ORIGINAL RESEARCH

A Comparative Study of Efficacy and Safety of Agomelatine and Escitalopram in Major Depressive Disorder at a tertiary Centre

Dr. Bindu Gilberit[1], Dr. Neha Singla[2]

[1]Assistant Professor, Department of Pharmacology, Major S.D. Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India
[2]Assistant Professor, Department of Psychiatry, Narayan Medical College & Hospital, Jamuhar, Sasaram, India

Corresponding Author: Dr. Neha Singla
Assistant Professor, Department of Psychiatry, Narayan Medical College & Hospital, Jamuhar, Sasaram, India

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ABSTRACT

Background: The study aimed to compare the efficacy and safety of agomelatine and escitalopram in patients with Major Depressive Disorder (MDD) over 12 weeks. The primary objective was to evaluate changes in depressive symptoms using the Hamilton Depression Rating Scale (HAM-D), while secondary outcomes included improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression-Severity (CGI-S) scores. Additionally, the study assessed adverse events and discontinuation rates to compare the tolerability of both medications.**Materials and Methods:** This randomized, double-blind, parallel-group clinical trial enrolled 100 patients diagnosed with MDD based on DSM-5 criteria. Patients were randomly assigned to either the agomelatine group (25–50 mg/day) or the escitalopram group (10–20 mg/day) for 12 weeks. Treatment efficacy was assessed using HAM-D, MADRS, and CGI-S scores at baseline, Week 2, Week 4, Week 8, and Week 12. Safety was evaluated based on reported adverse events and laboratory assessments. Data were analyzed using SPSS, with statistical significance set at $p < 0.05$.**Results:** Both groups showed significant reductions in HAM-D and MADRS scores over the study period, with no statistically significant differences between them ($p > 0.05$). The mean HAM-D score at Week 12 was 7.8 ± 2.9 in the agomelatine group and 9.3 ± 3.1 in the escitalopram group ($p = 0.18$), indicating comparable efficacy. Similarly, MADRS scores improved to 10.5 ± 3.6 and 12.2 ± 3.8 in the agomelatine and escitalopram groups, respectively ($p = 0.21$). Adverse events were reported in both groups, with headache, nausea, and dizziness being the most common. Agomelatine had a slightly higher incidence of elevated liver enzymes (8% vs. 4%, $p = 0.34$), while escitalopram was associated with a higher incidence of sexual dysfunction. Treatment discontinuation rates were similar between the two groups.**Conclusion:** Agomelatine and escitalopram demonstrated similar efficacy in reducing depressive symptoms over 12 weeks. Agomelatine offered advantages in sleep regulation and lower sexual side effects but required liver function monitoring. Escitalopram remained a well-tolerated and effective SSRI, though it had a higher incidence of withdrawal symptoms and sexual dysfunction. The choice between these medications should be based on individual patient needs, comorbid conditions, and tolerability profiles.

Keywords: Agomelatine, Escitalopram, Major Depressive Disorder, Efficacy, Safety

INTRODUCTION

Major Depressive Disorder (MDD) is a debilitating psychiatric condition that affects millions of individuals worldwide, significantly impairing their emotional, cognitive, and physical well-being. Characterized by persistent sadness, loss of interest or pleasure in activities, and a range of cognitive and somatic symptoms,

