

# Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials

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## ABSTRACT

**Background:** Selective serotonin reuptake inhibitors are increasingly used in the long-term treatment of depression. Much of the supporting evidence about the effects of these drugs comes from discontinuation trials, a variant of randomized controlled trials whose design is problematic to interpret. We conducted a systematic review to examine the efficacy and acceptability of long-term therapy with selective serotonin reuptake inhibitors relative to placebo in the treatment of unipolar depression.

**Methods:** We identified placebo-controlled randomized trials with a treatment duration of at least 6 months by searching MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials to update a recently published systematic review. Efficacy was defined in terms of response to treatment (50% improvement in depression score relative to baseline) and remission (score of 7 or below on the Hamilton rating scale for depression). Key secondary outcomes included quality of life, return to work, need for additional treatment and self-harm. Overall acceptability was defined in terms of dropouts for any reason over a course of treatment.

**Results:** Of the 2693 records identified initially, we included 6 randomized controlled trials that met our eligibility criteria. These studies had a moderate risk of bias, had assigned a total of 1299 participants with depression to either treatment or placebo and had followed both groups for 6–8 months. We observed statistically significant improvements in response to treatment (odds ratio [OR] 1.66, 95% confidence interval [CI] 1.12–2.48), but not in remission (OR 1.46, 95% CI 0.92–2.32) or acceptability (OR 0.87, 95% CI 0.67–1.14). The effects appeared greater among patients without comorbidities.

**Interpretation:** There is a lack of classic randomized controlled trials of serotonin reuptake inhibitors lasting more than 1 year for the treatment of depression. The results of our systematic review support current recommendations for 6–8 months of antidepressant treatment following initial recovery but provide no guidance for longer treatment.

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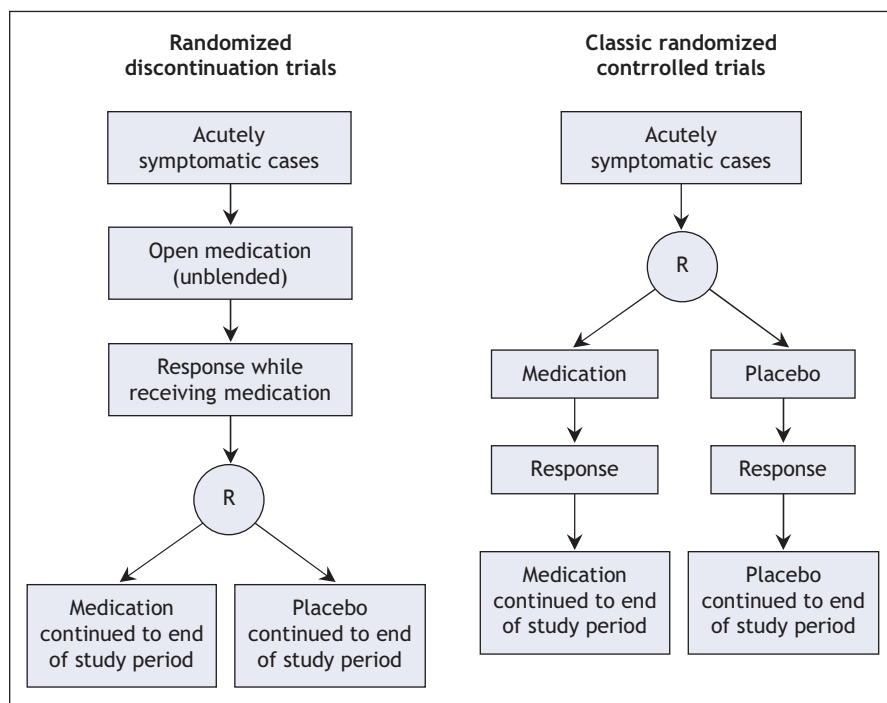
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Over the past decade, the use of selective serotonin reuptake inhibitors for the management of depression has increased dramatically, and preliminary evidence suggests that long-term use, for more than 1 or 2 years, accounts for much of this rise.<sup>1–3</sup> Clinical practice guidelines generally recommend a 6- to 9-month course following initial recovery after a first episode of depression and longer, sometimes indefinite, therapy after subsequent episodes, to prevent relapse.<sup>4–10</sup>

Long-term randomized controlled trials of antidepressants have typically used 1 of 2 possible designs, each answering different questions (Figure 1).<sup>11</sup> The most widely used design is called the “discontinuation trial,” a 2-phase study in which all participants are initially treated with an open (unblinded) course of drug therapy. Participants attaining a certain response during the open-treatment phase enter the second phase, during which they are randomly assigned to continue active drug treatment or to receive placebo.<sup>12–14</sup> Discontinuation trials are believed to minimize the number of participants with depression who must be exposed to placebo. This advantage comes at a cost, since the results apply only to patients with a response to the medication, not to those who experience spontaneous recovery; furthermore, withdrawal symptoms may lead to an overestimate of the true effect of the medication. When this design is used to test long-term therapy with selective serotonin reuptake inhibitors for the treatment of depression, the results are difficult to interpret with confidence because rates of spontaneous recovery in depression are potentially high and because withdrawal effects can mimic depression.<sup>13–15</sup>

