Research Paper

A comparative study of the clinical efficacy and safety of agomelatine with escitalopram in major depressive disorder patients: A randomized, parallel-group, phase IV study

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Received: 20-12-2014 **Revised: 18-12-2014** **Accepted: 29-07-2015**

ABSTRACT

Objective: To compare the efficacy of agomelatine with escitalopram in the treatment of major depressive disorder (MDD), improve sleep in MDD patients and study the adverse effects of agomelatine. **Materials and Methods:** Randomized, parallel-group, open-label study. The primary efficacy outcome was change from baseline to last post-baseline value in Hamilton depression rating scale and Leeds sleep evaluation questionnaire scale. Both parametric and nonparametric tests were applied for analysis. **Results:** Within-group and between-groups comparison of the mean HAMD17 scores showed statistically significant changes ($P < 0.0001$). Escitalopram showed early onset of response and remission compared to agomelatine at 10th week ($P < 0.0001$) and 14th week ($P < 0.0001$), respectively. In agomelatine, within-group and between-groups change of the mean LSEQ score was statistically significant at subsequent follow-up visits ($P < 0.0001$). **Conclusion:** Escitalopram is superior to agomelatine in efficacy, considering the early response, early remission, and better relief from symptoms of MDD in adults. Agomelatine may be preferred in MDD patients having insomnia as a predominant symptom. Liver function monitoring should be done in patients on long-term agomelatine therapy.

Key words: Agomelatine, antidepressants, escitalopram, insomnia, major depressive disorder

INTRODUCTION

Depression is defined as a common mental disorder that leads to impairment in an individual's ability to take care of his or her everyday responsibilities.[1] Depression would be the leading cause of disability in industrialized countries by 2030[2] and accounts for 4.5% of all human disabilities.[3] Major depressive disorder (MDD) is diagnosed when symptoms last for a minimum period of 2 weeks.[4] The circadian rhythm disruption is involved in the pathophysiology of depression.[5] The incidence of insomnia in depression is up

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.171883

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How to cite this article: Urade CS, Mahakalkar SM, Tiple PG. A comparative study of the clinical efficacy and safety of agomelatine with escitalopram in major depressive disorder patients: A randomized, parallel-group, phase IV study. J Pharmacol Pharmacother 2015;6:198-203.

to 80%. Sleep–wake cycle disturbance is one of the important symptoms of MDD. The most frequently reported sleep disturbances are nocturnal and early morning awakenings.[6] In the last 20 years, new antidepressant classes have been introduced in therapy, i.e. selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs). However, continuous stimulation of SSRI and SNRI receptors leads to adverse effects such as sexual dysfunction, gastrointestinal disturbances, weight gain, and somnolence. These side effects limit the use of SSRIs and SNRIs in the community.[5]

Agomelatine {*N*-[2-(7-methoxynaphthalen-1-yl) ethyl acetamide]} is an antidepressant that was approved in India by the Central Drugs Standard Control Organization (CDSCO) on 10th September 2012 for the treatment of MDD in adults.[7] It has potent melatonin agonist (MT1 and MT2 receptors) with 5- hydroxytryptamine$_{2C}$ (5-HT$_{2c}$) antagonist action.[8] Antidepressant action is due to increased norepinephrine and dopamine levels in the prefrontal cortex by 5-HT$_{2c}$ antagonism and sleep enhancement is by MT1 and MT2 agonism.[9] The antidepressant property of agomelatine is also proved in number of animal models of depression[5] with reported advantages over SSRIs, i.e. absence of sexual dysfunction, weight gain, serotonin syndrome, suicidal tendencies, cardiovascular effects, and discontinuation syndrome.[10] In the Indian population, very few published reports are available regarding the efficacy and safety of agomelatine over SSRIs/SNRIs in depression. Hence, this study was planned with the following objectives: (i) To compare the clinical efficacy of agomelatine with escitalopram in the treatment of MDD; (ii) to compare the efficacy of agomelatine with escitalopram in improving various aspects of sleep in MDD patients; and (iii) to study the adverse drug effects profile of agomelatine.

