ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2024;34(1):9-18
DOI:10.5152/pcp.2024.22498

The Effects of Fluoxetine and Agomelatine on Neurocognitive Functions and Sleep in Patients with Major Depressive Disorder

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ABSTRACT

Background: We aimed to evaluate the effects of 6 weeks of agomelatine versus fluoxetine treatment on cognition and sleep.

Methods: Agomelatine 25 mg/day and fluoxetine 20 mg/day were administered to major depressive disorder (MDD) patients. Assessments were conducted before the treatment and at the sixth week of treatment via psychometric measures and comprehensive neurocognitive assessments of various functions, including executive skills, attention, memory, verbal fluency, and speed of processing.

Results: They both improved the evaluated neurocognitive test scores ($P < .05$), except for the scores of the Digit Span Test ($P > .05$), but only fluoxetine significantly improved the scores of the Controlled Oral Word Association Test ($P = .018$). Only in relation to the subjective sleep quality part of the Pittsburgh Sleep Quality Index ($P = .035$) and the Trail Making Test-B (TMT-B) ($P = .046$) was there an important difference between the study groups, and agomelatine showed better effects than fluoxetine in these measures.

Conclusion: Both drugs improved the neurocognitive functioning in the participants. However, the better effect of agomelatine in improving the TMT-B scores suggests that it is a suitable option for MDD patients with noticeable executive disturbances.

ARTICLE HISTORY

Received: September 13, 2022
Revision requested: March 11, 2023
Last revision received: August 23, 2023
Accepted: September 21, 2023
Publication Date: February 2, 2024

INTRODUCTION

Depression is one of the main reasons for functional impairment, influencing 322 million people worldwide. It is more prevalent among females (5.1%) than males (3.6%).[1] However, there is a lack of sufficient treatment response to major depressive disorder (MDD), and the inadequacies in treatment cause difficulties in clinical practice. In a previous trial, despite the adequate treatment, nearly one-third of the patients with MDD did not experience remission.[2] In addition, treatment-resistant depressive patients require further attention, and in this group of patients, comorbidity of medical and psychiatric disorders is very common.[3]

There is growing evidence of deficits in neurocognitive functioning in MDD. In a study cohort of MDD patients, only 45% of the participants had intact neurocognitive functioning.[4] Neurocognitive impairment in depressed patients can be detected in attention, memory, executive functions, and mental processing speed.[5] In a meta-analysis, active MDD patients showed worse performance in 16 of the 16 neurocognitive measures than healthy controls.[6] In another meta-analysis with patients with MDD, disturbances in selective attention, long-term memory, and working memory were found to be present even in remission.[7] Neurocognitive disturbance negatively affects the depressed individual's capacity to deal with the requirements of ordinary activities and may indicate the need for MDD treatment.[8,9] Antidepressant treatment has been found to improve neurocognitive abilities and workplace outcomes in MDD patients.[10,11] Yet, neurocognitive impairments remain even in patients with MDD remission.[12,13] In addition, neurocognitive symptoms of depression have an adverse impact on the treatment course of MDD, as well as on functional recovery.[14,15]

Conventional antidepressants enhance central catecholamine transmission, and this pharmacodynamic action provides the basis for hypothesizing that antidepressants improve both the mood and cognitive

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Cite this article as: Aydın EF, Güleç M, Oral E, Daloğlu AG. The effects of fluoxetine and agomelatine on neurocognitive functions and sleep in patients with major depressive disorder. *Psychiatry Clin Psychopharmacol*. 2024;34(1):9-18.

symptoms associated with depression.[16] Despite this hypothesis, however, this subject has not been broadly researched in terms of the influences of diverse classes of antidepressants on the neurocognitive functions of patients with MDD. A scientometric analysis found that sertraline demonstrated a positive index of change from 1988 to 2017, while tricyclic antidepressants demonstrated a decline.[17] In a meta-analysis investigating the cognitive effects of different conventional antidepressants, no important difference was detected. In another study, an important improvement in the influence of antidepressants on psychomotor speed and delayed recall was reported.[18]