The second type of randomized trial used to test long-term therapy with selective serotonin reuptake inhibitors is a 2-arm parallel randomized controlled trial, hereafter referred to as a classic randomized controlled trial (Figure 1).<sup>16</sup> In this type of trial, participants with acute depression

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**Figure 1:** Two designs of randomized controlled trials used to investigate long-term antidepressant therapy.

are assigned to receive either placebo or active drug, and all those achieving a certain response, either to the drug or to the placebo, are followed. The advantage of classic randomized controlled trials is that data from all participants contribute to our understanding of the drug's real-world effectiveness. Their main drawback is that a greater number of acutely ill people may have to receive placebo than in a discontinuation trial.<sup>13</sup> Most classic trials of antidepressants are short-term studies. Fergusson and colleagues,<sup>17</sup> in a systematic review examining selective serotonin reuptake inhibitors and suicide, identified 702 classic trials involving a total of 18 413 participants, the majority of which (93%) lasted less than 6 months.

A recent systematic review based mainly on studies with discontinuation designs showed that, in a subgroup of patients who experienced recovery while taking medications, long-term therapy with selective serotonin reuptake inhibitors reduced the chances of relapse by up to 70% for up to 36 months, relative to patients whose therapy was discontinued earlier.<sup>6</sup> However, there has been no systematic review of classic randomized trials of long-term therapy with this drug class to determine the potential benefits in all patients with depression, including those with spontaneous recovery.

We sought to examine the efficacy and acceptability of long-term therapy with selective serotonin reuptake inhibitors relative to placebo in the treatment of moderate to severe depression, including subgroups of patients with major chronic health conditions. We also examined a number of key indicators of the quality of evidence and its clinical importance.

## Methods

### Literature search

We searched for trials of fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine and sertraline. We updated the search strategy used in the previous systematic review of selective serotonin reuptake inhibitors and suicide<sup>17</sup> to capture material indexed since the previous search date in MEDLINE (Ovid MEDLINE, to first week of May 2007) or EMBASE (Ovid EMBASE, to week 18 of 2007). The EMBASE search was limited to journals not indexed in MEDLINE.<sup>18</sup> We searched the Cochrane Central Register of Controlled Trials for any studies published from 2003 to the second quarter of 2007. The search strategy combined the index terms associated with "serotonin uptake inhibitors" and the text terms "SSRI," "fluoxetine," "Prozac," "sertraline," "Zoloft," "paroxetine," "Paxil," "fluvoxamine," "Luvox," "citalopram" and "Celexa"; we used the revised highly sensitive search strategy for controlled trials for the MEDLINE

search<sup>19</sup> and the Hedges balanced strategy for therapy for the EMBASE search.<sup>20</sup> The updated search strategy is presented in Appendix 1 (available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)).

### Study selection

To be eligible for this systematic review, trials had to involve patients who had a diagnosis of major depression (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, third edition revised, or fourth edition) and who were randomly assigned to receive monotherapy with a selective serotonin reuptake inhibitor or placebo according to the classic 2-arm parallel randomized controlled trial design. Trials reporting a 1- to 2-week placebo run-in period were eligible, because such trials have been shown to yield unbiased estimates of effectiveness.<sup>21</sup> We included participants 18 years of age or older. There were no comorbidity restrictions. Our definition of long-term treatment was treatment over a period of at least 6 months. Trials were limited to those published in English.

Two of us (D.D. and E.M.) checked the reference lists of all included studies for additional studies and secondary reports. Working independently, the same 2 coauthors checked search results to identify all suitable studies. Disagreement about trials to be included was resolved by consensus among 3 of the coauthors (J.G., D.M. and D.F.).

### Data abstraction

Standardized case-report forms were developed, pilot-tested and completed by 2 independent reviewers (D.D. and E.M.). The following data were abstracted: characteristics of study

population, interventions, study design, detailed inclusion and exclusion criteria, outcomes (including response and remission criteria), number of participants who completed the study and number of dropouts for any reason, method(s) of data analysis and trial funding. To handle missing data for primary outcomes, we used the published last-observation-carried-forward approach.

### Assessment of risk of bias

We used the latest version of the Cochrane risk-of-bias tool<sup>22</sup> to assess the risk of bias in the included studies (see Appendix 2, available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)). This instrument consists of 6 items. Two of the items assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (blinding) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. It requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances, for example, in relation to trial design or setting. Examples include methodologic issues such as those related to crossover designs and early trial termination.<sup>23</sup>

### Outcomes

A priori, we identified 3 primary outcomes: response by study outcome, as defined by a 50% improvement in depression score relative to baseline; remission, as defined by a conventional remission cut-point (a score of 7 or less on the Hamilton rating scale for depression); and total number of dropouts as a proxy measure of overall treatment acceptability.<sup>24</sup> We were also interested in key secondary outcomes, such as quality of life; the need for rescue therapy, such as admission to hospital, psychotherapy, pharmacotherapy or electroconvulsive therapy; self-harm (including attempted and completed suicide); and back-to-work status.

