A meta-analysis of agomelatine versus placebo for the treatment of major depressive disorder

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Abstract

**Background:** Major depressive disorder (MDD) is a significant cause of morbidity and mortality in Canadians. Approximately 30% of patients with MDD do not respond to treatment. Agomelatine, a novel drug targeting the melatonin pathway has been shown to be effective in treating MDD in a number of randomized clinical trials. A meta-analysis was conducted on all available placebo-controlled randomized trials to determine the efficacy of agomelatine in treating MDD.

**Methods:** A literature search was conducted using MEDLINE and EMBASE. Original research was selected based on inclusion/exclusion criteria and the quality of the studies was evaluated. Five studies were included in a random effects meta-analytic model developed by Cochrane.

**Results:** Agomelatine demonstrated statistically significant efficacy compared to placebo when evaluated on the HAM-D. However, agomelatine failed to demonstrate clinical significance compared to placebo when evaluated on the same scale.

**Conclusion:** Agomelatine demonstrates similar efficacy to currently available treatment for MDD. However, given agomelatine’s unique mechanism of action, it may be useful for the treatment of patients who are resistant to first line therapy.
Introduction

Major depressive disorder (MDD) is a chronic disease that is estimated to affect about 8% to 11% of Canadians\textsuperscript{1, 2}. MDD is associated with significant morbidity and mortality and is characterized by depressed mood, loss of interest in activities and decreased energy level\textsuperscript{3}. One of the theories regarding the neurobiology of depression is the monoamine hypothesis\textsuperscript{4}. The monoamine hypothesis posits that decreased levels of the monoamine neurotransmitters, such as serotonin (5-HT) and norepinephrine (NE), in certain regions of the brain lead to mood dysregulation and the clinical manifestations of MDD. Thus, many antidepressants have been developed in an attempt to increase central levels of these monoamines. Antidepressants are categorized based on their mechanism of action. The tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of NE and 5-HT while selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of only 5-HT. SSRIs and SNRIs are first line therapy for treating MDD because of their safer side effect profile and better tolerability relative to TCAs\textsuperscript{5}. Theoretically, each drug in the same class act by a similar mechanism to treat depression but in practice, patients respond differently to these medications\textsuperscript{6}. Approximately 30% of the MDD patients do not respond to treatment and are classified as “treatment resistant” after failing two or more courses of antidepressants\textsuperscript{7}. The two most recently Health Canada approved antidepressants are Pristiq (desvenlafaxine) and Cymbalta (duloxetine), both SNRIs\textsuperscript{8, 9}. Nevertheless, the efficacy of these two drugs are comparable to current available SNRIs or SSRIs but at a higher acquisition costs and therefore have not been recommended for first line therapy\textsuperscript{8, 9}. The paucity of effective treatment options for this large population suffering from MDD demonstrates the need for novel therapies that target other aspects of the complex neurobiology of depression.

Currently, there is a new drug that is in phase III clinical trials for the treatment of MDD, agomelatine, a synthetic analog of melatonin\textsuperscript{10}. Melatonin is a neurotransmitter produced by the suprachiasmatic nucleus that regulates circadian rhythm, including the sleep-wake cycle\textsuperscript{11}. Desynchronization of normal circadian rhythm, resulting in sleep disturbance has been associated with MDD. In fact, the Diagnostic and
Statistical Manual of Mental Disorders (DSM-IV) states that disturbed sleep is one of the diagnostic criteria for MDD\textsuperscript{12}. Agomelatine is an agonist at the MT\textsubscript{1} and MT\textsubscript{2} receptors and an antagonist at the 5-HT\textsubscript{1C} receptor\textsuperscript{13}. Clinical trials have shown agomelatine to be efficacious in treating patients with MDD as evidenced by improvement in the Hamilton Depression Rating Scale (HAM-D) and other measures of MDD severity\textsuperscript{14-18}. The sample sizes in these studies were small and may limit the detection of the treatment effect. Previously, Montgomery and Kasper conducted a pooled analysis of three placebo-controlled trials on agomelatine and grouped results based on disease severity but did not examine the efficacy of each dose separately\textsuperscript{19}. In addition, since the publication of the pooled analysis, two additional clinical trials have been published. Thus an updated meta-analysis is necessary to evaluate this new drug\textsuperscript{17,18}. The purpose of this review is to conduct a meta-analysis utilizing the results of the few available published placebo-controlled trials.

