline. Only one agent, reboxetine, was significantly worse than fluoxetine. The response rates of the other six agents did not differ significantly from fluoxetine.

The agents were also plotted with respect to their cumulative probability of being ranked at each of the possible 12 positions in order of efficacy and in order of acceptability. The cumulative probabilities of being among the four most efficacious treatments were: mirtazpine (24.4%), escitalopram (23.7%), venlafaxine (22.3%), and sertraline (20.3%) (Figure 2). As shown in Figure 2, there was a marked reduction in terms of likelihood of being among the top four efficacious agents for all other antidepressants.

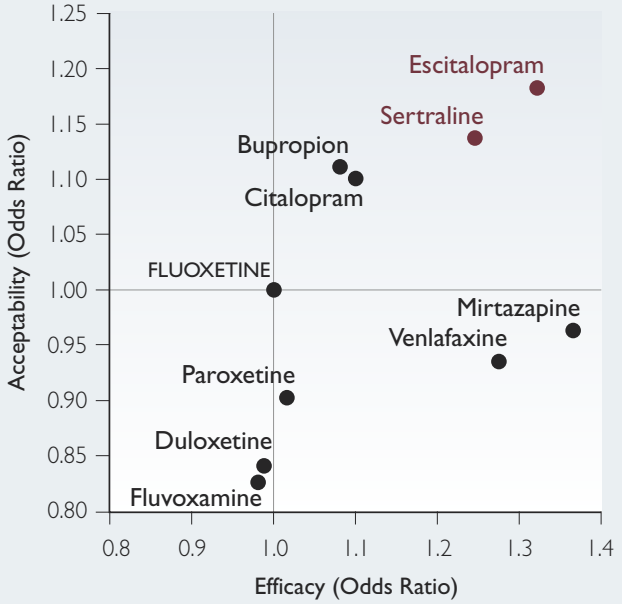
Several agents were rated more acceptable than fluoxetine: escitalopram (27.6%), sertraline (21.3%), bupropion (19.3%), and citalopram (18.7%), but these differences were not statistically significant. As with efficacy, the decrease in acceptability was substantial after these four agents, although reboxetine had a statistically significantly lower acceptability than fluoxetine (Figure 3).

Study conclusions. Among the 12 studied antidepressants, only two agents were ranked in the top four for efficacy and acceptability: escitalopram (ranked second in efficacy and first in acceptability) and sertraline (ranked fourth in efficacy and second in acceptability). Based on these findings, the authors considered escitalopram and sertraline to be the best options when starting antidepressant treatment for moderate-to-severe MDD.

Discussion

This study identified escitalopram and sertraline as the two antidepressants that provide modest clinical advantages over 10 other agents. The identified strengths of this trial, beyond a large sample size (more than 25,000 patients), include the methodology, employing a multiple-treatment meta-analytic technique to include direct and indirect comparisons among antidepressants, as well as the absence of sponsorship from pharmaceutical companies. A limitation of the study is the selection of response and accepting multiple definitions (either a 50% reduction on HAM-D or MADRS scales or a CGI rating of "improved" or "very much im-

FIGURE 1 **Comparative Efficacy and Acceptability of Newer Antidepressants (vs. Fluoxetine)[18]**



Note: milnacipran and reboxetine were omitted by the authors of this analysis because they were not available in North America.

FIGURE 2 **Cumulative Probabilities of Being Among Four Most Efficacious Newer Antidepressants[17]**