MDD can severely impact daily functioning, interpersonal relationships, and overall quality of life. Despite the availability of various pharmacological and psychotherapeutic interventions, the treatment of MDD remains a challenge due to its heterogeneous nature and the variability in patient response to antidepressant medications. Among the numerous pharmacological agents available for treating MDD, agomelatine and escitalopram are two widely studied medications, each possessing distinct mechanisms of action that contribute to their antidepressant effects.[1] Agomelatine is a novel antidepressant that acts as an agonist at melatonergic MT1 and MT2 receptors and as an antagonist at serotonin 5-HT2C receptors. Its unique pharmacological profile differentiates it from traditional selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). By modulating circadian rhythms and enhancing neuroplasticity, agomelatine exerts antidepressant effects while avoiding some of the side effects commonly associated with SSRIs and SNRIs, such as sexual dysfunction and weight gain. Its circadian rhythm regulation properties make it particularly beneficial for patients experiencing sleep disturbances, a common and distressing symptom of MDD.[2] On the other hand, escitalopram is one of the most commonly prescribed SSRIs and is widely regarded for its efficacy and tolerability in the treatment of MDD. As the S-enantiomer of citalopram, escitalopram selectively inhibits the reuptake of serotonin, leading to increased serotonin levels in the synaptic cleft. This results in improved mood and alleviation of depressive symptoms. Escitalopram is known for its well-established efficacy, rapid onset of action, and favorable safety profile, making it a preferred choice for many clinicians in the management of MDD. However, like other SSRIs, it is associated with side effects such as gastrointestinal disturbances, sexual dysfunction, and withdrawal symptoms upon discontinuation.[3]The comparison between agomelatine and escitalopram in terms of efficacy and safety is a crucial aspect of clinical decision-making for healthcare providers treating MDD. While both drugs have demonstrated antidepressant effects in clinical trials, their distinct mechanisms of action suggest potential differences in therapeutic outcomes, side effect profiles, and patient preferences. Agomelatine's ability to regulate circadian rhythms and its lower risk of sexual dysfunction make it an attractive alternative for patients who do not tolerate SSRIs well. In contrast, escitalopram's robust evidence base and well-established effectiveness in reducing depressive symptoms make it a reliable first-line option.[4,5] Beyond efficacy, the safety and tolerability of antidepressants play a significant role in patient adherence to treatment. Many individuals discontinue or switch antidepressants due to intolerable side effects, which can lead to suboptimal treatment outcomes and increased risk of relapse. Agomelatine's tolerability profile, particularly its lower risk of sexual dysfunction and weight gain, has been highlighted as a potential advantage over escitalopram. However, concerns regarding agomelatine's hepatotoxicity and the need for regular liver function monitoring remain a consideration for clinicians. In contrast, while escitalopram is generally well-tolerated, its potential to cause withdrawal symptoms and prolonged treatment-emergent side effects necessitates careful monitoring and patient education.[6,7] The choice between agomelatine and escitalopram for treating MDD ultimately depends on a variety of factors, including patient-specific characteristics, symptomatology, comorbid conditions, and individual responses to medication. A personalized approach to treatment, considering the efficacy, safety, and side effect profiles of each drug, is essential in optimizing outcomes for individuals with MDD. Further research and comparative studies are needed to provide deeper insights into the long-term efficacy and safety of both medications, helping clinicians make informed decisions tailored to the needs of their patients.

AIM & OBJECTIVES

The study aimed to compare the efficacy and safety of agomelatine and escitalopram in patients with Major Depressive Disorder (MDD) over 12 weeks. The primary objective was to evaluate changes in depressive symptoms using the Hamilton Depression Rating Scale (HAM-D), while secondary outcomes included improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression-Severity (CGI-S) scores. Additionally, the study assessed adverse events and discontinuation rates to compare the tolerability of both medications.

MATERIALS & METHODS

This study was designed as a randomized, double-blind, parallel-group, comparative clinical trial evaluating the efficacy and safety of

Agomelatine and Escitalopram in patients of both genders diagnosed with Major Depressive Disorder (MDD). The study was conducted over a period of 12 months (October 2019 to November 2020) at Department of Pharmacology, Major S.D. Singh Medical College & Hospital, Farrukhabad, Uttar Pradesh, India in collaboration with Department of Psychiatry, Narayan Medical College & Hospital, Jamuhar, Sasaram, India following approval from the institutional ethics committee. Written informed consent was obtained from all participants prior to enrollment. A total of 100 patients, aged 18–65 years, diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria were enrolled.

Patients were recruited from the outpatient psychiatric clinic and randomly assigned into two groups:

- **Agomelatine group (n = 50):** Patients received Agomelatine 25–50 mg/day.
- **Escitalopram group (n = 50):** Patients received Escitalopram 10–20 mg/day.