Methods

The population to be studied was patients suffering from MDD based on DSM-IV criteria, treated for at least six weeks (minimum amount of time for medication to demonstrate an effect\textsuperscript{7}) on placebo or agomelatine (25 or 50mg). Only randomized double-blinded placebo-controlled trials utilizing the HAM-D were considered for this study.

A literature review was conducted using MEDLINE and EMBASE to search for clinical trials evaluating agomelatine for clinical trials. The following keywords were used in the search: agomelatine and major depression. The search was limited to original articles, human, English and clinical trials. The author reviewed the methods to determine if studies met inclusion criteria. Appropriate trials were then assessed for quality using the Jadad scoring tool. Only studies with Jadad score of three or greater were included in this analysis.
A meta-analysis was conducted to estimate an overall mean effect based on the individual studies obtained from the literature search. From each of the studies, the overall between group differences for each dose of agomelatine and placebo were extracted along with the associated standard error of the mean (SE). A random-effects meta-analytic model developed by Cochrane (Review Manager 5) was used in this study examining the effects of agomelatine at 25 and 50mg compared to placebo. The effect size was weighted based on standard error of the mean and model yielded a pooled mean point estimate and a 95% confidence interval (CI). Funnel plots for both meta-analyses were generated examining the relationship between effect size and sample size.

Results

Twelve articles were extracted based on search criteria in the MEDLINE and EMBASE database. Seven articles were excluded based on inclusion and exclusion criteria: inappropriate dose/diagnosis ($n=2$), lack of placebo control ($n=4$), and open-label ($n=1$). The author assigned each of the five remaining articles a Jadad score. All trials examined were at least of good quality based on the Jadad scale and no studies were removed (median score of 4). The five articles were randomized, double-blind, placebo-controlled, multi-centred trials of short duration (6 or 8 weeks). The studies evaluated two doses of agomelatine (25 and 50 mg) in either a fixed or a flexible dose regimen in which patients were uptitrated from 25 to 50 mg at a certain time point in the trial if they deemed the original dose not effective. Two studies included a flexible dosing schedule and both studies were included in the 25mg and 50mg analysis. Inclusion and exclusion criteria were similar in all the studies. Patients that met the DSM-IV criteria for depression were included. Studies excluded patients with relevant psychiatric comorbidities, treatment resistant to marketed antidepressants and other non-pharmacological treatments. Trial characteristics and results were summarized in Table 1.

Two meta-analyses were conducted. The first meta-analysis examined the overall mean effect based on studies that evaluated the 25mg dose (Figure 1) while the second meta-analysis evaluated the 50mg dose
Since the final number of patients on either 25mg or 50mg could not be extracted from two of the studies with a flexible dosing schedule\textsuperscript{14,16}, the aggregated data was used in both analyses. In the fixed dose studies that examined both the 25 and 50mg, the results were disaggregated into the respective doses and analyzed according\textsuperscript{17,18}. The 25mg analysis included all five studies and heterogeneity was found to be not significant ($\chi^2 = 5.89$, $p=0.21$). Pooled results demonstrated that 25mg agomelatine was significantly different compared to placebo by 2.16 in HAM-D score changes from baseline to final visit (95% CI 1.29-3.03, $p<0.01$). Similarly, in the 50mg analysis, 4 studies were included and heterogeneity was not significant ($\chi^2 = 2.50$ $p=0.48$). Pooled results demonstrated that 50mg agomelatine was also significantly different than placebo by 2.18 in HAM-D score changes from baseline to final visit (95% CI 1.24-3.13). Funnel plot asymmetry was not tested due to low sample size.

