AN OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, PROSPECTIVE CLINICAL TRIAL FOR EVALUATION OF EFFICACY AND SAFETY OF AGOMELATINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT

AIM

Agomelatine is one of the newer antidepressant drugs with potent melatonergic properties which tend to resynchronize the circadian rhythm. This study attempts to compare the efficacy of Agomelatine with Fluoxetine in patients with Major Depressive Disorder.

METHODS

This is a prospective, interventional, open-label, randomized, comparative, parallel-group study conducted at a private psychiatry clinic in Central India as a part of multi-centre clinical trial. A total of 23 patients with Major Depressive Disorder (having a total score of >20 in HDRS-17 scale and a score of at least 4 in CGI-S) were screened at our site and out of them 21 patients were randomized to either Agomelatine or fluoxetine (11 on Agomelatine and 10 on fluoxetine treatment). These patients were followed up prospectively on Day 15th, Day 29th, Day 43rd and Day 57th after randomization and HDRS 17 scale along with CGI-S scale were applied at these visits. Tolerability to the study drugs were assessed by evaluation of adverse events reported voluntarily, observed on physical and systemic examination, or found on laboratory investigations during the study period.

RESULTS

It was found that patients from both the treatment groups (Agomelatine and Fluoxetine) showed statistically significant ($p<0.001$) improvement in major depression symptoms in terms of reduction in HDRS-17 score and CGI-S score. Also, in terms of safety, there was no reported serious adverse event with Agomelatine.

CONCLUSION

Agomelatine can be an important effective therapeutic option in the treatment of major depressive disorder. However, considering the small sample size from this center, it is suggested that the data/results presented in this report should be read in conjunction with the data from other centers.

KEYWORDS

Agomelatine, Fluoxetine, Major Depressive Disorder.

HOW TO CITE THIS ARTICLE: Thakre MN, Saoji AM, Mahajan SL. An open-label, randomized, parallel-group, prospective clinical trial for evaluation of efficacy and safety of agomelatine in patients with major depressive disorder. J Evid Based Med Healthc 2015; 2(58), 8914-18. DOI: 10.18410/jebmh/2015/1257

INTRODUCTION: Major depressive disorder is a disabling condition which adversely affects a person's family, work or school life, sleeping and eating habits, and general health. Major depressive disorder is estimated to have a lifetime prevalence of 16.6%, and is associated with significant morbidity and mortality.[1] Although antidepressants constitute first line treatment in the acute and long-term management of Major depressive disorder, the effect of treatment is often suboptimal; at least 30% of depressed patients fail to achieve a satisfactory response (usually defined as a 50% reduction in symptom scores from baseline) to the index antidepressant and fewer than 50% achieve remission (defined as the virtual elimination of symptoms).[2]

The introduction of selective serotonin re-uptake inhibitors (SSRIs) and subsequently serotonin and noradrenaline re-uptake inhibitors (SNRIs) was associated with better tolerability compared with the tricyclic and monoamine oxidase inhibitor antidepressants. This increased tolerability has been associated with improved adherence to treatment. Nevertheless, there is room for further improvement because SSRIs are still associated with a number of adverse events including gastrointestinal disturbances, weight gain, day-time sleepiness, sexual dysfunction and discontinuation effects.[3] Additionally, lower rates of response or remission with SSRIs compared with SNRIs—venlafaxine and milnacipran[4] and to the tricyclic antidepressants (TCAs)[5] have been reported.

Submission 03-12-2015, Peer Review 05-12-2015,
Acceptance 17-12-2015, Published 21-12-2015.
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DOI: 10.18410/jebmh/2015/1257

Agomelatine is the first melatonergic antidepressant acting as a potent MT1/MT2 receptor agonist with 5-HT2C receptor antagonist properties.[6] Both properties contribute to the antidepressant activity of agomelatine.[7] Agomelatine has been shown to resynchronize altered circadian rhythms both in an animal model of depression[7] and in healthy young men.[8] Its efficacy in major depression has been demonstrated both in placebo-controlled trials[9,10] and in direct head-to-head comparisons.[11,12] Agomelatine has been shown to induce a rapid beneficial effect on subjective sleep and daytime functioning already at the first week after treatment initiation versus venlafaxine and also to improve objective sleep disturbances in depressed patients.[13]

The current study was designed to compare the efficacy of Agomelatine versus fluoxetine while with additional attention to the insomnia component in patients with Major depressive disorder.

METHODOLOGY:

Study Design: The present study was a prospective, interventional, open-label, randomized, comparative, parallel-group study conducted at a private psychiatry clinic in Central India as a part of multi-centre clinical trial.