Considering the previous studies, it can be concluded that antidepressants developed according to the monoamine hypothesis can ameliorate the decline in neurocognitive functions. However, the antidepressant medication agomelatine was the first to shift away from the monoamine hypothesis in unipolar depression and to target the circadian system. In addition to its chronobiotic effect, agomelatine has clinically significant antidepressant properties. This compound achieves its antidepressant properties via the melatonin receptor (MT)1 and the MT2 agonism and antagonism of the 5-hydroxytryptamine (HT; serotonin) 2C receptors.[19] Besides its chronobiotic effect, agomelatine increases the dopamine and norepinephrine (NE) concentrations in the frontal cortex through antagonism of the 5HT-2C.[20] A recent study found that agomelatine, but not fluoxetine, increased the hippocampal brain-derived neurotrophic factor levels in an animal model of depression.[21] To date, however, there is insufficient information about the difference between agomelatine's effect on neurocognitive functions in unipolar depressed patients and any other antidepressant agent's effect. Therefore, our aim was to investigate whether there are different effects of agomelatine and fluoxetine, a widely used selective serotonin reuptake inhibitor (SSRI), on the neurocognitive functioning and sleep patterns in patients with MDD. We mainly hypothesized that due to its MT1 and MT2 agonism and serotonin-2C antagonism, agomelatine would show more favorable effects on these functions than flouxetine.

MATERIAL AND METHODS

Participants

Forty-eight participants [40 (83.33%) females and 8 (16.67%) males] aged 18-65 years who met the Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for unipolar MDD diagnosis, according to the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Version SCID-I, CV, were included in the study. The agomelatine group and the fluoxetine group consisted of 24 patients each. The demographic features were recorded for all participants via a sociodemographic data form. The mean age of the fluoxetine group was 28.46 ± 8.98, and the mean age of the agomelatine group was 26.04 ± 7.70. The mean years of education was 11.88 ± 4.72 years in the fluoxetine group and 12.33 ± 4.69 years in the agomelatine group. The mean intelligence quotient (IQ) score was 100.04 ± 7.43 in the fluoxetine group and 98.16 ± 9.19 in the agomelatine group. All the patients were gathered from the outpatient psychiatry clinic of the Atatürk University Medical Faculty. The protocol was approved by the Atatürk University Faculty of Medicine Clinical Research Ethical Committee (Date: April 26, 2012, Decision no: 3). Informed consent was procured from all the patients. All the study methods were in line with the Helsinki Declaration. All data were recorded anonymously.

The present single-center, noninterventional, open-label preliminary study was conducted in a naturalistic setting. This study constitutes a speciality thesis in medicine and was performed between April 2012 and July 2013. Neurocognitive tests and psychometric measures were administered twice over 6 weeks [baseline (T0) and 6 weeks after baseline (T6)]. The patients took no psychotropic medication for at least 1 month prior to the enrollment. The reasons for exclusions were mental retardation; any psychiatric diagnosis other than MDD, according to the DSM-IV, during or before the study period (the exclusion of other psychiatric disorders besides MDD was performed with SCID-I, CV according to the DSM-IV criteria); pregnancy or breastfeeding; women not using effective birth control methods; any neurological or medical comorbidity; known brain damage; any psychiatric disorder history except MDD in the first-degree relatives of the patient; and active suicidal ideations. All participants were fluent in Turkish. All were enrolled through referrals from the outpatient psychiatric clinic of the Atatürk University Medical Faculty. Major depressive patients who required antidepressant drug treatment in the outpatient psychiatric clinic's view and were planned to start a 20 mg/day fixed dose of fluoxetine or a 25 mg/day fixed dose of agomelatine, in accordance with their clinical conditions, were referred to the first author of the study for initial evaluations by the outpatient psychiatric clinic. The major depressive patients who met the inclusion criteria and were willing to take part in the research process were included. After the referral and patient selection process, fluoxetine (n=24) and agomelatine (n=24) groups were constituted randomly. Psychometric and neurocognitive assessments at T0 were then performed with these groups, and psychotropic medications were initiated by the outpatient psychiatric

MAIN POINTS

- Agomelatine and fluoxetine effectively improved sleep parameters.
- Agomelatine and fluoxetine significantly improved cognitive functioning.
- Agomelatine was significantly superior to fluoxetine in the subjective sleep quality part of the Pittsburgh Sleep Quality Index and Trail Making Test-B.

clinic, after which the patients were followed in the outpatient psychiatric clinic. The first author of the study performed the psychometric measures and conducted the neurocognitive tests, but he did not intervene clinically at any point. This author has the clinical training required to conduct neurocognitive tests. The neurocognitive tests were performed at 9:00 AM. Before the tests, the patients were free to eat and smoke. The neurocognitive tests were performed in a small, quiet room in the inpatient clinic of our department. Eventually, after the 6-weeks of follow-up, the neurocognitive assessments and psychometric measures were repeated with the same instruments.