MATERIALS AND METHODS

A prospective, randomized, active-controlled, parallel-group, comparative, open-label, phase IV study was conducted in a tertiary care hospital. Eligible subjects were of either sex who attended psychiatry outdoor clinic with clinical diagnosis of MDD as per the Diagnostic and Statistical Manual of Mental Disorder, fourth edition, Text revision (DSM-IV-TR) and fulfilled the criterion of Hamilton Depression Rating Score (HAMD-17) ≥22.[11] Other inclusion criteria were: (i) Age between 18 and 65 years with normal liver function and (ii) should be newly diagnosed MDD patient, i.e. patient having first consultation with the psychiatrist for the complaints suggestive of MDD. Exclusion criteria were: (i) Pregnant or nursing women; (ii) patients with high risk of suicidal tendency or previous suicide attempt within 6 months, bipolar disorder, anxiety symptoms such as panic attacks, obsessive–compulsive disorder, post-traumatic stress disorder, drug abuse or dependency, previous depression resistant to antidepressants, and those who had taken treatment with electroconvulsive therapy in the previous 3 months or formal psychotherapy within 1 month; (iii) patients on other antidepressants; and (iv) patients with neurological disorders (dementia, seizures, stroke), obesity with functional impairment, serious or unstable organic disorders (neoplasia, cardiovascular, pulmonary, uncontrolled type 1 or 2 diabetes).[12] This study was approved by the Institutional Ethics Committee and written informed consent was obtained from all subjects or their legally acceptable relative (LAR) as applicable. The trial was registered retrospectively with Clinical Trial Registry India (CTRI/2014/08/004904).

Eligible patients were randomized using computer-generated randomization method with allocation ratio of 1:1 to receive either agomelatine 25 mg/day or escitalopram 10 mg/day once daily for a period of 2 weeks. After 2 weeks of treatment, doses of both drugs were doubled if inadequate improvement of depressive symptoms was observed. The follow-up period was 24 weeks and total duration of study was 18 months. Subjects had to take one tablet (depending on allocation of drug group) daily in the evening around 8 pm.[12] The study medications were bought by the department for study purpose. Both study drug and comparator were from same manufacturer. The manufacturing company had no role in study design, data collection, and analysis, or preparation and publication of manuscript.

The primary efficacy outcome was the change from baseline to the last post-baseline value in Hamilton depression rating scale (HAMD$_{17}$) and Leeds sleep evaluation questionnaire scale (LSEQ). The HAMD$_{17}$, a 17-item scale, was used to check the severity of depression and evaluate the depressive symptoms.[11] The LSEQ comprises 10 points self-rating 100 mm line analog questions concerned with the aspects of sleep and early morning behavior. This visual analog scale consists of 100 mm horizontal line with two extreme states defined at the end of line. The subject responds by placing vertical mark on a line to indicate his present self-evaluation. It contains 10 questions pertaining to four consecutive aspects of sleep: (i) Getting to sleep, (ii) quality of sleep, (iii) awakening from sleep, and iv) behavior following wakefulness.[13] The response to treatment was assessed by ≥50% decrease in HAMD$_{17}$ score and the rate of remitters was defined as those who achieved HAMD$_{17}$ total score ≤7 during treatment. The HAMD$_{17}$ score <6 was defined as "no depression."[12,14]

Study visits

HAMD$_{17}$ score was assessed at weeks 0 and 2, then every 4 weeks up to week 24. LSEQ score was assessed at week 2, then every 4 weeks up to week 24. In the LSE questionnaire,

the patient answers about changes in sleep pattern due to consumption of drug. Hence, it is started from 2 weeks. The safety assessment included the adverse effects reported by the participants and also elicited by the clinician at every visit. Laboratory investigations such as liver function tests [serum glutamic–pyruvic transaminase (SGPT), serum glutamic–oxaloacetic transaminase (SGOT), and serum bilirubin], kidney function tests (blood urea and serum creatinine), and bodyweight were done at baseline, 10th week, and 24th week.