### Data analysis

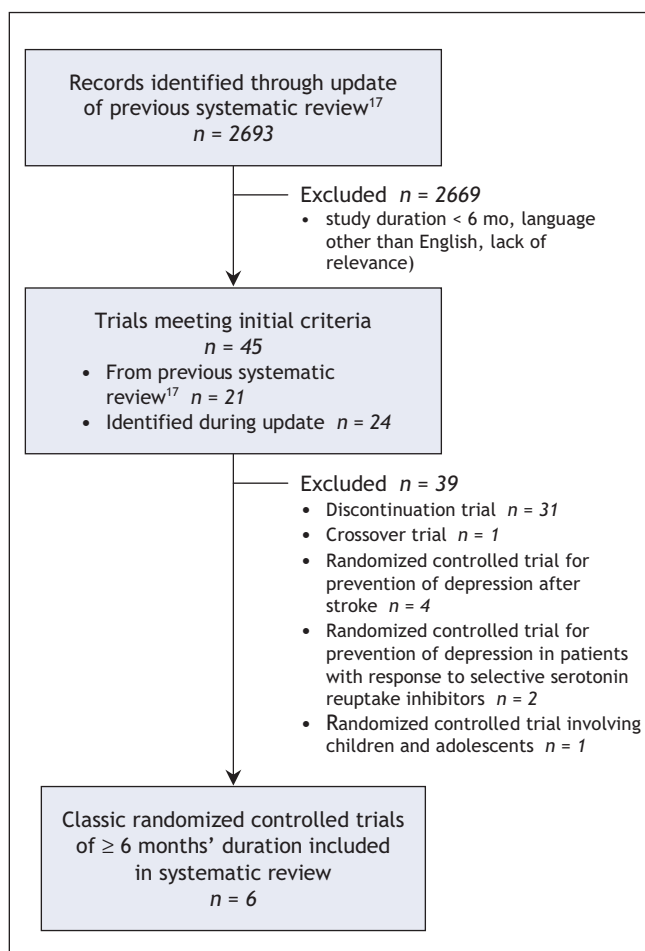
For each study, we calculated the odds ratio (OR) for each of the primary outcomes (response, remission and dropouts) with either selective serotonin reuptake inhibitor or placebo. Where clinically appropriate, we combined data from studies to estimate the pooled OR and 95% confidence intervals (CIs) using a DerSimonian and Laird random-effects model. Subgroup analyses were planned according to the presence or absence of comorbidities. An OR value greater than 1 indicates that more events occurred among patients who received selective serotonin reuptake inhibitors than among those who received placebo, and vice versa for OR values less than 1. Statistical consistency across randomized controlled trials was assessed by means of the  $I^2$  statistic. Potential publication bias was determined by visual inspection of an inverted funnel plot.

## Results

### Literature search

We identified 2693 records, of which 2669 were eliminated after initial screening because of study duration, language of publication and relevance. The remaining 24 citations were added to 21 potentially eligible studies identified from the original systematic review<sup>17</sup> for more detailed examination. Of the 45 eligible trials, we excluded 39. Thirty-two of these exclusions were based on study design (31 randomized discontinuation trials and 1 crossover trial). Six trials were excluded because they did not involve patients with diagnosed depression: 4 trials were for the prevention of poststroke depression, and 2 trials were for the prevention of depression in people who had experienced a response to antidepressant therapy. We excluded a 12-month classic randomized controlled trial because it involved only children and adolescents. (The excluded trials are listed in Appendix 3, available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)).

In the analyses reported here, we included 6 trials of 6–8 months' duration in which a total of 1299 patients with moderate to severe depression were randomly assigned to receive antidepressant therapy or placebo<sup>25–30</sup> (Figure 2, Table 1).



**Figure 2:** Flow diagram for identification of classic placebo-controlled randomized controlled trials.

Table 1: Summary of classic randomized controlled trials included in the systematic review of selective serotonin reuptake inhibitors for unipolar depression (part 1 of 2)

