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Comparing the effect of agomelatine and sertraline in treating patients with major depression disorder

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Abstract

Objectives: This study compared the effect of agomelatine and sertraline in treating patients with major depressive disorder (MDD).
Methods: This single-blinded clinical trial was conducted on 52 patients aged 18–65 years with major depression (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) in Kashan in 2020. The Hamilton Rating Scale was randomly assigned agomelatine (25–50 mg/day) or sertraline (50–200 mg/day) for 8 weeks. The main efficacy outcome was considered a mean change of HAM-D score from the baseline to the end of therapy.
Results: The drugs under study effectively reduced depressive symptoms at all time points. As a frequent analysis showed, changes in Hamilton score were found to be significant in both the groups over time ($F = 45.48$, $P < 0.001$). However, due to the differences between the two groups in terms of age and sex, the data were re-analyzed using a linear regression analysis with a random effect model approach. After removing the effect of age and sex as two confounding variables, we observed no significant differences between the two groups.
Conclusion: Agomelatine is more effective than sertraline in treating MDD.

Keywords: Agomelatine, Sertraline, Depression, Hamilton scale.

Introduction

According to the World Health Organization (WHO), depression has been the fourth leading cause of illness in the last decade. It is expected to become the second deadliest disease after cardiovascular by the end of 2020, and its treatment cost is unaffordable for most patients.[1] Major depressive disorder (MDD) is a debilitating condition, and has high prevalence and multisymptomatic nature, making it a leading contributor to global disability. To better understand this psychiatric disease, various pathophysiological mechanisms have been proposed, including changes in monoaminergic neurotransmission, imbalance of excitatory and inhibitory signaling in the brain, hyperactivity of the hypothalamic–pituitary–adrenal axis, and abnormalities in normal neurogenesis.[2]

Major depression is associated with disruption of circadian rhythm, behavior, and mental disorders. The human pineal gland is part of the diencephalon and regulates circadian rhythms and sleep through neurohormone melatonin. Melatonin secretion in the pineal gland is regulated by an internal circadian system located in the suprachiasmatic nucleus of the hypothalamus and is suppressed by light. Therefore, it has been suggested that melatonin level measurements can be used to diagnose depression.[3]

Sertraline, a selective serotonin reuptake inhibitor (SSRI), is commonly prescribed to treat several psychiatric disorders such as major depressive disorder.[4]

The currently available antidepressants can be classified into 13 different distinct classes based on their unique pharmacological mechanisms of action.[5]

Agomelatine in November 2008, it received approval from the European Medicines Agency in Europe for treatment of major depression in adults. It is a nonselective

(MT1/MT2) melatonin receptor agonist + serotonergic 5-HT2c antagonist. It is the first reported melatonergic drug having anxiolytic and antidepressant effects. In major depression, it is used with a daily dose of 25 mg. In seasonal affective disorder, it can be effective in very small doses (0.225–0.3 mg/day), without affecting sleep. The half-life of agomelatine is 1–2 h. Inhibition of 5HT2c is held responsible for its direct antidepressant effect. The advantage of agomelatine is not its better antidepressant effect but its improving effect on sleep together with its antidepressant effects. Indeed, conventional antidepressants often trigger sleep disorders. Agomelatine is metabolized basically by CYP1A1, CYP1A2, and CYP2C9.[6] Because of its antidepressant properties and effects in regulating circadian rhythms, agomelatine would help improve sleep quality and at the same time improve depressive symptoms.[3]

None of the melatonin receptor agonists exhibit a negative effect on the heart, renal dysfunction, and the respiratory system. In terms of side effects on the central nervous system, however, they are comparable to benzodiazepines and other hypnotics. Unlike benzodiazepines, none of the cognitive impairment, withdrawal syndromes, and rebound insomnia was reported in association with melatonin agonists.