Statistical analysis

Sample size was based on changes in primary outcome variable, i.e. changes in baseline to post-baseline value in $HAMD_{17}$ score. It was estimated by using the two-sided Student's *t*-test for independent samples at 5% type I error. A total of 32 patients per treatment group allowed the detection of a group difference of 2 points with 80% power for a standard deviation of 2.8 points.[11] However, by considering 10% dropout, the study was planned on 35 patients in each treatment group. Sample size was calculated using PS: Power and Sample Size Calculation version 3.1.2, 2014 by William D. Dupont and Walton D. Plummer.

Efficacy analysis was done by intention-to-treat analysis, i.e. patients who had baseline and at least one post-baseline data of $HAMD_{17}$ and LSEQ were included. The last observation carry forward strategy was applied for substituting missing data. For safety analysis, all randomized patients who had received at least one dose of the study medications were considered evaluable. Continuous variables were compared within group by paired *t*-test and between groups by unpaired *t*-test. Non-parametric variables were compared between groups by Mann–Whitney test and within-group comparison was performed by Friedman analysis of variance (ANOVA) followed by *post-hoc* Dunn's multiple comparison test. Categorical data were compared using Chi-square or Fisher's exact test as appropriate. *P* value ≤0.05 was considered statistically significant. GraphPad Prism version 6.00 by Dr. Harvey Motulsky was used for analysis.

RESULTS

The flow chart of the study participants is presented in Figure 1. Out of the 70 randomized subjects, 64 (escitalopram group = 32, agomelatine group = 32) were evaluable as per the intention-to-treat analysis, since 6 subjects were lost to follow-up. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Baseline $HAMD_{17}$ scores were comparable in the two treatment arms ($P = 0.4422$). Within-group analysis showed that decrease in $HAMD_{17}$ scores from baseline to subsequent visits in both arms was statistically significant ($P < 0.0001$). At the end of 24th week, the mean $HAMD_{17}$ scores in escitalopram group significantly decreased compared to agomelatine group ($P < 0.0001$) [Table 2]. The responder is defined as ≥ 50% decrease in $HAMD_{17}$ score from baseline at 24th week. Responder rate was 100% in both groups. However, time of onset of response differed in the two groups. Escitalopram showed early onset of response compared to agomelatine at the end of 10th week ($P < 0.0001$) [Figure 2]. Percentage of remitters (those patients who achieved $HAMD_{17}$ score ≤ 7) in escitalopram group was 78.12% against 62.5% in agomelatine group. Also, escitalopram showed faster remission than agomelatine at the end of 14th week ($P < 0.0001$) [Figure 3].

Baseline (2 weeks) LSEQ total score was comparable between the two groups ($P = 0.1525$). Within-group analysis showed that change in LSEQ score at every visit compared to baseline was statistically significant in both the arms. When compared between the two groups, decrease in the mean LSEQ score was statistically