Study	Population*	Comparators	Completion data	Outcome measures	Duration, mo	Funding	Analysis
Detke et al <sup>25</sup>	Major depressive disorder; single episode or recurrent; Clinical Global Impression-Severity score $\geq 4$ , Hamilton Depression Inventory 17 score $\geq 15$ (multisite European study, source population unclear)	Paroxetine (20 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 179</li> <li>Completion rate: paroxetine 78%, placebo 60%, overall 73%</li> <li>Dropouts due to side effects: paroxetine 6%, placebo 7%</li> <li>Dropouts due to lack of efficacy: paroxetine 6%, placebo 6%</li> </ul>	<ul style="list-style-type: none"> <li>Response: 50% reduction in Hamilton Depression Inventory 17 score relative to baseline</li> <li>Remission: Hamilton Depression Inventory score <math>\leq 7</math></li> </ul>	8	Eli Lilly & Co.	Last observation carried forward
Glassman et al <sup>26</sup>	Depression after myocardial infarction; single episode or recurrent; Hamilton Depression Inventory score $\geq 18$ (recruitment from multisite North American hospital)	Sertraline (50-200 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 369</li> <li>Completion rate: sertraline 72%, placebo 73%, overall 73%</li> <li>Dropouts due to side effects: sertraline 9%, placebo 6%</li> <li>Dropouts due to lack of efficacy: sertraline 3%, placebo 3%</li> </ul>	<ul style="list-style-type: none"> <li>Response: Clinical Global Impression-Improvement = 1 or 2</li> </ul>	6.5	Pfizer Inc.	Last observation carried forward
Gual et al <sup>27</sup>	Alcohol dependence and major depression;† single episode or recurrent, with or without dysthymia (recruitment from single-site addictions treatment unit)	Sertraline (50-150 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 83</li> <li>Completion rate: sertraline 55%, placebo 56%, overall 55%</li> <li>Dropouts due to side effects: unknown</li> <li>Dropouts due to lack of efficacy: unknown</li> </ul>	<ul style="list-style-type: none"> <li>Response: <math>\geq 50\%</math> reduction in Montgomery Asberg Depression Rating Scale score relative to baseline</li> <li>Remission: Hamilton Depression Inventory score <math>&lt; 7</math></li> </ul>	6	Unknown	Intention to treat (not carrying the last observation forward)
Hypericum Depression Trial Study Group <sup>28</sup>	Major depression; single episode or recurrent; Hamilton Depression Inventory 17 score $\geq 20$ , Global Assessment of Functioning score $\leq 60$ (outpatients from 12 academic and community clinics)	Sertraline (100 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 127</li> <li>Completion rate: sertraline 24%, placebo 24%, overall 23%</li> <li>Dropouts due to side effects (at 8 wk): sertraline 4%, placebo 3%</li> <li>Dropouts due to lack of efficacy (at 8 wk): sertraline 6%, placebo 9%</li> </ul>	<ul style="list-style-type: none"> <li>Full response: Clinical Global Impression-Improvement = 1 or 2 and Hamilton Depression Inventory 17 score <math>&lt; 8</math></li> <li>Partial response: Clinical Global Impression-Improvement = 1 or 2 combined with Hamilton Depression Inventory 17 score between 9 and 12 and <math>&lt; 50\%</math> relative to baseline</li> <li>Relapse: Clinical Global Impression-Severity = 4 and Hamilton Depression Inventory 17 score <math>&gt; 20</math></li> </ul>	6	National Center for Complementary Medicine, National Institute of Mental Health; Lichtwer Pharma; Pfizer	Last observation carried forward
Murray et al <sup>29</sup>	Depression after stroke;‡ Montgomery Asberg Depression Rating Scale score $\geq 10$ (recruitment from 4 stroke centres in Sweden)	Sertraline (50-100 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 123</li> <li>Completion rate: sertraline 61%, placebo 51%, overall 56%</li> <li>Dropouts due to side effects: sertraline 13%, placebo 8%</li> <li>Dropouts due to lack of efficacy: sertraline 26%, placebo 36%</li> </ul>	<ul style="list-style-type: none"> <li>Response: <math>\geq 50\%</math> reduction in Montgomery Asberg Depression Rating Scale score relative to baseline</li> <li>Remission: Montgomery Asberg Depression Rating Scale score <math>&lt; 10</math></li> </ul>	6	Pfizer, AFA Insurances, Wallenberg Foundation	Both types of analysis done (last observation carried forward, and intention to treat)



**Table 1:** Summary of classic randomized controlled trials included in the systematic review of selective serotonin reuptake inhibitors for unipolar depression (part 2 of 2)

Study	Population*	Comparators	Completion data	Outcome measures	Duration, mo	Funding	Analysis
Stahl <sup>30</sup>	Major depressive disorder; single episode or recurrent; Hamilton Depression Inventory 17 score $\geq 22$ ; Raskin Depression Scale score $\geq 8$ , low score on Covi Anxiety Scale (8 US centres; recruitment base unclear)	Citalopram (20–60 mg) daily or sertraline (50–150 mg) daily or placebo	<ul style="list-style-type: none"> <li>Total randomized = 316</li> <li>Completion rate: citalopram 34%, sertraline 34%, placebo 33%, overall 34%</li> <li>Dropouts due to side effects: citalopram 14%, sertraline 19%, placebo 10%</li> <li>Dropouts due to lack of efficacy: citalopram 8%, sertraline 11%, placebo 31%</li> </ul>	<ul style="list-style-type: none"> <li>Response: 50% reduction in Hamilton Depression Inventory 17 score relative to baseline</li> <li>Remission: Hamilton Depression Inventory 17 score <math>&lt; 8</math></li> </ul>	6	Forest Laboratories, Lundbeck, Pfizer	Last observation carried forward

\*More detailed descriptions of the inclusion and exclusion criteria are presented in Appendix 4 (available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)).

<sup>†</sup>As defined in the *Diagnostic and Statistical Manual of Mental Disorders* or the International Classification of Diseases, 10th edition.

<sup>‡</sup>Eligibility for study limited to patients who required treatment in hospital for their stroke.

None of the eligible trials lasted longer than 12 months, and 5 of the 6 studies were commercially sponsored.