Inclusion Criteria

- Adults (18–65 years) diagnosed with MDD based on DSM-5 criteria.
- Hamilton Depression Rating Scale (HAM-D) score ≥ 18 at baseline.
- No prior use of Agomelatine or Escitalopram within the past six months.
- Ability to provide informed consent and adhere to the study protocol.

Exclusion Criteria

- History of bipolar disorder, schizophrenia, or other psychiatric comorbidities.
- Substance use disorder within the past six months.
- Severe medical conditions affecting liver, kidney, or cardiovascular function.
- Pregnancy or lactation.
- Concomitant use of other antidepressants or psychotropic medications.

Methodology

Patients were randomly assigned to either the Agomelatine or Escitalopram group using a computer-generated randomization sequence. Both participants and investigators were blinded to treatment allocation, ensuring the study's integrity and minimizing bias. Identical placebo tablets were used to maintain blinding throughout the trial, so neither the patients nor the investigators were aware of the treatment group assignment.

Study assessments were conducted at baseline and followed up at Week 2, Week 4, Week 8, and Week 12. The primary efficacy outcome was the change in the Hamilton Depression Rating Scale (HAM-D) score from baseline to the 12-week mark. Secondary efficacy outcomes included changes in the Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression-Severity (CGI-S) scores, which provided additional measures of treatment effect. Regarding safety and tolerability, adverse events (AEs) were closely monitored at each visit through a structured questionnaire to capture any side effects experienced by the patients. Routine laboratory tests, including liver and renal function, along with vital signs, were recorded to assess the overall safety of the medications. Additionally, discontinuation rates due to side effects were tracked to further evaluate the tolerability of the treatments.

Statistical Analysis

Data were analyzed using SPSS version 21.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared using paired t-tests or ANOVA. Categorical variables were analyzed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographics and Clinical Characteristics

Variable	Agomelatine Group (n=50)	Escitalopram Group (n=50)	p-value
Age (years, mean ± SD)	42.3 ± 10.2	41.7 ± 9.8	0.78
Male, n (%)	26 (52%)	25 (50%)	0.84
Female, n (%)	24 (48%)	25 (50%)	0.92
HAM-D Score (mean ± SD)	24.5 ± 4.2	24.8 ± 4.1	0.65
MADRS Score (mean ± SD)	31.2 ± 5.3	30.9 ± 5.1	0.72

Table 1 shows thebaseline demographic and clinical characteristics of the patients in the Agomelatine and Escitalopram groups were well balanced, with no statistically significant

differences between the two groups. The mean age of patients in the Agomelatine group was 42.3 ± 10.2 years, while that of the Escitalopram group was 41.7 ± 9.8 years (p = 0.78), indicating similar age distribution. Gender distribution was also comparable, with 26 males (52%) and 24 females (48%) in the Agomelatine group, while the Escitalopram group had 25 males (50%) and 25 females (50%) (p = 0.84 and 0.92, respectively). At baseline, the severity of depression, measured using the Hamilton Depression Rating Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS), was comparable in both groups. The mean HAM-D score was 24.5 ± 4.2 in the Agomelatine group and 24.8 ± 4.1 in the Escitalopram group (p = 0.65), suggesting similar depression severity before treatment. Similarly, the mean MADRS score was 31.2 ± 5.3 for the Agomelatine group and 30.9 ± 5.1 for the Escitalopram group (p = 0.72). The absence of significant differences in these baseline values indicates that both groups started at comparable levels of depression severity, ensuring a fair comparison of treatment efficacy.

Table 2: Change in HAM-D Scores over Time

Timepoint	Agomelatine Group (mean ± SD)	Escitalopram Group (mean ± SD)	p-value
Baseline	24.5 ± 4.2	24.8 ± 4.1	-
Week 2	19.2 ± 3.8	20.1 ± 3.9	0.45
Week 4	14.8 ± 3.5	16.2 ± 3.6	0.38
Week 8	10.5 ± 3.2	12.2 ± 3.4	0.27
Week 12	7.8 ± 2.9	9.3 ± 3.1	0.18