Evaluation Tools

The Clinical Global Impression (CGI) Scale evaluates the functioning, severity of symptoms, and response of treatment. The CGI-Severity Scale (CGI-S) measures patient change relative to their initial assessment symptoms.

The Beck Depression Inventory (BDI) is a structured, multiple-choice self-report rating scale used to measure the severity of depression. The Turkish reliability and validity of the scale has been performed, and the Turkish BDI showed good reliability (Cronbach's α = 0.80).[22] In the present trial, the Cronbach's α of BDI was 0.79.

The Hamilton Depression Rating Scale (HAMD-17) is a scale administered by the clinician, and this scale evaluates the severity of depression. This scale's Turkish reliability and validity was performed by Akdemir et al[23], and the Turkish HDRS (Hamilton Depression Rating Scale) showed good reliability (Cronbach's α=0.75). Here, the Cronbach's α of HDRS was 0.78.

The Pittsburgh Sleep Quality Index (PSQI) evaluates sleep quality. The PSQI assesses the following 7 sleep domains: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleep medications (C6), and daytime dysfunction (C7). The component scores are combined to create an overall sleep quality score ranging from 0 to 21. A Turkish adaptation of the study was performed, and the Turkish PSQI showed good reliability (Cronbach's α=0.83).[24] Here, the Cronbach's α of PSQI was 0.82.

Previously, the effects of insomnia on neurocognitive functions have been widely discussed.[25] The Insomnia Severity Index (ISI) measures insomnia and perceived insomnia severity. A Turkish validity and reliability study was performed, and the Turkish ISI showed good reliability (Cronbach's α=0.79).[26] In the present investigation, the Cronbach's α of ISI was 0.80.

The neurocognitive assessment battery was aimed to test a wide range of neurocognitive functions, including executive skills, attention, memory, and verbal fluency. The tests we used in the present study were the Rey Auditory Verbal Learning and Memory Test (RAVLT), the Auditory Consonant Trigram Test (ACTT), the Controlled Oral Word Association Test (COWAT), the Digit Span Test (DST), the Trail Making Test A (TMT-A) and Trail Making Test B (TMT-B), the Stroop Color–Word Interference Test-TBAG (Tübitak Basic Sciences Research Group) Form (SCWT), and the Wisconsin Card Sorting Test (WCST). The RAVLT evaluates immediate memory span, new learning, delayed free recall, and recognition of verbal items; the ACTT assesses working memory; the COWAT assesses verbal fluency; the DST assesses short-term verbal memory; the TMT-A assesses speed of processing and the TMT-B evaluates mental flexibility and executive functions; the SCWT assesses executive functions; and the WCST assesses executive functions. Neurocognitive evaluation was performed in the test laboratory of our clinic. General intellectual abilities were measured by the Kent-EGY and Porteus Labyrinth tests for the evaluation of IQ.

Statistical Analysis

The Statistical Package for Social Sciences version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) was applied to conduct the statistical analyses. We used the Shapiro–Wilk test of normality to evaluate the distribution of the numeric variables. Data are presented as mean $\pm$ SD or median (first quartile-third quartile) for continuous variables depending on the normality of distribution and as frequency (percentage) for categorical variables. A between-group analysis of patients' characteristics (continuous variables) was conducted with the Student's *t*-test or the Mann-Whitney *U*-test depending on the normality of distribution. The between-group analysis of patients' characteristics (categorical variables) was performed with the Fisher's exact test. An analysis of assessment scores between T0 and T6, also between groups, was performed with 2-way repeated measures analysis of variances (ANOVA). We used Box's *M* test to assess the equality of covariances assumption. Analysis of the assessment scores that violated this assumption (PSQI C6 and Stroop 5) was done with the Pillai's trace multivariate test. In addition, pairwise comparisons of time and group effects were performed via ANOVA adjusted by Bonferroni correction. Internal reliability of the scales was assessed by calculating Cronbach's α coefficients. The *P*-value less than .05 was taken as the statistical significance level.