### Study populations

Participants ranged in age from 18 to 89 years and had been recruited from psychiatric outpatient clinics, private research clinics and general medical wards or through public advertisements. In addition to participants with depression who were free of medical or psychiatric comorbidities, a range of clinical subgroups was represented, including participants with significant medical comorbidities (myocardial infarction, stroke) and alcohol dependence. Detailed inclusion and exclusion criteria of the 6 trials are summarized in Appendix 4 (available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)). In the 3 studies in which history of depression was reported,<sup>25,26,30</sup> 20%–50% of participants had a history of recurrent depression.

### Interventions

Participants were randomly assigned to receive placebo or a selective serotonin reuptake inhibitor, specifically sertraline 50–200 mg/d,<sup>26–30</sup> citalopram 20–60 mg/d<sup>30</sup> or paroxetine 20 mg/d.<sup>25</sup>

### Assessment of risk of bias

Overall, the mean dropout rate across all 6 trials was 48% (range 27%–77%). For most of the included studies, we were unable to ascertain the risk of bias for several items because of poor reporting. Four of the included studies had unclear sequence generation, 3 had unclear allocation concealment, 2 had unclear blinding, and all had unclear selective outcome reporting. Four had a high risk of bias for incomplete outcome data, and 4 were assessed as unclear for “other biases” (Table 2). Visual inspection of the funnel plots did not suggest asymmetry (e.g., publication bias).

### Primary outcomes

For response to treatment (50% improvement in depression score relative to baseline), a pooled analysis of the 6 trials showed that selective serotonin reuptake inhibitors were superior to placebo at 6–8 months (OR 1.66, 95% CI 1.12–2.48;  $I^2 = 63.9\%$ ) (Figure 3). Subgroup analysis showed a statistically significant treatment effect among patients with depression who had no comorbidities (OR 2.13, 95% CI 1.11–4.08;  $I^2 = 76.8\%$ ) but not among those who had comorbidities (OR 1.32, 95% CI 0.84–2.06;  $I^2 = 30.8\%$ ) (Figure 3).

We obtained data on remission (score of 7 or below on the Hamilton rating scale for depression) from 4 trials.<sup>25,27,29,30</sup> Overall, the pooled difference between selective serotonin reuptake inhibitors and placebo was not statistically significant (OR 1.46, 95% CI 0.92–2.32;  $I^2 = 38\%$ ). However, participants without comorbidities had a significantly higher remission rate if they were taking selective serotonin reuptake inhibitors than if they were taking placebo (OR 2.06, 95% CI 1.41–3.01;  $I^2 = 0\%$ ), whereas the difference for participants with comorbidities was not statistically significant (OR 0.87, 95% CI 0.44–1.72;  $I^2 = 0\%$ ) (Figure 4).

For our measure of overall acceptability (total dropouts)

**Table 2:** Assessment of risk of bias\* in classic randomized controlled trials of selective serotonin reuptake inhibitors included in the systematic review

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other biases
Detke et al <sup>25</sup>	Unclear	Unclear	Low risk	High risk	Unclear	Unclear
Glassman et al <sup>26</sup>	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear
Gual et al <sup>27</sup>	Low risk	Low risk	Unclear	High risk	Unclear	Low risk
Hypericum Depression Trial Study Group <sup>28</sup>	Low risk	Low risk	Low risk	Unclear	Unclear	Unclear
Murray et al <sup>29</sup>	Unclear	Low risk	Unclear	High risk	Unclear	Low risk
Stahl <sup>30</sup>	Unclear	Unclear	Low risk	High risk	Unclear	Unclear