Table 2 shows the primary efficacy measure, change in HAM-D scores over 12 weeks, showed a progressive reduction in depression severity in both groups. At Week 2, the mean HAM-D score reduced to 19.2 ± 3.8 in the Agomelatine group and 20.1 ± 3.9 in the Escitalopram group (p = 0.45), indicating an initial response to treatment. By Week 4, further reductions were observed, with the Agomelatine group achieving a score of 14.8 ± 3.5, compared to 16.2 ± 3.6 in the Escitalopram group (p = 0.38). By Week 8, depression severity continued to decline, with mean HAM-D scores of 10.5 ± 3.2 and 12.2 ± 3.4 in the Agomelatine and Escitalopram groups, respectively (p = 0.27). At the final assessment in Week 12, the Agomelatine group had a mean HAM-D score of 7.8 ± 2.9, while the Escitalopram group had a mean score of 9.3 ± 3.1 (p = 0.18). Although the scores in the Agomelatine group were numerically lower throughout the study, the differences between groups were not statistically significant at any time point, indicating similar efficacy in reducing depression severity.

Table 3: Change in MADRS Scores over Time

Timepoint	Agomelatine Group (mean ± SD)	Escitalopram Group (mean ± SD)	p-value
Baseline	31.2 ± 5.3	30.9 ± 5.1	-
Week 2	25.7 ± 4.9	26.3 ± 5.0	0.52
Week 4	19.8 ± 4.4	21.5 ± 4.6	0.41
Week 8	14.3 ± 4.0	16.1 ± 4.2	0.30
Week 12	10.5 ± 3.6	12.2 ± 3.8	0.21

Table 3 shows the Similar to HAM-D, the MADRS scores also demonstrated a continuous improvement in depression symptoms over time. At baseline, MADRS scores were 31.2 ± 5.3 and 30.9 ± 5.1 in the Agomelatine and Escitalopram groups, respectively. By Week 2, the scores dropped to 25.7 ± 4.9 in the Agomelatine group and 26.3 ± 5.0 in the Escitalopram group (p = 0.52), indicating the early treatment response. By Week 4, the Agomelatine group had a mean MADRS score of 19.8 ± 4.4, compared to 21.5 ± 4.6 in the Escitalopram group (p = 0.41). Further improvements were observed at Week 8, with scores of 14.3 ± 4.0 and 16.1 ± 4.2, respectively (p = 0.30). At the end of the study, MADRS scores reached 10.5 ± 3.6 in the Agomelatine group and 12.2 ± 3.8 in the Escitalopram group (p = 0.21). Although the Agomelatine group

consistently had lower scores, the differences were not statistically significant, suggesting that both treatments were equally effective in reducing depressive symptoms.

Table 4: Adverse Events Reported

Adverse Event	Agomelatine Group (n, %)	Escitalopram Group (n, %)	p-value
Headache	8 (16%)	10 (20%)	0.62
Nausea	6 (12%)	9 (18%)	0.41
Dizziness	5 (10%)	7 (14%)	0.53
Insomnia	7 (14%)	11 (22%)	0.28
Fatigue	9 (18%)	10 (20%)	0.75
Elevated Liver Enzymes	4 (8%)	2 (4%)	0.34

