The Effect of Adding Agomelatine to Escitalopram in the Treatment of Major Depressive Disorder

Azadi H.[1, 2], Rashidpour P.[1, 2], Yassini Ardekani S.M.[1], Nadi Sakhvidi M.[1], Afshang H.[3], Bidaki R.[1, 2]
[1]Department of Psychiatry, Research Center of Addiction and Behavioral Sciences, [2]Diabetes Research Center, and [3]Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[1, 2, 3]Central Administration, Bahonar Sq., Yazd, 8916978477, Iran

Major Depressive Disorder (MDD) is a psychiatric illness that imposes a high cost on the patient and the community. Over the past few decades, a variety of treatments have been used to treat depression. One of the most common treatments for depression is medication. Today, specific serotonin reuptake inhibitors are the first line of treatment for major depression. Another drug that has been considered in the treatment of depression is agomelatine.

Objective *of this study was to evaluate the effect of adding agomelatine to Escitalopram in treatment of major depressive disorder.*

Materials and methods. *This study was a double-blind randomized clinical trial with before and after designs (b and a). In this study, 70 patients with MDD referred to psychiatric clinics affiliated with Yazd University of Medical Sciences were studied. Patients were randomly divided into two groups of 35 patients (agomelatine + Escitalopram and Escitalopram + placebo) and were treated for 12 weeks. Depression Scale was the Hamilton Depression Inventory and was assessed before treatment, 1, 2, and 3 months after treatment. Variables such as gender, age, marital status, level of education, occupation, and duration of illness were also collected. The data were entered into SPSS version 18 software and analyzed using statistical tests.*

Results. *Of the 70 patients studied, 31 (44.3%) were male and 39 (55.7%) were female. There was not significant difference between gender distribution (p=0.810), marital status(p=0.789), job (p=0.651) and educational level (p=0.794). Also, no significant difference was found between the mean variables: age (p=0.563) and duration of depression (p=0.958). There was a statistically significant difference between the mean score of depression 2 months after treatment (p=0.10) and 3 months after treatment (p=0.023) in the two groups. Also the mean depression score after treatment compared to before, was significantly lower in both groups (p=0.000). Also, no significant difference was found between the frequency of drug side effects in the two groups (p=0.970).*

Conclusion. *Adding agomelatine to Escitalopram is more effective than mood-boosting depression as a result of depression or depressive disorder alone.*

Future researchers in the field of MDD treatment could consider investigating the long-term effects and comparative efficacy of combining agomelatine with other antidepressants beyond Escitalopram to further enhance treatment outcomes for patients with MDD.

Keywords: *depression; escitalopram; agomelatine; mental health.*
Contact: *Reza Bidaki;* ***reza_bidaki@yahoo.com***
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Major Depressive Disorder (MDD)[1] is considered a psychiatric illness that imposes a high cost on the patient and the community [1, 2]. According to the symptoms listed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[2], the main symptoms of major depressive disorder include pervasive low mood and a lack of interest and pleasure, which accompany other symptoms such as sleeping problems, appetite, energy levels, concentration, and psychomotor activity. These symptoms must be present for at least two weeks, as must feelings of worthlessness and thoughts of suicide and death [3].

Suicidal thoughts and behaviors are one of the most disturbing outcomes of depression, which is the third leading cause of death in 15–24-year-olds and the fourth leading cause of premature death and disability. According to the National Burden of Disease (NBD) studies in Iran, depression is the third health problem in the country [4–6]. It is estimated that the prevalence of major depressive disorder during life is 5–17%, while the prevalence of major depression in Iran is estimated at 25% [7]. MDD has a multifactorial etiology that results from biological, genetic, psychological, and environmental factors. According to the results of studies in the last decade, MDD is associated with an imbalance of neurotransmitters such as serotonin, dopamine, noradrenaline, and glutamate, disturbances in the hypothalamic-pituitary-adrenal dysregulation in inflammatory pathways, oxidative damage, decreased levels of antioxidants, and mitochondrial disorders. Diet, sleep, and exercise are three such influences that play an important role in the etiology, exacerbation, and treatment of depression [8–10]. A variety of treatments for depression have been used over the past few decades,

[1]Major depressive disorder (MDD), also known simply as depression, is a mental disorder characterized by at least two weeks of pervasive low mood.