Patient Population: Enrolled study subjects were adult patients (age 18-65 years) of either sex, diagnosed to be suffering from major depressive disorder, with a total score of >20 in HDRS-17 scale (Hamilton Depression Rating Scale) and a score of at least 4 in CGI-S (Clinical Global Impressions Scale). Female subjects of child-bearing potential were required to have a negative serum pregnancy test at screening and to have consented for using a valid and effective form of contraception throughout the study. Written informed consent was obtained prior to any screening procedure from all study subjects and/or their legally-acceptable representatives.

A patient was excluded from the trial if any of the following was present:

1. Patients recording ≥20 % reduction in HDRS-17 score at the baseline (at the time of study treatment allocation) as against the same recorded at the time of screening.
2. Those with psychotic symptoms at presentation were excluded (Psychotic depression).
3. History of bipolar disorder (I or II), schizophrenia, schizoaffective disorder, eating disorder, or obsessive compulsive disorder.
4. Patients not responding to the administration of an appropriate dose of two different earlier antidepressant treatments (including fluoxetine) for at least 4 weeks each, for the current and earlier episodes.
5. History of not responding to fluoxetine monotherapy for at least 4 weeks.
6. Pregnant woman and lactating mother.
7. Substance or alcohol abuse in the last 30 days, dependence in the last 6 months.
8. Patients with a high risk of suicidal behaviour, scoring >3 on item No. 3 of HDRS-17 scale.
9. Concomitant psychotropic medication, including herbal preparations.
10. Neurologic disorders (dementia, seizure and stroke) or serious or uncontrolled diseases (hypertension, angina pectoris, myocardial infarction, diabetes mellitus etc.).
11. Hepatic insufficiency (SGOT/SGPT ≥2.0 x ULN) or Renal insufficiency (serum creatinine ≥1.5 x ULN).
12. Clinically significant abnormalities on physical examination or laboratory tests.
13. Ongoing use of prohibited medications (Ex: TCA antidepressants, SSRIs, sedatives-hypnotics and melatonin & its other derivatives). Washout period according to drug's half-life is allowed before screening (at least 7 days). During washout period and initial 2 weeks of the study, if required only zolpidem (max 10 mg/day) is allowed.
14. Unsuitability for enrolment otherwise as decided by investigator.
15. Patients having participated in any type of clinical study within the last one month of the screening date.

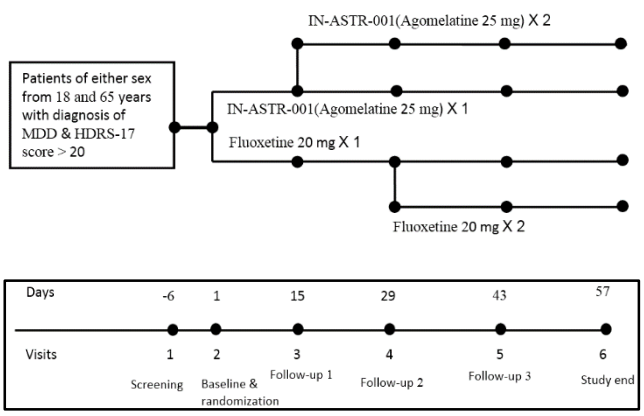

Fig. 1: Study design flow chart

The study was conducted with prior permission from the Drug Controller General of India (DCG I) and Central India Medical Research Ethics Committee, Nagpur.

Enrolled patients were randomized to take orally one tablet of either Agomelatine 25 mg in the evening or fluoxetine 20 mg in the morning. On Day 15 (Visit 3), escalation of the Agomelatine dosage was attempted on the basis of the patients' clinical response (HDRS-17 score) and tolerability to the drug during the first 2 weeks. Similarly, fluoxetine dose escalation was attempted on 29th day (Visit 4). If the study drug had been tolerated and the improvement on HDRS-17 score was less than 30% of the base line score, the dose of Agomelatine/fluoxetine was escalated to 2 tablets/capsules on visit 3/ visit 4 respectively. The dosage schedule decided on visit 3 for Agomelatine and on visit 4 (for fluoxetine) were continued through the end of 57th day. Patients with more severe depression were prescribed zolpidem oral tablets during the screen-randomization period and initial 2weeks of randomization as a rescue medication.