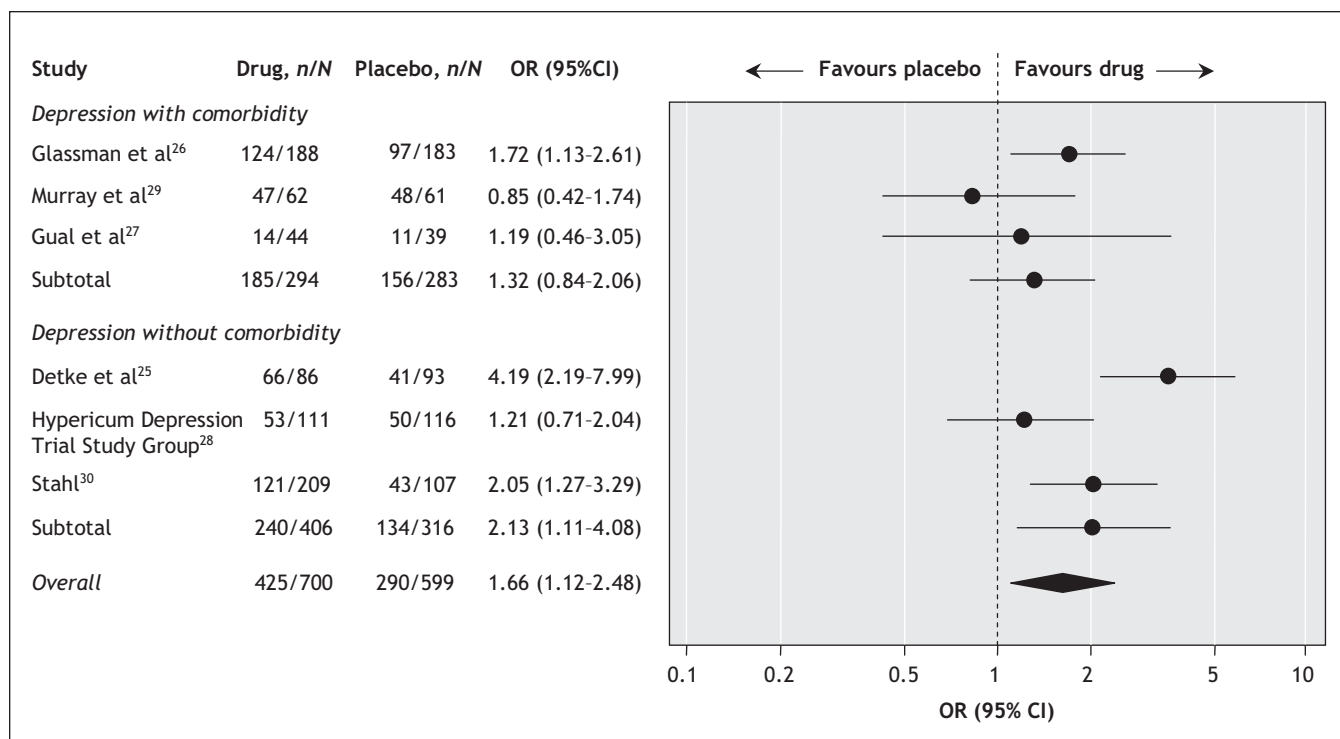
\*Ratings based on Cochrane risk-of-bias tool<sup>22</sup> and explained in Appendix 2 (available online at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)).

there was no statistically significant difference between selective serotonin reuptake inhibitors and placebo (OR 0.87, 95% CI 0.67–1.14;  $I^2 = 21.3\%$ ) (Figure 5).

### Secondary outcomes

Five of the 6 trials reported quality of life at the end of the trial (Table 3). Because a range of measures was used, we did not pool the data. One of the 5 trials reported improvements in all domains of a multidomain quality-of-life score,<sup>25</sup> and another reported a quality-of-life summary statistic favouring selective serotonin reuptake inhibitors ( $p < 0.01$ ), but the subscale breakdown was not reported.<sup>30</sup> A third trial reported results of a 10-cm visual analogue scale that favoured selective sero-

tonin reuptake inhibitors,<sup>29</sup> and a fourth reported quality-of-life improvements restricted to mood subscales,<sup>27</sup> with no statistically significant differences in other subscales. None of the trials provided information on the need for specific rescue therapies, including admission to hospital for psychiatric reasons, psychotherapy, pharmacotherapy or electroconvulsive therapy. Four trials did not specifically report on suicide or self-harm.<sup>26,27,29,30</sup> In the 2 trials that reported on suicide or self-harm, there was a total of 1 completed suicide among patients receiving placebo and none among patients receiving selective serotonin reuptake inhibitor.<sup>25,28</sup> Information on back-to-work status was not reported in any of the trials. One of the 6 trials stratified outcomes by the number of previous



**Figure 3:** Pooled analysis of response to treatment (50% improvement in depression score relative to baseline) in 6 classic randomized controlled trials of selective serotonin reuptake inhibitors in patients with major depression. The vertical line represents no difference between compared treatments.

depressive episodes and reported a higher response rate among patients with a history of recurrent depression.<sup>26</sup>

## Interpretation

No trials assessing the efficacy of selective serotonin reuptake inhibitor therapy over a period of more than 1 year met our eligibility criteria. Only 6 trials met our eligibility criteria; these studies, which had a moderate risk of bias, had randomly assigned a total of 1299 participants with depression to receive placebo or selective serotonin reuptake inhibitor and had followed both groups for 6–8 months. The mean dropout rate after 6–8 months was 48% (range 27%–87%), which exceeds the 15% maximum previously recommended for studies lasting longer than 3 months.<sup>31</sup> High dropout rates tend to reduce the level of confidence in the internal validity of trial results, as well as their applicability to general clinical practice. The only classic randomized clinical trial extending past 8 months that we identified was excluded from our review (see Appendix 3, at [www.cmaj.ca/cgi/content/full/178/10/1293/DC2](http://www.cmaj.ca/cgi/content/full/178/10/1293/DC2)). That study involved children and adolescents with depression, and participants with a response to medication or placebo were followed for 12 months. However, with an overall completion rate of only 16%, the trial was difficult to evaluate.