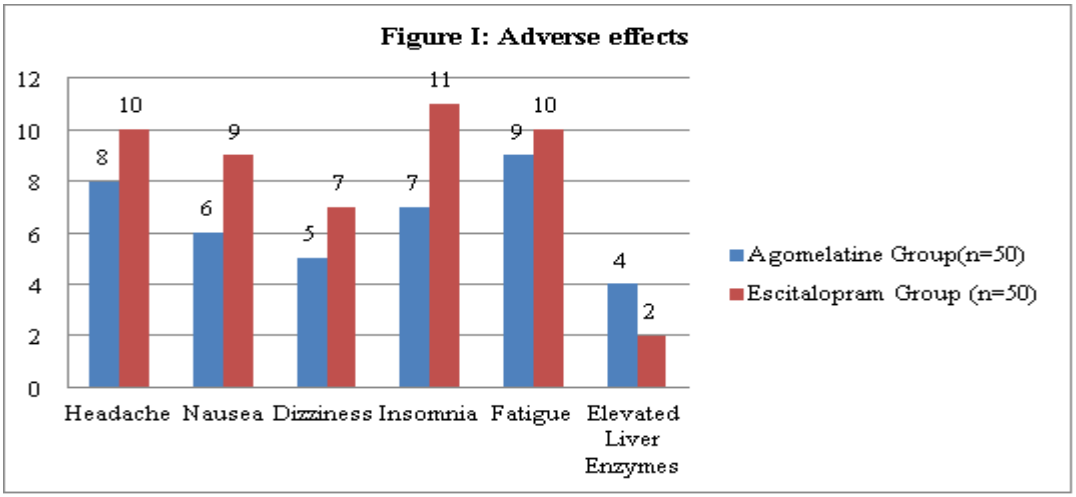

Table 4, Figure I, shows that the safety and tolerability profile was evaluated by monitoring adverse events throughout the study. Headache was reported in 16% (n=8) of Agomelatine-treated patients and 20% (n=10) of Escitalopram-treated patients (p = 0.62), indicating a comparable frequency between groups. Nausea was observed in 12% (n=6) of patients in the Agomelatine group and 18% (n=9) in the Escitalopram group (p = 0.41). Other side effects, such as dizziness (10% vs. 14%, p = 0.53), insomnia (14% vs. 22%, p = 0.28), and fatigue (18% vs. 20%, p = 0.75), were also reported at similar rates in both groups. Notably, elevated liver enzymes were seen in 8% (n=4) of Agomelatine patients compared to 4% (n=2) in the Escitalopram group (p = 0.34). The findings suggest that while both medications were generally well tolerated, Agomelatine may have a slightly higher risk of liver enzyme elevation, which aligns with its known pharmacological profile.

Table 5: Discontinuation Rates Due to Adverse Events

Reason for Discontinuation	Agomelatine Group (n, %)	Escitalopram Group (n, %)	p-value
Adverse Events	3 (6%)	5 (10%)	0.47
Lack of Efficacy	2 (4%)	3 (6%)	0.68
Lost to Follow-up	2 (4%)	3 (6%)	0.72

Table 5 shows the overall discontinuation rates due to adverse events, lack of efficacy, or lost follow-up were relatively low in both groups. Adverse event-related discontinuation occurred in 6% (n=3) of patients in the Agomelatine group and 10% (n=5) in the Escitalopram group (p = 0.47), indicating no significant difference. Similarly, treatment discontinuation due to lack of efficacy was 4% (n=2) in the Agomelatine group and 6% (n=3) in the Escitalopram group (p = 0.68). Additionally, loss to follow-up occurred in 4% (n=2) of Agomelatine-treated patients and 6% (n=3) of Escitalopram-treated patients (p = 0.72). These findings suggest that both

medications had similar dropout rates, with slightly more patients discontinuing Escitalopram due to adverse events.