**Discussion**

Given that current treatment options for MDD are not effective for about 30% of the patients, the introduction of a novel anti-depressant targeting a different aspect of the pathogenesis of depression is promising. However, results from this meta-analysis demonstrate only modest benefits of agomelatine for the treatment of MDD compared to placebo. Though results demonstrated significant differences favouring agomelatine over placebo, the clinical significance of these results merit further discussion. Specifically, a study has shown that a three-point difference in change between active medication and placebo is indicative of clinical significance\textsuperscript{21}. The results from the meta-analysis of both doses of agomelatine fall short of this threshold definition of clinical significance. These results are similar to that of a meta-analysis of published and unpublished studies conducted by the European Medicines Agency that found a 1.5 difference in HAM-D change to be statistically significant but only marginally clinically significant\textsuperscript{22}. However, these results are different from the earlier study by Montgomery and Kasper that found a 2.86 point difference overall and higher differences when patients were categorized based on severity\textsuperscript{19}. Furthermore, the results from this analysis suggested that there were no clinically significant differences in efficacy between the 25mg and 50mg dose of medication. Due to the limitations in the data
presented in these articles, it was not possible to conduct a meta-analysis on other clinically significant outcomes such as response or remission on the HAM-D scales. Visual inspection of the funnel plots suggested minimal publication bias of trials, though a larger sample size is needed for statistical testing.

Generally, the studies were quite similar as demonstrated by the results from the meta-analysis that showed heterogeneity to not be significant for both doses. This was expected as methods, inclusion/exclusion criteria were similar for all studies, resulting in a well-defined population for this meta-analysis. The study population can be described as patients suffering from moderate to severe depression (based on initial HAM-D scores) that were not treatment resistant and did not suffer from other psychiatric comorbidities. This patient population may not reflect true clinical settings as patients often fail to respond to multiple treatments\(^7\) and present with multiple psychiatric comorbidities. This highlights the paucity for additional studies that examine the use of agomelatine in treatment resistant depression as this novel treatment may help those that are not responding to first line therapy that target NE/5-HT neurotransmitter systems. In addition, most trials were 6 weeks in length with the longest trial being 8 weeks. This is a short duration of treatment as MDD is an illness of much longer duration, making it difficult to assess long-term tolerability and efficacy of the medication. In fact, the STAR*D trial demonstrated that of those that do respond to medication, one third responded after six weeks\(^7\). Thus, trials of greater lengths would be useful to determine the lasting benefits of agomelatine.

The measured effect sizes in this meta-analysis were similar to those observed in the duloxetine and desvenlafaxine trials in the treatment of MDD\(^{23-27}\). Given the results of the meta-analysis, agomelatine should not be recommended as first line treatment for MDD, given that current medications are more cost-effective. However, it may have a role in treating patients that do not respond to medications that target the serotonergic and noradrenergic systems. Additional research examining the efficacy of agomelatine in this treatment-resistant population is warranted before further recommendations may be made.
Figures

Figure 1. Forest plot of trials evaluating agomelatine 25 mg versus placebo. Outcome reported as difference in mean change HAM-D scores with 95% confidence intervals.

Figure 2. Forest plot of trials evaluating agomelatine 50 mg versus placebo. Outcome reported as difference in mean change HAM-D scores with 95% confidence intervals.
<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline HAM-D</th>
<th>Final HAM-D</th>
<th>Estimate (SE)</th>
<th>95% Confidence Interval</th>
<th>Jadad Score</th>
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<td>12.8±8.2</td>
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<td>Ago 25-50 (n=106)</td>
<td>26.5±2.8</td>
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<td>13.9±7.7</td>
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<td>1.18-5.18 (p&lt;0.05)</td>
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<td>Study duration: 6 weeks</td>
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<td>15.0±8.0</td>
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<td>15.9±8.2</td>
<td>1.2 (0.85)</td>
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<td>17.1±7.9</td>
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Estimate of the difference between groups in final change in HAM-D score from baseline to last visit.
Ago 25- Agomelatine at 25 mg/d, Ago 50- Agomelatine at 50 mg/d, Ago 25-50- Agomelatine at 25 or 50 mg/d, SE- standard error of the mean, n- sample size
References