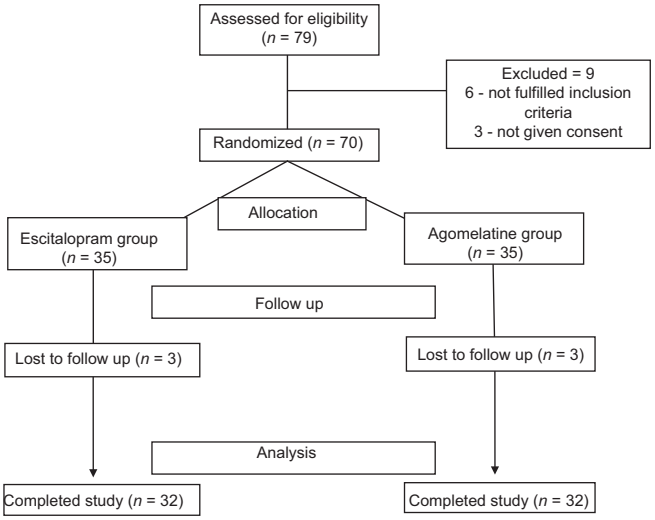

Figure 1: Flow chart of the study participants

Table 1: Baseline demographic and clinical characteristics of MDD patients

Characteristics	Escitalopram group	Agomelatine group	*P* value
Age (years)	38.56 (13.48)	35.69 (11.71)	0.3659[$]
Male:female ratio	43.75:56.25	37.5:62.5	
Weight (kg)	57.50 (7.10)	57.66 (7.97)	0.9342[$]
SGPT (IU/l)	20.97 (4.75)	18.59 (5.27)	0.0630[$]
SGOT (IU/l)	20.56 (5.69)	20.81 (4.86)	0.8503[#]
Serum bilirubin (mg/dl)	0.90 (0.11)	0.90 (0.10)	0.9714[#]
Blood urea (mg/dl)	22.50 (4.00)	21.03 (3.00)	0.1016[$]
Serum creatinine (mg/dl)	0.99 (0.13)	0.96 (0.15)	0.4889[$]
$HAMD_{17}$ scale	27.22 (4.19)	27.94 (4.23)	0.4422[#]
LSEQ scale	95.19 (1.23)	94.66 (1.86)	0.1525[#]

Values are expressed as mean (SD). [$]Unpaired "*t*"-test, [#]Mann–Whitney test applied. MDD=Major depressive disorder, SGPT=Serum glutamic-pyruvic transaminase, SGOT=Serum glutamic–oxaloacetic transaminase, HAMD=Hamilton depression rating score, LSEQ=Leeds sleep evaluation questionnaire scale

significant in agomelatine group compared to escitalopram group at subsequent follow-up visits and at the end of 24th week ($P < 0.0001$) [Table 3].

Safety data analysis revealed that 5 out of 32 patients (15.62%) in the agomelatine group and 6 out of 32 patients (18.75%) in the escitalopram group reported at least one adverse event. However, the difference was not statistically significant. The adverse events reported were headache, drowsiness, anxiety, and insomnia [Table 4]. All adverse events were mild in severity and did not require treatment interruption or study drug withdrawal. No statistically significant weight gain was observed in both groups compared to baseline (agomelatine group: $P = 0.7736$, escitalopram: $P = 0.1609$). Statistically significant increase in liver enzyme (SGPT, SGOT) activities was observed in both groups compared to baseline at the end of 24th week. However, the level of enzymes was increased above the normal range only in agomelatine group [Table 5]. Other parameters such as serum bilirubin, blood urea, and serum creatinine were in normal range in both groups at 24th week.

Table 2: Between-groups comparison of $HAMD_{17}$ scores

Visits	HAMD17 scores (n=32)		P value
	Escitalopram	Agomelatine	
Baseline	27.22±4.19	27.94±4.23	0.4422#
2 weeks	26.19±4.05	26.88±4.01	0.4383#
6 weeks	16.34±4.02	22.00±3.94	<0.0001#
10 weeks	10.63±2.80	16.88±3.49	<0.0001#
14 weeks	6.96±1.97	12.31±3.18	<0.0001#
18 weeks	5.41±1.50	8.22±2.94	<0.0001#
22 weeks	4.72±1.71	6.28±1.99	<0.0001#
24 weeks	4.41±1.79	5.87±1.96	0.0001#
P value	<0.0001$	<0.0001$	

Values expressed as mean±SD. $HAMD_{17}$=Hamilton depression rating scale 17 items. #Mann–Whitney test applied (between-groups comparison). $Friedman test with *post-hoc* Dunn's multiple comparison test applied (within-group comparison). HAMD=Hamilton depression rating score

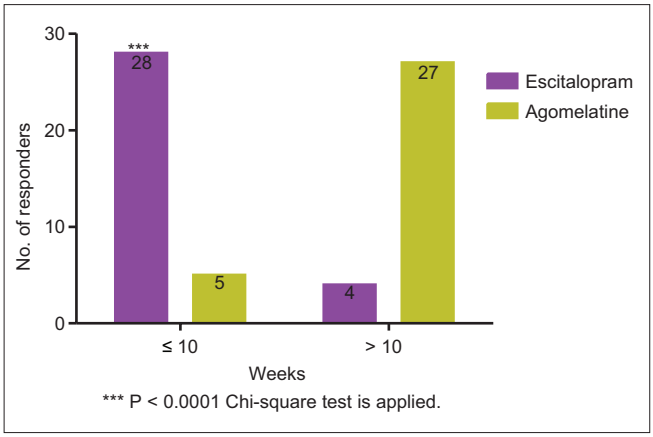

Figure 2: Comparison of time–response relationship between escitalopram and agomelatine groups