We observed statistically significant improvements in response to treatment but not in remission or acceptability (which might have been due to lack of power) after 6–8 months of selective serotonin reuptake inhibitor therapy. The effects appeared greater in patients without comorbidities. However, given the limited reporting of participants' course of illness, we were unable to determine whether particular

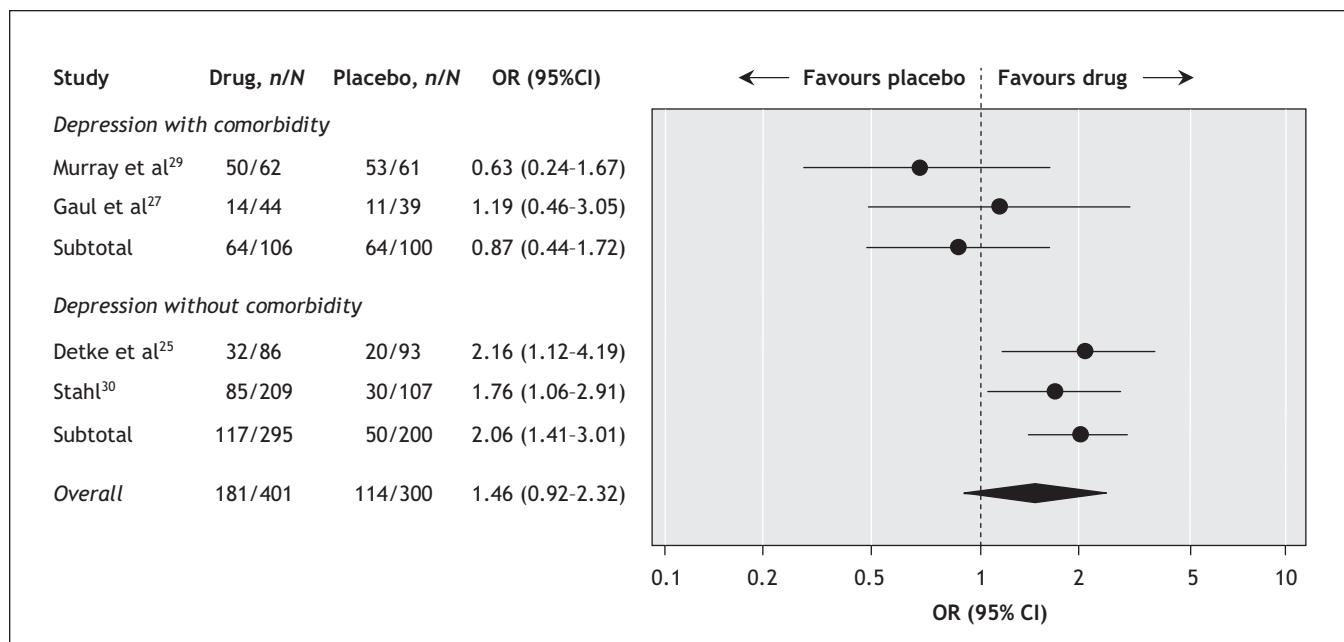
subgroups, such as those with highly recurrent depression, benefited more than those with single episodes. Furthermore, we found few data about the long-term effects of selective serotonin reuptake inhibitors on a range of important clinical outcomes, such as time off work, the need for co-interventions and self-harm, relative to those of placebo.

The study populations had been recruited from a range of settings, including psychiatric clinics, general medical hospitals and private community clinics. Groups with a higher prevalence of severe or recurrent depression may benefit most from antidepressants, and the distribution of more severe depressive illness may differ across these settings.<sup>32–34</sup>

One of the strengths of our systematic review is that it focused on classic long-term randomized controlled trials of selective serotonin reuptake inhibitors for the treatment of depression. Previous reviews included and were dominated by studies with discontinuation designs, which are difficult to interpret and which may overestimate the benefits of treatments.

Our study has several limitations. Because of resource constraints, we included only studies published in English, but this restriction is unlikely to have biased our results.<sup>35,36</sup> We did not detect any evidence of publication bias.

The main limitations of our review reflect the weaknesses of the included studies. The studies were at moderate risk of bias and failed to report key methodologic issues. No study reported data beyond 12 months. The most commonly reported outcome was “response to treatment” rather than “full remission.” Response was defined in terms of a 50% improvement in depression scores relative to baseline, whereas “full remission” was defined by pre-established cut-points on depression scores. Full remission from depression correlates with better longer-term functional recovery, lower risk of relapse and



**Figure 4:** Pooled analysis of remission (score of 7 or below on the Hamilton rating scale for depression) in 4 classic randomized controlled trials of selective serotonin reuptake inhibitors in patients with major depression. The vertical line represents no difference between compared treatments.