Agomelatine does not have anticholinergic and antihistaminergic properties. One of its side effects is the risk of hepatotoxicity, which is recommended to measure aminotransferase levels before starting treatment and after 3, 6, 12, 24 weeks and after increasing the dose.[7]

Also, this medication is least likely to impair sexual functioning. therefore, when the goal is to treat depression and sexual dysfunction, can use agomelatine.[8]

Objectives

Considering that agomelatine is a potent agonist at melatonin receptors and an antagonist at serotonin-2C (5-HT2C) receptors and the side effects of sertraline, we compare these drugs in treatment of MDD patients.

Methods

This single-blind clinical trial was conducted through a clinical trial framework among depressed patients who were referred to a psychiatric clinic and underwent outpatient basis treatment in medical centers under the auspices of Kashan University of Medical Sciences in 2020. In this study, the inclusion criteria included age: 18–65, major depressed patients based on the Hamilton Scale and clinical interview based on the criteria on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and no liver disease or liver impairment test. The exclusion criteria included pregnancy and lactation, lifetime history of bipolar disorder and other psychiatric disorders, other antidepressant users, and patients with suicidal ideation.

At first, the clinical research purpose and approach were explained to each depressive patient. After obtaining their written consent, we asked patients to fill in the Hamilton questionnaire and a questionnaire, demographic information, and medical history. Finally, 52 participants were found eligible for the study based on the initial interview, the questionnaire, Hamilton diagnostic criteria, and laboratory results. Patients were assigned into two groups in a 1:1 ratio to sertraline and agomelatine groups, via a permuted block randomization method. The target doses were 50–200 mg/day for sertraline and 25–50 mg/day for agomelatine for the 8 weeks of treatment. Patients were monitored every 2 weeks after the 1st month of treatment, and the Hamilton criterion was recalculated.

The intended effect was to reduce the total HAM-D score from the beginning to the end of treatment. The HAM-D24 was used to assess the severity of depressive symptoms. Severe depression was marked by scores ≥35. The scores of mild or moderate depression were ≥20 but <35. Any patients with scores ≤7 were considered to have no depressive symptoms.[8] Laboratory tests were performed at the beginning and end of the study. Side effects of treatment were recorded throughout the study.

We should note that 8 participants left the study, 5 patients from the intervention group and 3 ones from the control group, which did not affect the results of this study [Figure1].

The Hamilton Depression Rating Scale is the most commonly used instrument for assessing symptoms of depression. The instrument is designed to be administered by clinicians after a structured or unstructured interview of the patient to determine their symptoms. This scale has 21 questions: 17 questions about depressive symptoms and 4 questions about other factors and disorders that may be associated with depression. Some of the questions of this scale are scored between 0 and 2 and some between 0 and 4. A total score is calculated by summing the individual scores from each question. The validity of Persian version has been reported by Gharaei from 0.85 to 0.89 in 2000.[9]

Statistical analysis

Statistical analyses were run using MS Excel 2007 and SPSS 16. Quantitative variables were shown in terms of mean±standard deviation or median with a range. We used percentages to report qualitative variables. An independent samples *t*-test was used to compare the

groups, and the Chi-square test was used to evaluate the qualitative variables. $P < 0.05$ was considered statistically significant. The mean Hamilton score was analyzed by the one-way repeated measures ANOVA method. Box and Mauchly's tests were used to assess the data sphericity and variance equality of the data prior to analysis. Based on Mauchly's test, the Greenhouse–Geisser correction coefficient was used.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. This study has been registered in Iranian Registry of Clinical Trials with IRCT registration number 2020047046977N1 and Ethic Committee reference number IR.KAUMS.MEDNT.REC.1398.139.