Efficacy Assessments: Impact of the study drug on major depression was assessed in each patient by applying the HDRS-17 scale at visit 2 (Day 1, enrolment/baseline), visit 3 (Day 15, follow-up 1), visit 4 (Day 29, follow-up 2), visit 5 (Day 42, follow-up 3) and visit 6 (Day 57, end of study). Primary efficacy criterion was change in HDRS-17 score at last post-baseline assessment from the score at baseline score. Patients with a decrease of ≥50% in score at last post-baseline evaluation compared with that at baseline were considered treatment responders. Those having a score of ≤7 were considered as remitters. Total insomnia score (from insomnia component of HDRS-17) at last assessment was compared with base line score to look into the effects of the study drugs on insomnia.

Tolerability & Safety Assessments: Tolerability to the study drug was assessed by evaluation of adverse events reported voluntarily, observed, or found on enquiry during the study period.

Patients' vital signs and findings of physical and systemic examination were recorded on all study visits. Laboratory investigations [hemogram, urine examination, liver function tests, kidney function tests, serum sodium and pregnancy test (in female patients of childbearing potential)] and recording of electrocardiogram (ECG) were done at screening and repeated at study end. On the day of follow-up visit 4 i.e. after 28-day treatment, liver enzymes, serum sodium, Clotting time & Bleeding time were monitored. Values of laboratory parameters, vital signs, findings of physical examination and ECG reports were checked for any clinically significant change during the study in both treatment groups.

Data Analysis: Demography, efficacy, and safety data in the two groups were compared for statistical significance of observed difference by applying non-parametric tests. Results were expressed as Mean±Standard Deviation. For paired level of significance (i.e. comparison between post-baseline and baseline values), Wilcoxon test has been used; for between groups comparison, Mann-Whitney test has been applied. Statistical significance was fixed at 5% level.

RESULTS: A total of 23 patients were screened and out of them 21 patients were randomized to study medications (11 on Agomelatine and 10 on fluoxetine treatment) at our site. Baselines characteristics with respect to age, body weight, and other depression parameters were similar in both treatment groups (Table 1). None of the patients enrolled in the study had any chronic co-morbid conditions like thyroid disorder, diabetes mellitus, hypertension, bronchial asthma or COPD etc. And none were on any concomitant medications at the start of study medication excluding zolpidem.

All the patients in the fluoxetine group had completed total duration of treatment. 3 patients in Agomelatine group were lost to follow-up; rest had completed 57 days of duration of treatment. Dose of study medication was doubled (2 tablets) on 15th day in 9 patients out of 11 patients in the Agomelatine group. In fluoxetine group only two patients had dose escalation on 29th day.

Parameter	Agomelatine (N=11)	Fluoxetine (N=10)
Age (Years) (Mean±SD)	35.18±9.47	38.8±11.75
Sex ratio (Female: Male)	7:4	4:6
Body weight (kg) (Mean±SD)	57.90±3.50	60.20±3.65
Duration of MDD (years) (Mean±SD)	0.57±0.56	0.59±0.62
Duration of current episode (months) (Mean±SD)	3.90±3.14	3.40±1.44
HDRS-17 score (Mean±SD)	22.72±1.73	22.40±2.01
Total insomnia score (Mean±SD)	3.63±0.67	4.0±0.94
CGI-S score (Mean±SD)	4.09±0.30	4.10±0.31

Table 1: Baseline characteristics of patients randomized in the study at our site

Treatment Group	Baseline	15th day	29th day	43rd day	57th day	P value
Agomelatine	22.72±1.73	19.27±3.4	15.44±5.24	9.12±1.12	6.62±1.59	<0.001
Fluoxetine	22.40±2.01	16.0±3.29	12.50±3.30	8.20±2.65	6.10±1.79	<0.001
P value	0.694	0.038	0.157	0.373	0.527	

Table 2: HDRS-17 score (Mean±SD) at baseline and post-baseline assessment time points

(P value in the last column: 57th day vs baseline; and P value in the last row: Agomelatine vs Fluoxetine)

Treatment Group	Baseline	15th day	29th day	43rd day	57th day	P value
Agomelatine	4.09±0.30	3.27±0.64	2.55±1.01	1.50±0.53	1.12±0.35	<0.001
Fluoxetine	4.10±0.31	3.0±0.81	2.20±0.63	1.40±0.69	1.10±0.32	<0.001
P value	0.947	0.404	0.366	0.743	0.876	

Table 3: CGI-S score at various time points of assessment in the two treatment groups

(P value in the last column: 57th day vs baseline; and P value in the last row: Agomelatine vs Fluoxetine)

After completion of 57-day treatment, HDRS17 scores in the two treatment groups decreased to 6.62±1.59 and 6.10±1.79 from treatment initiation values 22.72±1.73 and 22.40±2.01 in Agomelatine and fluoxetine groups respectively (P <0.001 for both the groups) (refer table 2). Similarly, the CGI-S score decreased from baseline values 4.09±0.30 and 4.10±0.31 to 1.12±0.35 and 1.10±0.32 in Agomelatine and fluoxetine treated groups respectively (P < 0.001 for both the groups) (refer table 3). There were no significant differences between the two treatment groups as far as the improvement is concerned. (Refer to tables 2 & 3)