RESULTS

The agomelatine group (n=24) and fluoxetine group (n=24) comprised equal numbers of patients at T0. When the study finished, in the sixth week (T6), 18 (75.00%) patients from the fluoxetine group and 14 (58.33%) patients from the agomelatine group were reevaluated. Six (25.00%) patients from the fluoxetine group and 10 (41.67%) from the agomelatine group were classified as

Table 1. Patients' Characteristics and Analysis Results with Regard to Groups at Baseline (T0) (n = 48)

	Fluoxetine	Agomelatine	*P*
Age	28.46 ± 8.98	26.04 ± 7.70	.322[a]
Sex			
Male	3 (12.50%)	5 (20.83%)	.701[b]
Female	21 (87.50%)	19 (79.17%)	
Duration of education	11.88 ± 4.72	12.33 ± 4.70	.738[a]
Intelligence quotient score	100.04 ± 7.44	98.17 ± 9.19	.447[a]
Duration of episode (weeks)	3 (2.5-8.5)	4 (2-12)	.686[c]

Data are presented as mean ± SD or median (first quartile-third quartile) for continuous variables depending on the normality of distribution and as frequency (percentage) for categorical variables.
[a]Student's *t*-test.
[b]Fisher's exact test.
[c]Mann-Whitney *U*-test.

dropouts. There were no significant differences among the 2 groups considering their age, gender, years of education, MDD episode duration, or IQ ($P > .05$) (these features are displayed in Table 1 for the assessment at T0 and in Table 2 for the assessment at T6). In the initial assessment of the participants at T0, no significant difference was found between the groups in the scores of HAMD-17, BDI, and CGI-S ($P > .05$; Table 3). When we considered the antidepressant effects from T0 to T6, there were no significant differences between the 2 groups ($P > .05$; Table 3). In terms of sleep parameters, fluoxetine displayed statistically significant improvements in the ISI, the C5, and C7 subtests of the PSQI, and the total scores of the PSQI ($P < .05$) over 6 weeks of treatment. In addition, agomelatine resulted in statistically significant improvements in the ISI; C1, C2, C5, and C7 subtests of the PSQI and in the overall scores of the PSQI ($P < .05$) in this period. Only in terms of the PSQI C1 subtest over 6 weeks between the groups was agomelatine statistically significantly superior to fluoxetine ($P = .035$; Tables 3 and 4).

Table 2. Patients' Characteristics and Analysis Results with Regard to Groups at the Sixth Week (T6) (n = 32)

	Fluoxetine	Agomelatine	*P*
Age	30.44 ± 9.51	26.79 ± 8.18	.261[a]
Sex			
Male	2 (11.11%)	3 (21.43%)	.631[b]
Female	16 (88.89%)	11 (78.57%)	
Duration of education	11.22 ± 5.17	12.64 ± 5.29	.451[a]
Intelligence quotient score	99.44 ± 7.08	97.57 ± 10.01	.558[a]
Duration of episode (weeks)	3 (3-5)	5 (2-12)	.515[c]

Data are presented as mean ± SD or median (first quartile-third quartile) for continuous variables depending on the normality of distribution and as frequency (percentage) for categorical variables.
[a]Student's *t*-test.
[b]Fisher's exact test.
[c]Mann-Whitney *U*-test.

Table 3. Clinical Characteristics and Analysis Results with Regard to Time and Groups

	Fluoxetine	Agomelatine	P^b	P^a
HAMD-17 score				
T0	21.28 ± 4.25	23.71 ± 3.47	.093	Box's *M* = .754 Time < .001; Group = .033 Time and group* = .895
T6	5.78 ± 4.65	8.50 ± 5.14	.127	
P^c	**<.001**	**<.001**		
Change[d]	−15.50 ± 6.38	−15.21 ± 5.49		
BDI score				
T0	26.72 ± 8.47	30.93 ± 7.59	.155	Box's *M* = 977 Time < .001; Group = .091 Time and group* = .643
T6	11.17 ± 10.44	17.00 ± 10.76	.132	
P^c	**<.001**	**<.001**		
Change[d]	−15.56 ± 9.68	−13.93 ± 9.81		
CGI-S severity score				
T0	4.11 ± 0.58	4.29 ± 0.47	.368	Box's *M* = .364 Time < .001; Group = .149 Time and group* = .336
T6	1.56 ± 0.86	2.07 ± 1.21	.167	
P^c	**<.001**	**<.001**		
Change[d]	−2.56 ± 0.92	−2.21 ± 1.05		

Data are given as mean ± SD.
BDI, Beck Depression Inventory; CGI-S, Clinical Global Impression-Severity Scale; HAMD-17, Hamilton Depression Rating Scale; T0, baseline; T6, 6 weeks after baseline.
[a]Two-way repeated measures analysis of variance.
[b]Pairwise comparisons for Group (fluoxetine vs. agomelatine).
[c]Pairwise comparisons for Time (T0 vs. T6).
[d]Difference between T6 and T0; negative values represent decrease and positive values represent increase in scores.
**P*-values represent between-group analysis of change.[e]Significant *P*-values are shown in bold fonts. *P*-values less than .05 ($P < .05$) are considered as statistically significant.