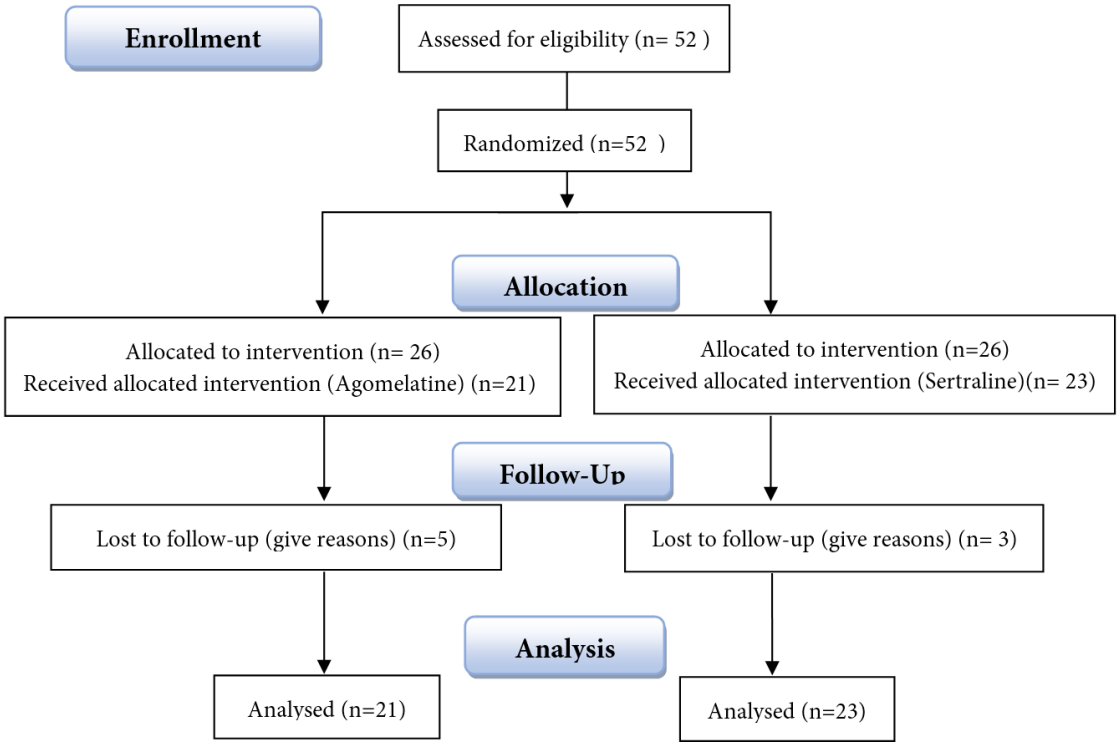

Figure 1. Consort Flowchart

Results

The results of descriptive analysis [Table 1] showed that the mean value of participants' age in the intervention group was 51.5 (8.3) and in the control group was 40.58. In the control group (sertraline), 1 male (6.7%) and 25 females (67.6%) and, in the intervention group (agomelatine), 14 males (93.3%) and 12 females (32.4%) participated in this study. The total number of participants in the study was 37 females and 15 males. There was a significant difference between the two groups in terms of age and gender ($P < 0.05$).

The results of repeated measures analysis of variance indicated significant changes in Hamilton score in both the groups over time [Tables 2] ($F=45.48$, $P<0.001$). In other words, both drugs had a significant effect on reducing the depression score. The results of the intergroup comparison showed that there was a clinically meaningful difference between the two groups ($F=4.45$, $P=0.04$), which indicated a higher rate of score reduction in the sertraline-treated group [Figure 1]. However, due to the remarkable differences between the two groups in terms of gender composition and age, the data were re-analyzed by a linear regression method and a random effect model [Table 3] after eliminating the effect of age and gender as two confounding variables, although no significant difference was observed between the two groups.

Based on the results obtained from the model, no significant difference was observed between the two groups in terms of depression scores. Therefore, it is concluded that the therapeutic effect of agomelatine is similar to that of sertraline.

The data in Table 4 show drug side effects. In the group treated with agomelatine in the 2nd week, headache, anxiety, dizziness, insomnia, insomnia, and irritability were observed. Anxiety, fatigue, and irritability side effects

lasted until the 4th week, but in the continuation of treatment, these complications were not seen. There was no evidence of liver failure and sexual conflicts during the study.