Treatment Group	Baseline	15th day	29th day	43rd day	57th day
Agomelatine	0/11	0/11	1/9	7/8	8/8
Fluoxetine	0/10	0/10	4/10	9/10	10/10

Table 4: Treatment responders (patients with ≥50% reduction in HDRS-17 score)

Treatment Group	Baseline	15th day	29th day	43rd day	57th day
Agomelatine	0/11	0/11	0/9	0/8	7/8
Fluoxetine	0/10	0/10	0/10	4/10	8/10

Table 5: Treatment remitters (patients with HDRS-17 score ≤7)

Treatment responders mean patients with more than 50% reduction in HDRS-17 score.

All the patients (100%) in both the treatment groups were treatment responders at the end of treatment period. (Refer table-4).

Treatment remitters means patients with HDRS-17 score ≤7. No patient in either group had achieved remission by 29th day. But, 7 patients in Agomelatine group (87.5%) and 8 patients (80%) in the fluoxetine group were treatment remitters at the end of study period. (Refer table-5).

Treatment Group	Baseline	15th day	29th day	43rd day	57th day
Agomelatine	0/11	0/11	5/9	8/8	8/8
Fluoxetine	0/10	0/10	8/10	9/10	10/10

Table 6: Number of patients having CGI-I score of ≤2 at post-baseline assessment time points

As per the CGI-I score, all the patients in both the treatment groups i.e. 8 out of 8 in Agomelatine group and 10 out of 10 in fluoxetine group were having CGI-I score of ≤2 on 57th day of treatment.

Treatment Group	Baseline	15th day	29th day	43rd day	57th day	P value
Agomelatine	3.64±0.67	2.81±0.87	2.55±1.42	1.12±0.99	0.63±0.74	<0.001
Fluoxetine	4.0±0.94	2.70±0.67	1.70±0.94	0.80±0.63	0.50±0.79	<0.001
P value	0.319	0.735	0.138	0.410	0.720	

Table 7: Insomnia total score at baseline and post-baseline assessment time points

Insomnia total score was reduced statistically significant in both the treatment groups at the end of study compared to baseline (P value <0.001), however in between comparison between the drug groups did not yield any significant result.

Laboratory Parameters: Mean values of haematology and biochemistry investigation results at screening and study end period for two treatment groups were within normal limits. Results of the analysis did not reveal clinically significant deviation of values of any of the parameters.

Electrocardiogram (ECG): Findings of the ECG of all patients enrolled at this site were reported as within normal limits and did not indicated any significant deviation in either treatment group.

Blood Pressure and Heart Rate: There was no clinically significant variation observed in both parameters during the study in both the treatment groups.

Adverse Events Reported: 15 adverse events were reported in 7 patients in Agomelatine treatment group. These include headache, heaviness in head, giddiness, flu-like symptoms, dryness of mouth, throat and irritability. 9 adverse events were reported in 6 patients in fluoxetine group. These include headache, giddiness, gastro-intestinal complaints, restlessness and body ache. Most of these adverse events were of mild to moderate in severity and none of them led to study medication discontinuation. No death or serious adverse event was reported in any patients in either treatment group.

DISCUSSION & CONCLUSION: Patients from both the treatment groups showed improvement in major depression symptoms in terms of reduction in HDRS-17 score. The reductions in HDRS-17 scores in both the treatment groups were statistically significant (P<0.001, table 2). This is also corroborated by the similar reduction in CGI-S score at the study end period (P<0.001, table 3). The results are in line with the previous placebo controlled studies of Agomelatine showing superior response and remission rates with Agomelatine.[9] Also it was seen that both the study medications significantly improved insomnia and there was no significant difference between the two groups (table 7).

If we compare Agomelatine with fluoxetine, Agomelatine was found to be equally effective as fluoxetine in terms of improvement in various efficacy parameters like change in HDRS-17, response and remission rate. However, in few of the reported studies, fluoxetine was found to be superior to Agomelatine in terms of change in HDRS-17, response and remission rate.[14,15] In terms of safety, there was no reported

serious adverse event which is in line with those reported in literature.[9,14,15]

In conclusion, the results showed that Agomelatine could be an important effective therapeutic option in the treatment of major depressive disorder. Considering the small sample size from this center, it is suggested that the data/results presented in this report should be read in conjunction with the data from other centers.

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