In the neuropsychological tests, fluoxetine showed statistically significant improvements in readings 5 and 7 of the RAVLT, the COWAT, the ACTT, the TMT-A, parts 4 and 5 of the SCWT, and perseverative errors of the WCST ($P < .05$). In the agomelatine group, there were significant changes in readings 5 and 7 of the RAVLT, the ACTT, both the TMT-A and TMT-B, part 4 of the SCWT, and perseverative errors of the WCST ($P < .05$; Table 5). When we compared the group effects, on the neuropsychological tests, the only statistically significant difference was found in the TMT-B test, where agomelatine's effect was statistically superior to that of fluoxetine ($P = .046$; Table 5).

DISCUSSION

From the present study, we see that the short-term use of either agomelatine or fluoxetine for 6 weeks in MDD outpatients effectively reduced the severity of depressive symptoms, as determined by the BDI, HAMD-17, and CGI-S scores. In an 8-week follow-up study of treatment with either agomelatine or fluoxetine in MDD patients, each agent was equally effective in treating depressive symptoms.[27] In a randomized, open-labeled, prospective observational study, it was found that agomelatine and fluoxetine had similar antidepressant effects after 12

Table 4. Sleep Characteristics and Analysis Results with Regard to Time and Groups

	Fluoxetine	Agomelatine	P^b	P^a
ISI score				
T0	13.18 ± 6.62	17.50 ± 6.51	.079	Box's *M* = .884 Time < .001 Group = .127 Time and group* = .266
T6	7.29 ± 5.47	8.79 ± 6.14	.481	
P^c	**.002**	**<.001**		
Change[d]	−5.88 ± 7.38	−8.71 ± 6.32		
PSQI C1 score				
T0	1.44 ± 0.78	2.07 ± 0.62	**.020**	Box's *M* = .468 Time < .001; Group = .185 **Time and group* = .035**
T6	1.17 ± 0.71	1.14 ± 0.86	.932	
P^c	.165	**<.001**		
Change[d]	−0.28 ± 0.89	−0.93 ± 0.73		
PSQI C2 score				
T0	1.72 ± 0.89	2.43 ± 0.94	**.038**	Box's *M* = .776 Time = .002; Group = .036 Time and group* = .401
T6	1.17 ± 0.92	1.50 ± 0.85	.304	
P^c	.065	**.008**		
Change[d]	−0.56 ± 1.34	−0.93 ± 1.07		
PSQI C3 score				
T0	0.94 ± 1.00	1.71 ± 1.27	.064	Box's *M* = .124 Time = .144; Group = .035 Time and group* = .568
T6	0.72 ± 0.96	1.21 ± 0.97	.163	
P^c	.490	.176		
Change[d]	−0.22 ± 0.94	−0.50 ± 1.74		
PSQI C4 score				
T0	1.00 ± 1.33	1.43 ± 1.40	.383	Box's *M* = .903 Time = .253; Group = .634 Time and group* = .418
T6	0.89 ± 1.37	0.79 ± 1.12	.821	
P^c	.797	.195		
Change[d]	−0.11 ± 1.84	−0.64 ± 1.78		
PSQI C5 score				
T0	1.72 ± 0.46	1.86 ± 0.53	.450	Box's *M* = .930 Time < .001; Group = .358 Time and group* = .944
T6	1.17 ± 0.51	1.29 ± 0.47	.505	
P^c	**.001**	**.002**		
Change[d]	−0.56 ± 0.62	−0.57 ± 0.65		
PSQI C6 score				
T0	0.11 ± 0.47	0.43 ± 0.94	.220	Box's *M* = N/A Time = .366; Group = .028 Time and group* = .091
T6	0.00 ± 0.00	0.79 ± 1.25	**.012**	
P^c	.536	.086		
Change[d]	−0.11 ± 0.47	0.36 ± 1.01		
PSQI C7 score				
T0	1.89 ± 0.76	1.93 ± 0.92	.894	Box's *M* = .435 Time < .001; Group = .770 Time and group* = .924
T6	0.78 ± 0.88	0.86 ± 0.66	.781	
P^c	**<.001**	**.002**		
Change[d]	−1.11 ± 1.08	−1.07 ± 1.27		

(*Continued*)

Table 4. Sleep Characteristics and Analysis Results with Regard to Time and Groups (*Continued*)

	Fluoxetine	Agomelatine	P^b	P^a
PSQI total score				
T0	8.83 ± 2.92	11.86 ± 3.18	**.009**	Box's *M* = .380 Time < .001; Group = .008 Time and group* = .355
T6	5.89 ± 3.31	7.57 ± 2.77	.136	
P^c	**.004**	**<.001**		
Change[d]	−2.94 ± 3.46	−4.29 ± 4.63		

Data are given as mean ± SD.