In the sertraline-treated group, symptoms of loss of appetite, hypersomnia, dizziness, anxiety, palpitations, and sexual dysfunction were observed. The side effect of sexual dysfunction lasted throughout the study, which was associated with treatment dissatisfaction. Due to heart palpitations and unbearable anxiety, one patient left the study.

Table 1. demographic and clinical characteristics of patients

Characteristics		**Study group**		**P-value**
		Sertraline (N=26)	**Agomelatine** (N=26)	
Age (years) Mean ±SD		40.5 (13.1)	51.54(8.3)	0.001*
Marital status	Single (%)	4(80.0)	1(20.0)	0.438
	Married (%)	20(46.5)	23(53.5)	
	divorced/widow (%)	2(66.7)	1(33.3)	
Sex	Males (%)	1(6.7)	14(93.3)	0.000*
	Females (%)	25(67.6)	12(32.4)	
Job	Housewife (%)	21(65.6)	11(34)	0.055
	Unemployed (%)	1(25)	3(75)	
	Retired (%)	1(20)	4(80)	
	Worker (%)	0(0)	2(100)	
	Others (%)	3(33.3)	6(66.7)	
Education	Primary education (%)	4(57.1)	3(42.9)	0.423
	intermediate Education (%)	8(40.0)	12(60.0)	
	Diploma (%)	2(28.6)	5(71.4)	
	Bachelor (%)	8(66.7)	4(33.3)	
	High education and higher	4(66.7)	2(33.3)	

Table 2. Changes in Hamilton scores in weeks 0 to 8 based on demographic variables

characteristics		**Agomelatine**					**Sertraline**				
		Week 0	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**
Sex	Men	26.7 (6.8)	21.1 (6.1)	17.7 (6.5)	15.2 (8.0)	14.1 (8.8)	32.0 (-)	17.0 (-)	18.0 (-)	9.0 (-)	7.0 (-)
	Female	21.5 (7.2)	17.2 (9.2)	13.4 (8.1)	11.9 (8.7)	10.4 (7.9)	22.7 (6.5)	15.8 (6.2)	11.8 (7.1)	10.1 (6.7)	8.4 (7.3)
Job	Housewife	20.6 (6.9)	16.2 (8.9)	13.0 (8.5)	12.0 (9.1)	10.1 (8.3)	23.3 (6.1)	17.1 (5.6)	13.0 (6.9)	11.3 (6.7)	9.4 (7.5)
	Unemployed	31.3 (7.6)	25.0 (7.9)	21.3 (4.7)	17.3 (9.4)	13.0 (11.2)	14.0 (-)	5.0 (-)	6.0 (-)	4.0 (-)	2.0 (-)
	Retired	27.0 (4.9)	20.2 (2.5)	19.0 (5.0)	16.7 (6.0)	13.4 (4.0)	20.0 (-)	16.0 (-)	12.0(-)	6.0 (-)	6.0 (-)
	Worker	26.5 (6.3)	18.5 (2.1)	12.5 (2.1)	16.0 (9.8)	16.0 (9.8)	0	0	0	0	0
	Others	25.1 (8.0)	21.8 (8.1)	16.6 (8.1)	12.0 (8.8)	14.5 (11.0)	25.3 (11.5)	11.0 (6.0)	7.3 (9.2)	4.6 (3.7)	3.6 (2.8)
Education	Elementary School	22.7 (6.3)	18.1 (7.6)	14.3 (7.6)	11.6 (7.6)	11.3 (8.3)	21.5 (6.2)	15.7 (6.0)	11.7 (6.8)	9.5 (6.3)	7.3 (6.5)
	Diploma	26.8 (8.4)	21.0 (8.6)	19.8 (8.5)	18.2 (10.5)	13.9 (11.1)	29.5 (7.7)	22.5 (2.1)	15.5 (3.5)	16.0 (1.4)	13.5 (9.1)
	College education	26.3 (9.2)	21.0 (8.5)	15.8 (6.2)	15.1 (7.9)	14.0 (7.7)	23.5 (7.3)	15.0 (6.3)	11.8 (7.9)	9.6 (7.3)	8.5 (7.7)