[2]The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, is the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders, the taxonomic and diagnostic tool published by the American Psychiatric Association.

and researchers believe that effectiveness, economic costs, side effects, and response rate should be the criteria for treatment selection. Currently, a wide range of antidepressants are available, each with specific therapeutic effects and side effects [11]. According to the World Health Organization (WHO), the first-line option for the treatment of patients with major depressive disorder is dedicated to selective serotonin reuptake inhibitors (SSRIs) [1].

The scientific justification for using the combination of citalopram and agomelatine to treat depression lies in the potential synergistic effects of these two antidepressants. Agomelatine, as indicated in a meta-analysis of placebo-controlled trials, has shown a lower treatment discontinuation rate compared to placebo, suggesting its efficacy in managing major depressive disorder. On the other hand, citalopram, a commonly prescribed antidepressant, is known for its effectiveness in treating depression. By combining these two medications, patients may benefit from the unique mechanisms of action of each drug, potentially enhancing the overall therapeutic response and improving outcomes in individuals with depression. These drugs are among the most widely used in the treatment of major depression and have recently entered the Iranian pharmaceutical market. They seem to have fewer side effects compared to traditional drugs. Nowadays, agomelatine is another drug that has been considered in the treatment of depression.

The search results indicate that in studies evaluating the use of antidepressants, including combination therapies, for the treatment of MDD, the dosage regimen and adjustments are typically based on established guidelines and individual patient response. For example, a meta-analysis of placebo-controlled trials found that agomelatine had a lower treatment discontinuation rate compared to placebo, suggesting its efficacy in managing MDD. Similarly, citalopram, a commonly prescribed antidepressant, is known for its effectiveness in treating depression.

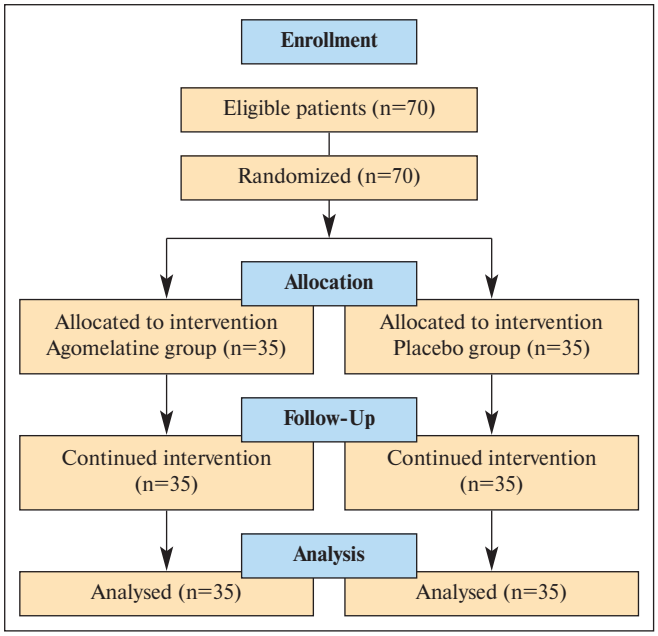
When evaluating the combination of citalopram and agomelatine, the dosage adjustments would likely be made based on factors such as symptom severity, tolerability, and therapeutic response, as is common practice in the treatment of MDD [12]. Given that a limited number of studies have been focused on the effect of agomelatine in the treatment of depression and its comparison with the effects of other drugs, the present study was carried out to investigate the effect of adding agomelatine to Escitalopram in the treatment of major depressive disorder [1]. Selective serotonin reuptake inhibitors (SSRIs) are a widely used type of antidepressant. They're mainly prescribed to treat depression, particularly persistent or severe cases, and are often used in combination with a talking therapy such as cognitive behavioral therapy (CBT).

Material and methods. This study was a randomized clinical trial with a before and after design; the research population included all patients with major depression (based on the diagnosis of a psychiatrist) referred to university clinics in Yazd. Inclusion criteria include: at least 18 years old, no drug use, no chronic disease (diabetes, hypertension, mental disorders, chronic kidney failure), no major dietary changes in recent months, ability to speak Persian, minimum literacy level, high level of consciousness, suitable conditions for completing the questionnaire, no verbal and hearing problems so that they can communicate, no underlying diseases such as diabetes, cardiovascular disease, lung cancer, and willingness to participate in research. Exclusion criteria included withdrawal from the study, drug sensitivity, having comorbidity, and having major psychiatric disorders or systemic medical diseases (see Figure).