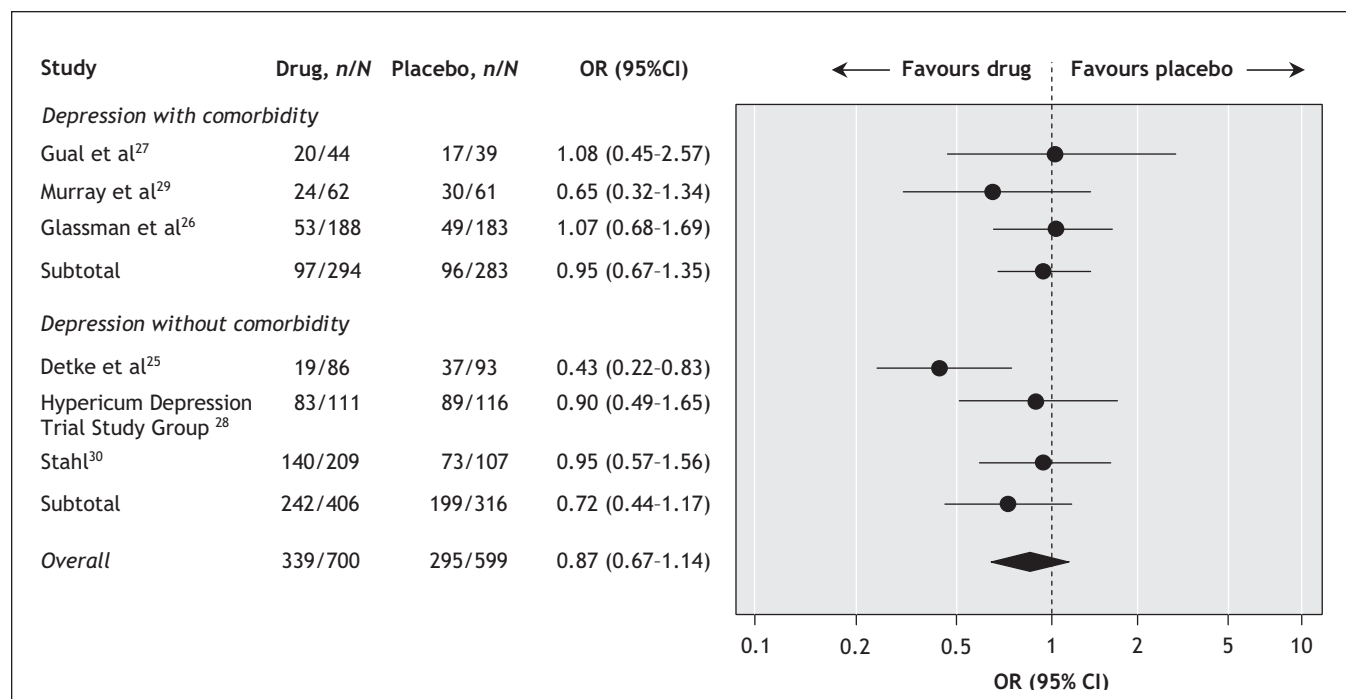
higher levels of patient satisfaction than partial response without remission.<sup>37</sup> Another limitation is that 4 of the 6 included trials reported outcomes in terms of the “last observation carried forward,” a method that may underestimate true treatment effects in short-term trials but overestimate active interventions in long-term trials.<sup>38</sup> Five of the 6 studies were commercially sponsored. This might have led to an exaggeration of treatment effects, since industry-sponsored trials have been shown to be 4 times as likely as independent studies to demonstrate positive effects of the sponsor’s drug.<sup>39–41</sup>

Similar to concerns with shorter-term trials of selective serotonin reuptake inhibitors, the study participants in the in-

cluded trials may not be representative of those seen in everyday practice.<sup>42</sup> For example, 5 of the 6 trials excluded patients with substance abuse, a common comorbidity, and all trials excluded patients with suicidal ideation, one of the diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

## Conclusion

Despite the widespread use of long-term therapy with selective serotonin reuptake inhibitors, relatively few trials have compared long-term outcomes between patients with depres-



**Figure 5:** Pooled analysis of overall acceptability (total dropouts) in 6 classic randomized controlled trials of selective serotonin reuptake inhibitors in patients with major depression. The vertical line represents no difference between compared treatments.

**Table 3:** Secondary outcomes in classic randomized trials of selective serotonin reuptake inhibitors included in the systematic review

Study	Rescue therapy*	Back-to-work status	Suicide, suicide attempt or self-harm	Overall quality-of-life
Detke et al <sup>25</sup>	Not reported	Not reported	1 suicide (placebo group)	Sheehan Disability Scale (favoured drug)
Glassman et al <sup>26</sup>	Not reported	Not reported	Not reported	Not reported
Gual et al <sup>27</sup>	Not reported	Not reported	Not reported	Medical Outcomes Study 36-item Short Form (favoured drug)
Hypericum Depression Trial Study Group <sup>28</sup>	Not reported	Not reported	“No serious adverse events”	Not reported at end point
Murray et al <sup>29</sup>	Not reported	Not applicable†	Not reported	Visual analogue scale (favoured drug)
Stahl <sup>30</sup>	Not reported	Not reported	Not reported	Symptom Checklist-56 (favoured drug)

\*Medications, psychotherapy, electroconvulsive therapy or admission to hospital.

†Mean age of participants (who had depression following stroke) was 70 years.



sion who recover spontaneously and those who recover because of medication. Most treatment guidelines recommend a minimum of 6–9 months of antidepressant treatment following initial recovery from depression. Our observations, based on limited evidence, support current recommendations that treatment continue for at least 6–9 months after recovery from an episode of depression, particularly in those without major comorbidities. Longer-term treatment should be undertaken only in selected cases and with an appreciation of the uncertainties surrounding the practice. Future studies should examine long-term use of selective serotonin reuptake inhibitors in depression using clinically relevant outcomes for all patients with depression, including those who experience spontaneous resolution.

This article has been peer reviewed.

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