Table 3. Results of linear regression analysis with random effect model

characteristics	Coef	std. Err.	Z	p>|z|	95% Conf.	Interval
Femail	-3.87	2.38	-1.63	0.10	-8.54	0.79
Age	0.08	0.08	0.98	0.32	-0.08	0.24
Agomelatine	0.38	2.33	0.16	0.87	-4.19	4.95
Cons	14.32	4.31	3.32	0.00	5.87	22.77
Sigma _ u	5.81					
Sigma _ e	6.46					
rho	0.44 (fraction of variance due to u_ i)					

Table 4. Frequency of side effects in both groups of Agomelatine and Sertraline

Adverse event	Agomelatine (n=26) N (%)	Sertraline (n=26) N (%)
Sexual dysfunction	0	1(3.8)
Headache	1(3.8)	0
Tremor	0	1(3.8)
Sweeting	0	1(3.8)
Anxiety	2(7.7)	2(7.7)
Liver dysfunction	0	0
Dizziness	1(3.8)	1(3.8)
Sleep disturbance	2(7.7)	2(7.7)
Gastrointestinal disorders*	0	3(11.8)
Fatigue	4(15.5)	1(3.8)
Palpitation	0	1(3.8)
Irritability	1(1.38)	0
Without adverse events	15(57.7)	13(50.0)

* Gastrointestinal disorders include nausea, diarrhea, constipation, dry mouth, loss of appetite.

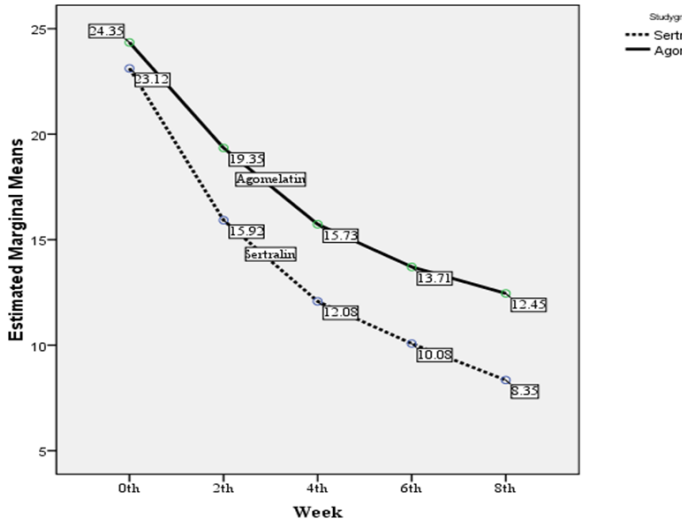

Figure 1. Changes in a mean difference of HAMD-24 score in both treatment groups over time

Discussion

In this study, we examined the effects of two medicines, sertraline and agomelatine on major depression. It was found that 25–50 mg/day of agomelatine resulted in a similar response to 25–200 mg/day of sertraline. Mehta study, about the efficiency of agomelatine and sertraline in major depression, showed similar efficiency at the end of the 8th in both the groups.[10] Lam showed the rapid response of agomelatine in weeks 1 and 2 in major depression treatment.[11] Kennedy observed obvious recovery signs in weeks 1 and 2 compared to venlafaxine and placebo. He also concluded that the effect of agomelatine is persistent for a longer period.[12] Akpinar also compared the efficacy and tolerability of agomelatine versus sertraline during 12 weeks. In this study, complete remission was 33.3% in the agomelatine group and 46.7% in the sertraline group.[13] Thalas also pointed out the positive effect of agomelatine on improving sleep quality and its initial rapid response and the absence of sexual side effects in comparison with sertraline.[14] Due to the fact that one of the side effects of agomelatine is liver disorders, in the present study, after testing patients at the beginning and during treatment, there was no evidence of liver damage. However, in Freiesleben 's study that compared the extent of liver damage in Agomelatine and four other antidepressant medicines (sertraline, paroxetine, escitalopram, and fluoxetine) and placebo, the highest rate of liver damage related to agomelatine (4.6%) was usually reversible and this complication was observed as a severe liver disorder in some rare samples. They have also emphasized preciously evaluating liver function in patients during the treatment period.[15]