Ethical Considerations. This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, and registered with the protocol number "IR.SSU.MEDICINE.REC.1398.305". Participants were provided written informed consent and were included in the study after they were provided information on treatment methods. This trial was also registered in the Iranian Registry of Clinical Trials (IRCT20130311012782N52) and was conducted in accordance with the Declaration of Helsinki.

Intervention. According to the method used in this study, patients who were diagnosed with major depression by a psychiatrist based on DSM-5 were included in the study after applying the inclusion and exclusion criteria. Next, patients were divided into two groups of 35 using the random allocation method. The randomization method was using a random number table, and patients were divided into one of two intervention groups (agomelatine + Escitalopram) or a control (Escitalopram + placebo).

In the first group, 25–50 mg of imported oral agomelatine from Abidi Pharmaceutical Company were administered as a single daily dose, and 10–20 mg of oral Escitalopram was made by Abidi Pharmaceutical Company as a single daily dose for 12 weeks. In the second group, 10–20 mg of oral Escitalopram were administered as a single daily dose with a placebo prepared similar to agomelatine and administered at the same dose and duration. All patients were called in one month, two months, and three months after treatment, and the Hamilton Depression Rating Scale (HDRS) was completed for them. Patients were also evaluated for the presence or absence of drug side effects during treatment. Finally, the data obtained from the two groups were evaluated and compared.



Consort Flow Diagram

Outcomes. A two-part questionnaire including demographic information and the Hamilton Depression Rating Scale (HDRS) was used as a data collection tool. The first part of the questionnaire was demographic, which included personal characteristics including gender, age, marital status, level of education, occupation, and duration of illness.

The second part was the Hamilton Depression Inventory [1], which was completed by a psychiatric assistant in the clinic before and after the intervention (1 month, 2 months, and 3 months after the start of treatment). The Hamilton Depression Rating Scale (HAM-D)[3] was developed by Hamilton (1960). The 9 items are made up of a 5-item scale (graded from zero to 4) and are used to measure the severity of depression in depressed people.

A score of zero indicates a lack of depressive symptoms; a score of 1 indicates doubt about the presence of symptoms; a score of two indicates a mild symptom; a score of three indicates moderate symptoms; and a score of 4 indicates severe symptoms. The remaining 8 items are scored on a scale. There are three options from zero to two, where a score of zero indicates the absence of symptoms, a score of 1 indicates doubt about the symptoms, and a score of 2 indicates the obvious presence of symptoms. Scores between 0 and 6 indicate normal people; scores 7 to 17 indicate mild depression; scores 18 to 24 indicate moderate depression; and scores above 24 indicate severe depression. The reliability and validity of this questionnaire were 0.85 and 0.89, respectively [13].

Sampling and Blinding. The convenience sampling method was used in this study, which was done in an easy way, and patients were included in the study in the order of time to visit the clinic if the admission requirements were met. The sample size required for the study was determined using the sample size estimation formula to compare the means and taking into account the 95% confidence level ($Z1-a / 2 = 1.96$), 80% test power ($Z1-b = 0.84$), depression score standard deviation, which was estimated to be 17.1, and the minimum significant difference between the intervention and control groups, which was considered to be 0.8, which was estimated to be 33 patients in each group. Was increased in each group [13]. The number of patients was increased to 35 in each group for more assurance [13]. According to the randomization method, the researcher first completed the information related to the questionnaire, and the questionnaire wrote on the completed questionnaire a number between 1 and 70. Then the questionnaires were given to the statistical consultant, and he divided the patients into two groups of 35 people based on the numbers written in the questionnaire and using a table of random numbers.

According to the blinding method, patients were unaware of the type of drug received (agomelatine or placebo), and an agomelatine or placebo drug with similar shape and packaging was prepared and provided to patients. Also, the drug is provided to the patients by the executor of the plan, but another psychiatrist who is not in the study collects data and examines the patients.

Statistical Analysis. All registered data were analyzed using SPSS software version 20 for Windows (SPSS, Chicago, IL). For descriptive statistics, the mean ± SD index was used for quantitative variables with a normal distribution. The chi-square test and T-test were used for the comparison of data between the two groups. A paired T-test was used to compare the mean of quantitative data before and after treatment. P values of less than 0.05 were considered significant for all analyses.

Results. Out of 70 patients, 31 (44.3%) were male and 39 (55.7%) were female. The mean age of the patients was 34.30±11.24 years with a minimum age of 18 and a maximum age of 59 years, and the mean duration of depression was 10.57±4.53 months with a minimum time of 3 and a maximum time of 24 months.