C1, subjective sleep quality; C2, sleep latency; C3, sleep duration; C4, habitual sleep efficiency; C5, sleep disturbances; C6, use of sleep medications; C7, daytime dysfunction; ISI, Insomnia Severity Index; N/A, cannot be computed because at least 1 variance is equal to zero; PSQI, Pittsburgh Sleep Quality Index, T0, baseline; T6, 6 weeks after baseline.

[a]Two-way repeated measures analysis of variance.

[b]Pairwise comparisons for Group (fluoxetine vs. agomelatine).

[c]Pairwise comparisons for Time (T0 vs. T6).

[d]Difference between T6 and T0; negative values represent decrease and positive values represent increase in scores.

*P-values represent between-group analysis of change.[e]Significant *P*-values are shown in bold fonts. *P*-values less than .05 (*P*<.05) are considered as statistically significant.

weeks of follow-up.[28] In an open-label, observational follow-up study, agomelatine's efficacy was not significantly different from sertraline.[29] A pooled analysis of 4 follow-up clinical trials revealed that agomelatine is at least as efficacious as escitalopram, fluoxetine, and sertraline.[30] In addition, a meta-analysis revealed that agomelatine had similar efficacy with standard antidepressants.[31] A network meta-analysis revealed that agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants [range of odds ratios 1.19-1.96].[32] These studies and our results indicate that agomelatine is an antidepressant, with efficacy similar to that of standard antidepressants.

Our results suggest that both treatments—agomelatine and fluoxetine—bring about significant improvements in terms of sleep parameters. The only significant difference was found in the subjective sleep quality subtest of the PSQI in favor of agomelatine. In another comparison study including MDD patients, both agomelatine and fluoxetine were found to be equally effective in terms of sleep.[27] Compared with escitalopram, in MDD patients, agomelatine displayed more clinical benefits on sleep-wake quality in a 24-week clinical trial.[33] In addition to circadian rhythm regulation, agomelatine also increases slow-wave sleep, which decreases depression.[34] Concerning the effects of agomelatine, as mentioned above, it may ameliorate sleep quality better than SSRIs do in MDD patients.

In this report, we have presented the cognitive effects of antidepressant treatment with 2 different antidepressants. In our study, we demonstrated significant improvement in verbal memory, verbal fluency, working memory, attention,

Table 5. Neurocognitive Measures and Analysis Results with Regard to Time and Groups

	Fluoxetine	Agomelatine	P^b	P^a
RAVLT reading 5				
T0	11.61 ± 1.79	12.23 ± 1.64	.333	Box's *M*=.239 Time=.001; Group=.269 Time and group*=.908
T6	13.17 ± 2.01	13.69 ± 1.55	.437	
P^c	**.006**	**.024**		
Change[d]	1.56 ± 2.62	1.46 ± 1.45		
RAVLT reading 7				
T0	10.83 ± 2.04	10.77 ± 2.98	.944	Box's *M*=.159 Time=.002; Group=.888 Time and group*=.649
T6	11.89 ± 1.60	12.15 ± 2.15	.697	
P^c	**.030**	**.017**		
Change[d]	1.06 ± 2.15	1.38 ± 1.66		
RAVLT recognition				
T0	14.17 ± 1.04	14.23 ± 1.01	.889	Box's *M*=.782 Time=.289; Group=.959 Time and group*=.823
T6	14.41 ± 0.62	14.38 ± 0.65	.908	
P^c	.329	.575		
Change[d]	0.24 ± 0.90	0.15 ± 1.07		
COWAT				
T0	36.44 ± 9.98	34.46 ± 13.94	.647	Box's *M*=.325 Time=.100; Group=.390 Time and group*=.130
T6	40.06 ± 11.09	34.62 ± 13.99	.237	
P^c	**.018**	.928		
Change[d]	3.61 ± 6.93	0.15 ± 4.67		
ACTT				
T0	44.17 ± 6.45	44.54 ± 8.74	.892	Box's *M*=.553 Time < .001; Group=.887 Time and group*=.218
T6	48.17 ± 7.66	47.00 ± 8.58	.694	
P^c	**<.001**	**.013**		
Change[d]	4.00 ± 3.38	2.46 ± 3.33		
DST forward				
T0	5.83 ± 1.50	6.21 ± 2.72	.618	Box's *M*=.116 Time=.017; Group=.545 Time and group*=.616
T6	6.17 ± 1.54	6.71 ± 2.89	.496	
P^c	.136	.051		
Change[d]	0.33 ± 0.84	0.50 ± 1.02		
DST backward				
T0	5.17 ± 2.15	6.14 ± 2.63	.256	Box's *M*=.558 Time=.883; Group=.223 Time and group*=.713
T6	5.33 ± 1.71	6.07 ± 2.06	.277	
P^c	.698	.883		
Change[d]	0.17 ± 1.50	−0.07 ± 2.13		
TMT-A				
T0	38.87 ± 15.83	35.87 ± 16.20	.602	Box's M=.536 Time < .001; Group=.933 Time and group*=.131
T6	28.54 ± 11.26	30.70 ± 15.22	.647	
P^c	**<.001**	**.047**		
Change[d]	−10.34 ± 10.07	−5.17 ± 8.29		
TMT-B				
T0	94.96 ± 53.61	114.29 ± 64.45	.362	Box's *M*=.061 Time=.043; Group=.911 Time and group* = **.046**
T6	94.71 ± 43.66	79.06 ± 43.21	.321	
P^c	.982	**.009**		
Change[d]	−0.25 ± 55.21	−35.23 ± 33.97		