Howland found that agomelatine had no clear advantage rather than other antidepressant medicines. Due to its unique pharmacological effect and toleration profile, agomelatine should also only be concerned as an alternative medicine for those patients that would not respond to other antidepressant medicines.[16]

In the early weeks of the present study, there were no signs of rapid recovery in patients taking agomelatine compared to sertraline. Nonetheless, in both the groups, an effective recovery process was observed in the long run (end of week 8). However, in some studies, initial rapid recovery (weeks 2 and 4) was observed with regard to agomelatine. As an example, Lam examined the effect of a new antidepressant medicine, agomelatine, and found a rapid response of Agomelatine in weeks 1 and 2 in major depression treatment, which was inconsistent with later long-term recovery response. By contrast, no clinical recovery was felt by patients taking old antidepressant medicines until weeks 4–6.[12]

In this study, side effects such as drowsiness, insomnia, dizziness, fatigue, stress, and irritability were observed temporarily and partially early in treatment and resolved after some time (after the 4th week). Sweating, abdominal pain, nausea, diarrhea, vomiting, constipation, back pain, fatigue, headache, dizziness, drowsiness, and deficiency. Sleep, fatigue, and stress.[17]

In many types of research, agomelatine has shown unique features, compared to other antidepressant medicines including sertraline.[13,17]

Plesnicar found that in mid-term and long-term periods, agomelatine had good effectiveness on major depression. Its side effect profile was the same as placebo. This is important in adherence to treatment and good compliance.[19] Kandy showed that there was double effectiveness in the agomelatine group in depression symptoms and social performance improvement compared to the placebo group.[20] Kennedy et al mentioned in their research the antidepressant effects of agomelatine in the short-term (6–8 weeks) and long-term (6 months) and also relapse prevention (more than 10 months). These researchers also expressed that this medicine has improved sleep patterns early in treatment. They have found no evidence of sexual disorder, weight gain, or symptoms of antidepressant medicine quit, and they have suggested agomelatine as a new treatment approach for major depression treatment.[21] Peter coomassie found that agomelatine in compound with other antidepressants (SNRI and SSRI) was effective and tolerable in major depression treatment. One of the main symptoms of depression is sleep disturbance. Sedative hypnotics are applied to improve sleep disturbance. However, some research showed that patients treated with agomelatine did not need extra sleeping pills.[22] As an example, Olieh reached a better effect of agomelatine in comparison to placebo for improvement of sleep disorder and depression mood.[23] Hsing *et al.*'s study and other studies compared agomelatine with other antidepressant medicines in major depression patients, and they concluded that patients who took agomelatine did not need to take sleep tranquilizer pills.[24-26]

According to the research, all effective medicines for major depression treatment have different and various advantages and disadvantages in general. However, it is important to apply medicines with more positive effects and fewer side effects for patients' treatment. Although agomelatine has shown similar effects in major depression patients' recovery, this medicine can lead to better improvement in depression symptoms and better compliance to treatment because of having no sexual complications (which causes dissatisfaction and treatment quit inpatients). Another noteworthy point is about liver disorders caused by taking agomelatine that no cases were observed in this research.

Conclusions

This study confirms that agomelatine, like sertraline, is effective in treating major depression. This medicine can lead to better improvement in depression symptoms and better compliance to treatment because of having no sexual complications. Another noteworthy point is about liver disorders caused by taking agomelatine that no cases were observed in this research. Thus, the probability of this complication should not deprive the patients of the benefits of the medicine.

Acknowledgment

None.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

World Health Organization: WHO;
Major depressive disorder: MDD;
Sertraline, a selective serotonin reuptake inhibitor: SSRI.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. This study has been registered in Iranian Registry of Clinical Trials with IRCT registration number 2020047046977N1 and Ethic Committee reference number IR.KAUMS.MEDNT.REC.1398.139.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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