The results of the study on the comparison of demographic characteristics in the two groups are shown in Table 1. According to the results of the table, no statistically significant difference was found between the mean age and duration of depression in the two groups. Also, there was no statistically significant difference between the frequency distribution of gender, occupation, marital status, and level of education in the two groups.

The results of the study on the frequency distribution of drug side effects in the two groups are shown in Table 2. Its analysis using the Chi-Square test showed that there is no statistically significant difference between the frequency distribution of drug side effects in the two groups.

The results of the study on the mean depression score in the pre-treatment, one-month, two-month, and three-month groups after treatment are shown in Table 3. Analysis of Table 3 using a T-test showed that the mean depression score at two months and three months after treatment in the agomelatine + Escitalopram group was significantly lower than the Escitalopram group. Also, according to the results of the paired T-test, it was found that the mean depression score three

Table 1. *The comparison of demographic characteristics in the two groups*

Variables	Agomelatine + Escitalopram group, n (%) / mean ± SD	Escitalopram + placebo group, n (%) / mean ± SD	p-value
Age, year	35.08±11.6	35.51±10.9	0.563*
Duration of depression, months	10.54±4.62	10.60±4.51	0.958*
Gender:			
male	15 (42.9)	16 (45.7)	0.810**
female	20 (57.1)	19 (54.3)	
Job:			
freelance	9 (25.7)	10 (28.6)	
employee	15 (42.9)	10 (28.6)	0.651**
housewife	11 (31.4)	19 (42.9)	
Marital status:			
single	8 (22.9)	11 (31.4)	0.789**
married	27 (77.1)	24 (68.6)	
Educational level			
illiterate	1 (2.8)	3 (8.6)	
elementary-cycle	9 (25.8)	7 (20)	0.794**
diploma	14 (40)	15 (42.9)	
bachelor's degree and higher	11 (31.4)	10 (28.6)	

* – T-test; ** – Chi-Square Test.

[3]The HDRS (also known as the Ham-D) is the most widely used clinician-administered depression assessment scale.

months after treatment compared to before treatment in both groups decreased significantly.

Discussion. Escitalopram is considered to be one of the selective serotonin reuptake inhibitors commonly used today in the treatment of depression. Azorin et al., during a study in Germany, reviewed three clinical trials (systematic reviews) of 506 patients in total and found that Escitalopram was more effective than Escitalopram in treating major depression [14]. Also, Li concluded in a study that the six-week treatment period with a dose of 20–40 mg of Escitalopram has the same effect and tolerability compared to a dose of 10–20 mg of it [15]. A study in China concluded that administration of Escitalopram at a dose of 10–20 mg per day is as effective and safe as Escitalopram at 20–40 mg daily in the short-term treatment of patients with depression [16]. Favre in another study confirmed the advantage of Escitalopram over other antidepressants for both acute and long-term treatment of depression, especially in patients with severe disease [17]. Nowadays, agomelatine is another drug that has been considered in the treatment of depression. In a study on animals in Canada, Barden demonstrated the drug's effect on improving depression [18]. Domotor, during a study in Hungary on three treatment groups that were treated for 12 weeks, concluded that in the first group (treated with an inaccurate dose of agomelatine), after this period, 43.7% responded to treatment, and 12.5% (two patients) have entered the recovery phase. In the second group (treated with the exact dose of agomelatonin at a dose of 25 to 50 mg daily), the response rate was 23.8% and the improvement rate was 47.6%, which showed a statistically significant difference between the improvement rates in the two groups with P = 0.034 (specific dose medicine improves). Also, in the third group (treated with the exact dose of agomelatine and 10 to 20 mg daily of Escitalopram), no significant difference was observed compared to the second group.

According to the results of this study, the exact dose of agomelatine has the same effectiveness as Escitalopram [19]. This was consistent with the results of our study on the effectiveness of agomelatine + Escitalopram therapy in relieving depression, although in this study the effect of adding Escitalopram to agomelatine alone was not studied (unlike our study, which studied the effect of adding agomelatine to Escitalopram alone), and this may be the reason for the lack of statistically significant differences between the two groups.