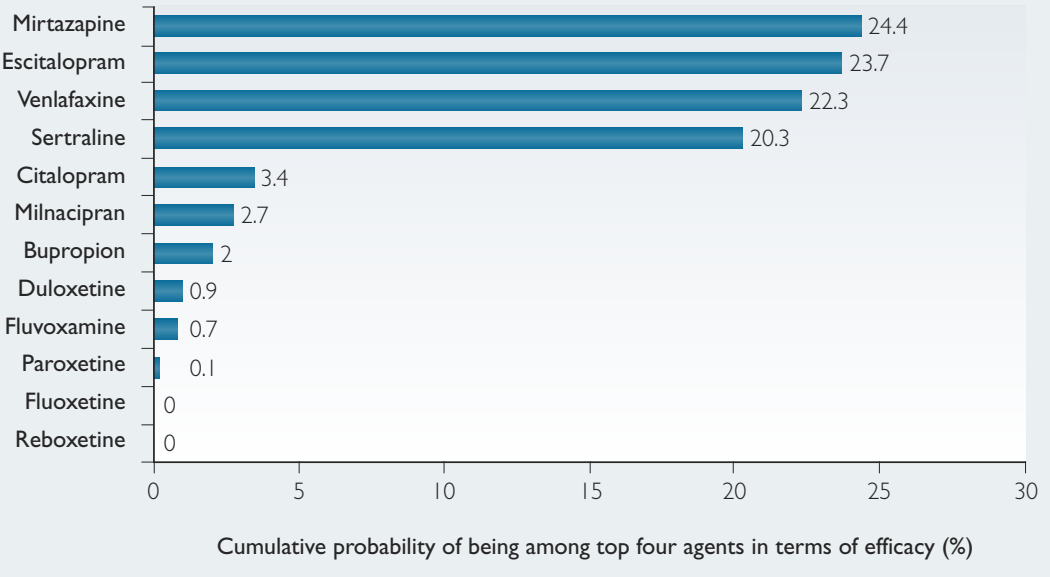
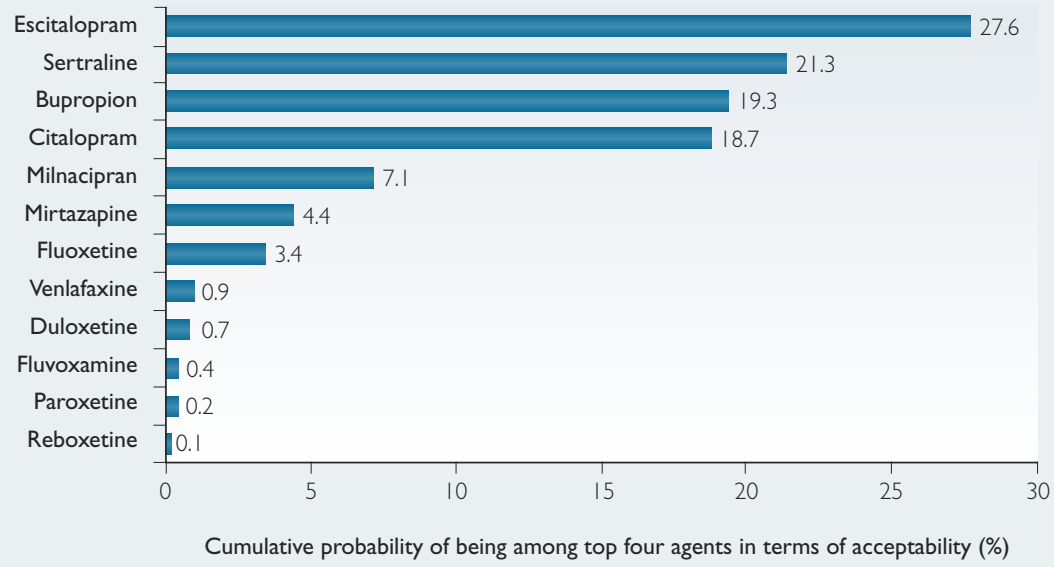


FIGURE 3 Cumulative Probabilities of Being Among Four Most Acceptable Newer Antidepressants[17]



proved") rather than remission (usually defined as an absolute reduction in symptoms, HAM-D ≤ 7 or MADRS ≤ 10). It should also be acknowledged that the use of drop-outs as a proxy for acceptability does not adequately explore side effects or discontinuation symptoms across these agents. Neither does the composite ranking address social functioning or cost-effectiveness.

Among the 12 studied antidepressants, only two agents were ranked in the top four for efficacy and acceptability: escitalopram (ranked second in efficacy and first in acceptability) and sertraline (ranked fourth in efficacy and second in acceptability).

Conclusions from several other meta-analyses and systematic reviews are consistent with the results from this study. In one meta-analysis of 10 studies comparing escitalopram to other SSRIs or to venlafaxine,[7] the authors reported that escitalopram was significantly superior to the SSRIs and comparable to venlafaxine based on reductions on the MADRS. The same group expanded the meta-analysis to include an additional 2,000 patients and trials involving duloxetine.[19] Using a composite plot of efficacy and acceptability that was similar to the Cipriani method, this group confirmed the clinical superiority of escitalopram, particularly in comparison to the SNRIs, duloxetine and venlafaxine (Figure 4).

Montgomery et al also examined the evidence for superiority in efficacy among antidepressants.[9] To label an antidepressant as definitively superior, the authors required evidence of superiority on the primary efficacy measure from two pivotal studies in moderate-to-severe MDD. Alternatively, a label of superiority could be conferred on an agent based on the results of one pivotal study supported by consistent results from meta-analyses. They concluded, based on these criteria, that three antidepressants were superior: clomipramine, venlafaxine, and escitalopram. Escitalopram was the only agent found to have definite superiority in the treatment of severe depression.