DISCUSSION

The study results indicate that both escitalopram and agomelatine were beneficial in reducing depressive symptoms in MDD patients, as the rate of remission was 100% in both groups at the end of 24th week. Twenty-five (78.12%) patients in escitalopram group and 18 (56.25%) patients in agomelatine group fulfilled the criterion of "no depression," i.e. $HAMD_{17}$ score below 6.[14,15] However, mean $HAMD_{17}$ score of escitalopram was less than agomelatine, which signifies that the efficacy of escitalopram was better than that of agomelatine in controlling MDD symptoms at the end of 24th week ($P = 0.001$). This is contradictory to the study findings of Corruble *et al.*[16] and Quera-Salva *et al.*[12] Moreover, escitalopram showed faster onset of response and remission compared to agomelatine. We could not find any relevant study comparing the onset of action between these drugs in terms of response or remission. The probable reason for this difference between the response and remission as effected by the two drugs may be attributed to their respective mechanism of action in relieving depression. Escitalopram causes the antidepressant effect through serotonin transporter (SERT) blocking action and also by functional desensitization of 5-HT1A autoreceptor on chronic administration in dorsal raphe nuclei.[9] Thus, together produces therapeutic effect by increasing the serotonin level in synapse which elevates the mood and causes reversal of MDD. The antidepressant effect of agomelatine is due to inhibition of 5-HT_{2c} receptor that leads to rise in noradrenaline and dopamine levels in the synapse, rather than serotonin.[9] As there is no report available on the kinetics of the two receptor actions (5-HT1A, SERT for escitalopram and 5-HT_{2c} for agomelatine), it may be possible that the serotonergic mechanism used by escitalopram has faster kinetics compared to the noradrenaline and dopamine mechanism utilized by agomelatine for its antidepressant action. However, further studies are required to reveal the truth.

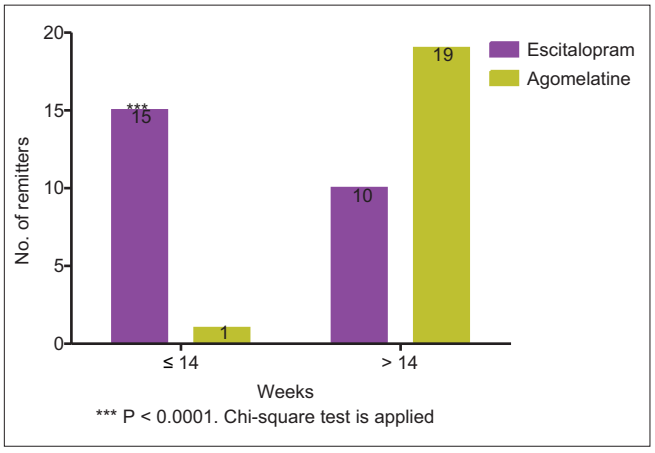

Figure 3: Onset of remission in escitalopram and agomelatine groups

Table 3: Between-groups comparison of LSEQ scores

Visits	LSEQ scores (*n*=32)		*P* value
	Escitalopram	Agomelatine	
Baseline (2 weeks)	95.19±1.23	94.66±1.86	0.1525#
6 weeks	85.97±2.35	51.88±3.34	<0.0001#
10 weeks	73.78±4.22	24.94±3.65	<0.0001#
14 weeks	59.69±5.41	10.03±2.36	<0.0001#
18 weeks	47.88±6.46	5.19±1.61	<0.0001#
22 weeks	38.63±7.95	2.81±2.53	<0.0001#
24 weeks	33.34±10.26	2.31±2.80	<0.0001#
P value	<0.0001$	<0.0001$	

Values expressed as mean±SD. LSEQ=Leeds sleep evaluation questionnaire scale. Lower scores indicate improved sleep. #Mann–Whitney test applied (between-groups comparison). $Friedman test with *post-hoc* Dunn's multiple comparison test applied (within-group comparison)