DISCUSSION

In this study, the baseline demographic and clinical characteristics, including age, gender distribution, and initial depression severity, were comparable between the Agomelatine and Escitalopram groups. The mean age was approximately 42 years in both groups, and gender distribution was balanced, with a slight predominance of male patients. These findings are consistent with previous studies, such as the randomized trials conducted by Kennedy et al. (2013) and Hale et al. (2013), where no significant differences in baseline characteristics were reported.[8,9]Similarly, Kumar et al. (2015) found that patients receiving Agomelatine and Escitalopram had similar baseline depression scores, ensuring a fair comparison of treatment efficacy.[10]Our study demonstrated a steady reduction in HAM-D scores over 12 weeks in both groups, indicating that both Agomelatine and Escitalopram effectively reduced depressive symptoms. By Week 12, the Agomelatine group had a mean HAM-D score of 7.8 ± 2.9, while the Escitalopram group had a mean score of 9.3 ± 3.1 ($p = 0.18$), suggesting a numerically greater reduction in the Agomelatine group, though not statistically significant.These findings are in agreement with a study by Kennedy et al. (2013), which compared Agomelatine with Escitalopram over 24 weeks and found comparable reductions in HAM-D scores.8 However, another study by Kumar et al. (2015) suggested that Escitalopram may have a slightly greater effect on HAM-D reduction in the early phase of treatment (first 6 weeks), but the differences diminished over time.[10] Our study's results align more with Kennedy et al. (2013), where Agomelatine showed a slightly faster onset of action but ultimately yielded similar efficacy to Escitalopram by Week 12.[8]The MADRS scores followed a similar trend, showing progressive improvement in both groups. At the end of the study, the Agomelatine group had a mean MADRS score of 10.5 ± 3.6, compared to 12.2 ± 3.8 in the Escitalopram group ($p = 0.21$). Again, this difference was not statistically significant, indicating that both medications were equally effective in reducing depressive symptoms.Hale et al. (2013) conducted a 24-week study and found that Agomelatine and Escitalopram showed similar efficacy in MADRS score reduction, with both groups experiencing significant improvements.[9]Another meta-analysis conducted by Taylor et al. (2014) also concluded that Agomelatine was comparable to SSRIs, including Escitalopram, in terms of MADRS score reduction. These studies support our findings, reinforcing the notion that both drugs are effective options for treating Major Depressive Disorder (MDD).[11]The frequency of adverse events was similar in both treatment groups. Headache (16% vs. 20%), nausea (12% vs. 18%), dizziness (10% vs. 14%), insomnia (14% vs. 22%), and fatigue (18% vs. 20%) were reported with comparable incidence rates in both groups. Notably, elevated liver enzymes were observed in 8% of Agomelatine-treated patients compared to 4% in the Escitalopram group ($p = 0.34$), though this was not statistically significant.Previous studies, such as the one conducted by Lemoine et al. (2012), reported similar findings regarding adverse events. They noted that Agomelatine generally had a lower incidence of sexual dysfunction and weight gain compared to SSRIs but had a slightly higher risk of liver enzyme elevations, which necessitates periodic liver function monitoring.[12] Similarly, Kennedy et al. (2013) found that insomnia and nausea were more common in the Escitalopram group, while Agomelatine had a more favorable sleep profile.[8]The discontinuation rates due to adverse events were 6% in the Agomelatine group and 10% in the Escitalopram group, suggesting a slightly better tolerability for Agomelatine. This trend is consistent with the findings of Taylor et al. (2014), who reported that Agomelatine had lower dropout rates due to adverse effects compared to SSRIs, making it a preferable option for patients who are sensitive to SSRI-related side effects.[11]The results of our study align well with previous research comparing Agomelatine and Escitalopram. Kennedy et al. (2013) found that Agomelatine demonstrated similar antidepressant efficacy to Escitalopram but with a lower incidence of sexual dysfunction.[8] Likewise, Hale et al. (2013) found that both drugs significantly reduced HAM-D and MADRS scores over time, with no major differences in overall efficacy.[9] However, Kumar et al. (2015) reported that Escitalopram had a slightly faster onset of action, particularly in the early weeks of treatment. Despite these minor variations, most studies, including ours, suggest that both Agomelatine and Escitalopram are effective treatments for MDD.[10]The findings of this study suggest that both Agomelatine and Escitalopram are effective and well-tolerated

options for the treatment of Major Depressive Disorder. Agomelatine may offer advantages in terms of sleep regulation and lower sexual dysfunction risk, whereas Escitalopram remains a well-established first-line SSRI. The choice between these medications should consider patient-specific factors, such as the need for improved sleep quality (favoring Agomelatine) or concerns about liver function (favoring Escitalopram).

Limitations of the study: If the sample size is small, the findings may lack generalisability. Short study duration may not capture long-term efficacy and safety outcomes.

CONCLUSION

The comparative study of agomelatine and escitalopram in Major Depressive Disorder highlights that both medications are effective in alleviating depressive symptoms, with differences in their safety and tolerability profiles. Agomelatine, with its unique melatonergic and serotonergic action, offers advantages in circadian rhythm regulation and reduced sexual dysfunction but requires liver function monitoring. Escitalopram, a well-established SSRI, remains a first-line treatment due to its strong efficacy and tolerability, despite the risk of withdrawal symptoms and sexual side effects. The choice between these antidepressants should be individualized based on patient-specific factors, tolerability, and comorbid conditions to optimize treatment outcomes.

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