(*Continued*)

Table 5. Neurocognitive Measures and Analysis Results with Regard to Time and Groups (*Continued*)

	Fluoxetine	Agomelatine	P^b	P^a
Stroop-4				
T0	18.28 ± 4.38	16.82 ± 4.31	.360	Box's *M*=.941 Time < .001; Group=.292 Time and group*=.927
T6	16.04 ± 3.60	14.67 ± 3.11	.272	
P^c	**.002**	**.007**		
Change[d]	−2.23 ± 2.70	−2.14 ± 2.78		
Stroop-5				
T0	32.17 ± 11.77	25.37 ± 4.96	.053	Box's *M*=.011 Time < .001; Group=.032 Time and group*=.206
T6	23.69 ± 4.82	21.02 ± 3.95	.107	
P^c	**<.001**	.076		
Change[d]	−8.48 ± 11.23	−4.36 ± 4.38		
WCST completed categories				
T0	4.67 ± 1.88	3.54 ± 2.54	.165	Box's *M*=.453 Time=.905; Group=.154 Time and group*=.905
T6	4.72 ± 1.93	3.54 ± 2.82	.175	
P^c	.854	1.000		
Change[d]	0.06 ± 1.11	0.00 ± 1.47		
WCST perseverative errors				
T0	21.00 ± 13.09	23.62 ± 12.86	.585	Box's *M*=.168 Time < .001; Group=.788 Time and group*=.349
T6	15.28 ± 12.36	15.00 ± 11.68	.950	
P^c	**.007**	**.001**		
Change[d]	−5.72 ± 5.94	−8.62 ± 10.90		

Data are given as mean ± SD. ACTT, Auditory Consonant Trigram Test; COWAT, Controlled Oral Word Association Test; DST, Digit Span Test; RAVLT, Rey Auditory Verbal Learning and Memory Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; T0, baseline; T6, 6 weeks after baseline.

[a]Two-way repeated measures analysis of variance.

[b]Pairwise comparisons for Group (fluoxetine vs. agomelatine).

[c]Pairwise comparisons for Time (T0 vs. T6).

[d]Difference between T6 and T0; negative values represent decrease and positive values represent increase in scores.

*P-values represent between groups analysis of change.[e]Significant *P*-values are shown in bold values. *P*-values less than .05 (*P*<.05) are considered as statistically significant.

psychomotor speed, and executive functions over 6 weeks of fluoxetine treatment in MDD outpatients. We also found significant improvements in verbal memory, working memory, attention, psychomotor speed, and executive functions with 6 weeks of agomelatine treatment in MDD outpatients. Between agomelatine and fluoxetine, the only significant difference was found in the TMT-B test, and agomelatine was superior to fluoxetine in this domain.