Table 4: Adverse effects of treatment groups

Adverse effects	Escitalopram (%)	Agomelatine (%)	*P* value
Headache	3 (9.4)	2 (6.2)	1.000
Drowsiness	1 (3.1)	3 (9.4)	0.613
Anxiety	1 (3.1)	0 (0)	1.000
Insomnia	1 (3.1)	0 (0)	1.000

Fisher's exact test was applied to calculate *P* value

Table 5: Within-group comparison of liver enzymes

Groups	Baseline	10 weeks	24 weeks
Alanine transferase (SGPT) (normal range: 0-35 IU/l)			
Escitalopram	20.97 (4.75)	23.25 (4.29)*	24.13 (4.25)**
Agomelatine	18.59 (5.27)	33.06 (4.23)***	39.53 (5.74)***
Aspartate transferase (SGOT) (normal range: 0-35 IU/l)			
Escitalopram	20.56 (5.69)	22.16 (4.97)	23.13 (4.75)**
Agomelatine	20.81 (4.86)	36.25 (4.45)***	40.44 (5.48)***
Serum bilirubin (normal range: 0.3-1.2 mg/dl)			
Escitalopram	0.90 (0.12)	0.98 (0.13)*	1.0 (0.13)***
Agomelatine	0.90 (0.10)	1.04 (0.11)***	1.0 (0.12)***

Values expressed as mean±SD, repeated measures ANOVA with Bonferroni's multiple comparisons *post-hoc* test *$P<0.05$ **$P<0.01$ ***$P<0.001$ compared to baseline

In this study, agomelatine showed better improvement in sleep aspects than escitalopram with respect to their mechanisms. Agomelatine has melatonergic action (MT1 and MT2 receptor agonist).[5,17] These receptors are located in suprachiasmatic nucleus (SCN) which is involved in the regulation of circadian rhythm of the body. As circadian rhythm disruption is involved in the pathophysiology of depression, patients may have delayed sleep, shortened latency to the first episode of rapid eye movement sleep, fragmented sleep, and early wakening.[5,18] Thus, due to melatonergic action, agomelatine helps in restoration of disturbed circadian rhythm and improves the quality of sleep.[6] Escitalopram is less efficacious in improving sleep aspects, which may be due to lack of melatonergic mechanism. This observation is in line with Quera-Salva *et al*.,[12] Martinotti *et al*.,[17] Kasper *et al*.,[19] and Lemoine *et al*.[20]

In our study, clinically significant elevation in SGPT and SGOT values, i.e. above the upper limit of normal range, was observed only in agomelatine group at the end of 24th week. These are in consensus with the report of Hale *et al*.,[11] but not with that of Martinotti *et al*.[17] The values regarding kidney functions and weight were within normal range in both groups at the end of study. However, no study is available which monitored blood urea and serum creatinine level in patients treated with agomelatine. Moreover, in case of weight measurement, three studies (Quera-Salva *et al*.,[12] Hale *et al*.,[11] Lemoine *et al*.[20]) are in agreement with our study results. Headache and drowsiness due to both drugs were well tolerated in the present study. No statistically significant difference was observed between the two drugs in relation to these adverse effects. Anxiety and insomnia were the additional adverse effects reported in escitalopram group.

Strengths of the study

- The present study was a 24-week study. As MDD is long-lasting disease, such long-duration treatment is helpful in relieving the symptoms. The contribution of such a study can be helpful in planning treatment of MDD
- We have calculated and compared the onset of response and remission of agomelatine and escitalopram. Such observations were not done in previous studies.

Limitation of the study

An open-label study and applied last observation carry forward method for analysis.

Future perspectives

In view of the disagreement of our report with other studies about the efficacy of agomelatine compared to escitalopram (SSRI) in response, remission, and improvement of symptoms at the end of 24th week in MDD patients, more comparative clinical trials on these drugs will clarify the exact status of agomelatine in the treatment of MDD.

CONCLUSION

- Escitalopram is superior to agomelatine in efficacy, considering the early response, early remission, and better relief from symptoms of MDD in adults
- Agomelatine may be preferred in MDD patients having insomnia as a predominant symptom
- Liver function monitoring should be done in patients on long-term agomelatine therapy.

Financial support and sponsorship

This study did not receive special funding.

Conflicts of interest

There are no conflicts of interest.

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