Other investigators have used meta-analytic techniques to assess the relative efficacy of venlafaxine in comparison to SSRIs.[13,21] These authors reported modest clinical advantage based on remission endpoints and without consideration of tolerability or

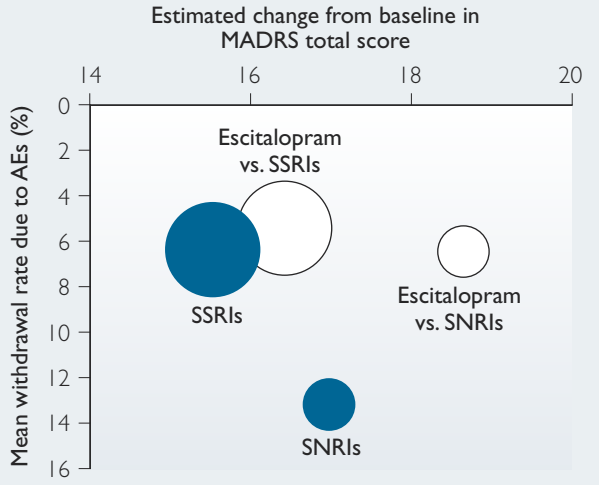
discontinuation rates. In the case of mirtazapine, there is evidence to support a faster onset of action than SSRIs, however this effect was not sustained at the end of six to 12 weeks of treatment.[22] A larger meta-analysis involving 12 antidepressants (10 were identical to those used in the Cipriani analysis) also used response as an endpoint.[12] This trial included 203 efficacy and effectiveness studies and reported no differences across agents. Differences in inclusion criteria for trials and meta-analytic methods may at least partially account for the discrepant findings.

The balance between efficacy and tolerability has important implications for social and occupational functioning in patients who require ongoing antidepressant treatment. Recent evidence suggests that primary-care providers do not decide on drug treatment or referral for depression on the basis of questionnaire scores alone,[23] and that they consider practical wisdom and clinical judgment to be more important than objective assessments.[24] Assessment of function may, therefore, provide additional, important efficacy information over and above that provided by measuring response and remission.

In this regard, emerging data show that escitalopram has an ability to improve functional outcomes in MDD and in generalized anxiety disorder.[25,26] In a study comparing escitalopram to the SNRI, duloxetine, in MDD, one of the pre-defined secondary endpoints was the change from baseline in the Sheehan Disability Score (SDS), which measures functional impairment.[25] The investigators reported that the SDS total scores were significantly better for the escitalopram treatment group at week 8 and at week 24 compared to those for duloxetine-treated patients. These observations may provide insight into the favorable results reported for escitalopram by Cipriani et al. Patients who take a medication that is efficacious (*i.e.*, reduces symptoms) and acceptable (*i.e.*, enhances the likelihood of continued therapy) have a better chance of achieving superior functional improvements compared to those who take an agent that is less efficacious and/or not as well accepted.

In the Canadian healthcare environment, cost is a factor that must also be considered when initiating pharmacotherapy for MDD. Cipriani et al recognized this variable when endorsing sertraline over escitalopram as the most cost-effective agent. This assessment was not based on a formal cost analysis, but simply on the observation that sertraline is generic in the United States and Europe, and therefore has a lower cost in most countries. However, in Canada, the acquisition costs of the maximum recommended doses of escitalopram and generic sertraline are comparable. With this in mind, in the Canadian context, escitalopram should be considered a first-line option for MDD, along with sertraline.

FIGURE 4 **Plot of Estimated Mean Treatment Differences From Baseline to Week 8 in MADRS and Withdrawals Due to AEs[19]**



Adapted from: Kennedy et al.[19]

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Conclusion

One of the major challenges in the management of MDD is the selection of an antidepressant. The ideal antidepressant combines efficacy and acceptability, which enhances the likelihood of long-term adherence and functional recovery.

Many efforts have been made to assess the relative efficacy and acceptability of the various antidepressants for the management of MDD. The recently published analysis by Cipriani et al offers practical evidence that physicians can use to help guide their decisions. The favorable rankings of escitalopram and sertraline for efficacy and acceptability in this analysis led the authors to conclude that these agents should be preferred over other newer antidepressants for the acute management of MDD. Canadian clinicians should view these results as providing reassurance that selecting one of these agents is a reasonable choice based on the best available evidence.

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