Table 2. *Frequency distribution of drug side effects in the two groups*

Variables	Agomelatine + Escitalopram group, n (%)	Escitalopram + placebo group, n (%)	p-value
Nausea / vomiting	3 (8.6)	3 (8.6)	
Drowsiness	2 (5.7)	2 (5.7)	
Headache / dizziness	3 (8.9)	2 (5.7)	0.970
Other*	1 (2.9)	2 (5.7)	
No side effects	26 (74.3)	26 (74.3)	

* – Decreased libido, confusion, decreased appetite.

According to the results of another study in 2013 on two groups (first group agomelatine and second group Escitalopram) who were treated for 24 weeks, the rate of improvement of depressive symptoms at the end of week 12 in both groups was 60.9% and 54.4%, respectively, and at the end of week 24 in the two groups was 69.6% and 63.1%, respectively, which was not statistically significant [20]. The reason for this can be attributed to the difference in the questionnaires in the two studies (our study was the HDRS, and the study was the Oxford Capabilities Questionnaire for Mental Health (OxCAP-MH).

However, the feeling of health in the group treated with agomelatine was significantly higher than the group treated with Escitalopram in the study. Also, the quality of sleep in the agomelatin group was significantly higher. The rate of emotion reduction in the agomelatine group was significantly lower than the Escitalopram group (28% vs. 60%) [20]; the above results are in line with the results of our study. According to the results of another study conducted by Quera on two groups (first group agomelatine and second group Escitalopram) who were treated for 24 weeks using the HDRS, the REM sleep delay in the second group was more significant than the first group. According to the results of this study, the number of sleep cycles in the first group was maintained during treatment, but the number of sleep cycles decreased in the second group each time (every two weeks), and this decrease was statistically significant. Also, the rate of daily drowsiness in the first group was significantly lower than that in the second group [21]. But similar studies have been carried out on comparing the effect of agomelatine with other selective serotonin reuptake inhibitors. Kasper conducted a study in Australia on two groups of patients who were treated for 12 weeks (the first group was treated with a daily dose of 20–25 mg of agomelatine, and the second group was treated with SSRI and SNRI drugs including venlafaxine, sertraline, fluoxetine, paroxetine, and Escitalopram) using the Hamilton questionnaire and concluded that the mean score reduction of the Hamilton questionnaire at the end of the eighth week was higher in the first group than in the second

Table 3. *Mean score of depression at specified times in the two groups*

Time	Agomelatine + Escitalopram group, mean ± SD	Escitalopram + placebo group, mean ± SD	p-value
Before treatment	17.08±1.42	17.20±1.69	0.761*
One months after treatment	15.11±1.47	15.42±1.57	0.392*
Two months after treatment	9.57±2.27	11.25±3.00	0.010*
Three months after treatment	7.91±1.54	8.77±1.53	0.023*
Difference mean before treatment & three months after treatment	9.17±0.4	8.43±0.16	
P-value	<0.0001**	<0.0001**	

* – T-test; ** – Paired T-test.

group. Also, the response rate to treatment in the first group was significantly higher than the second group [22], which was consistent with the results of this study on the greater effectiveness of agomelatine than Escitalopram. Hale, in another study on two groups (first group agomelatine and second group fluoxetine) who were treated for 8 weeks using the Hamilton questionnaire, concluded that the mean score reduction of the Hamilton questionnaire at the end of the eighth week in the agomelatine group compared to the fluoxetine group was higher. Also, the response rate to treatment in the first group was 71.7% and in the second group was 63.8%, which was not statistically significant. Finally, according to the results of this study, agomelatine has a greater antidepressant effect than fluoxetine [23].

The limitations of the study discussed in the manuscript include:

1. Lack of Comparison with Other Antidepressants: The study primarily focused on comparing the effectiveness of agomelatine and Escitalopram, without directly comparing the combination therapy of agomelatine and Escitalopram with other common antidepressants. This limitation restricts the broader understanding of the comparative efficacy of combination therapies involving agomelatine.
2. Short Treatment Duration: The study's duration of treatment may have been relatively short, potentially limiting the ability to observe long-term effects and differences between the treatment groups over an extended period. Longer-term studies could provide more comprehensive insights into the sustained effectiveness and tolerability of the treatments.
3. Small Sample Size: The study may have had a limited sample size, which could impact the generalizability of the findings. A larger and more diverse sample could enhance the study's reliability and applicability to a broader population of patients with MDD.

Conclusion. According to the results of the study, it can be said that both drug regimens have been effective in improving depression in patients, but the addition of agomelatine to Escitalopram is more effective in relieving depression in patients with major depressive disorder than taking Escitalopram alone.

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