In our study, patients who received both treatments displayed significant improvements in cognitive functioning. In a meta-analysis, antidepressants showed significant positive effects on psychomotor speed and delayed recall.[35] However, there are contradictory research results about the cognitive influences of different groups of antidepressants. In a 24-week fluoxetine treatment study, MDD patients improved in working memory, speed of information processing, and some executive functions.[36] In an 8-week, randomized longitudinal study with 1008

patients using sertraline, escitalopram, or venlafaxine extended release, improvements were only found in executive function and cognitive flexibility. In attention, response inhibition, verbal memory, information processing, and decision speed, there was an absence of improvement, and no difference was recorded between the antidepressants.[37]

Our report shows that agomelatine and fluoxetine display cognitive enhancement in attention, working memory, and executive functions in patients with MDD. These functions depend on the sound functioning of the dorsolateral prefrontal cortex, medial prefrontal cortex, and the interconnections these cortical areas establish with fronto-thalamic-striatal circuits.[38] Neurocognition is mediated by neural circuits including different neurotransmitter systems. Serotonin, NE, and dopaminergic (DA) neurons play important roles in bridging cognition and depression. Serotonergic neurons regulate neuronal activity in the prefrontal cortex; in addition, serotonin is involved in the regulation of cognitive flexibility and attention.[39] Furthermore, the neurotransmitter classically related to working memory is dopamine,[40] and both the NE and DA systems are necessary for the prefrontal functions.[41]

Agomelatine is an antidepressant that shifts away from the monoamine hypothesis, and there are a few studies on the cognitive effects of this medication. In a 12-week study with fibromyalgia patients, agomelatine 25 mg/day did not have a significant effect on neuropsychological tests.[42] In another study, however, agomelatine showed significant improvements in the d2 (d2 test of attention) and TMT-A/B test for MDD patients.[43] In yet another study with MDD outpatients, agomelatine displayed significant improvements in both the TMT-A and TMT-B tests.[44] In our results, agomelatine also showed significant improvements. Through 5HT-2C antagonism, agomelatine increases dopamine and NE levels in the frontal cortex, and as stated above, these are key neurotransmitters in cognitive functions. Fluoxetine also increases extracellular concentrations of NE and dopamine levels in prefrontal cortex.[45] Even with the same 5HT-2C receptor effect of agomelatine and fluoxetine, we had different results, and agomelatine improved the TMT-B test results better than fluoxetine did. The reason for this difference in executive function could be the circadian regulation effect of agomelatine. Nevertheless, caution must be taken in suggesting such an explanation. In recent research, it was shown that agomelatine treatment increased hippocampal neurogenesis.[46] It has also been found that both agomelatine and fluoxetine corrected abnormalities in anxiety/depression-like behavior and social memory performance,[47] while fluoxetine improved the spatial learning and memory of rats with chronic mild stress.[48] These effects of antidepressants could explain our results showing cognitive enhancements in neuropsychological outcomes. However, these are all animal studies, and our aim was not to determine a relationship between these neural mechanisms and the neuropsychological functions in MDD.

In our trial, fluoxetine and agomelatine did not show statistically significant improvements in the DST performances. Bastos et al[49] showed that the scores of the DST did not increase or decrease with fluoxetine use. This outcome may point out that fluoxetine does not strongly influence auditory attention capacity and working memory (mean effect size = 0.23) in the treatment of moderately depressed adult patients. In accordance with this suggestion, Lin et al[50] found that patients with higher baseline scores of forward DST have better treatment outcomes for severely depressed populations (HAMD-17, mean $\pm$ SD = 30.7 $\pm$ 6.6) taking fluoxetine. According to the literature review we carried out, no agomelatine study has investigated the effects on DST scores.

While there were statistically significant improvements in the COWAT performances with fluoxetine, there were no statistically significant changes in the COWAT scores in the agomelatine group in the present study. It was also found that the depressed patients who responded to fluoxetine also performed significantly better on the COWAT.[51] From the neuroanatomical point of view, because the left anterior cingulate and left dorsolateral prefrontal cortex are activated during verbal fluency tests like the COWAT, activation of these brain structures may differ between the fluoxetine responders and nonresponders. These data are also supported by neuroimaging studies demonstrating increased baseline dorsolateral prefrontal and rostral anterior cingulate cortical activity in depressive patients who subsequently responded to an antidepressant drug regimen.[51] Like the fluoxetine study presented above, only 1 research work has investigated the effects of agomelatine on the COWAT scores. Bruno et al[42] showed that treatment with agomelatine did not have a significant influence on the COWAT in fibromyalgia patients with marked depressive symptoms.[42] In animal models, the blockade of 5HT-2C receptors exerted by agomelatine increased the extracellular levels of dopamine and noradrenaline in the frontal cortex; this mechanism may yield an improvement in the neurocognitive function (executive) associated with the frontal lobe.[42] The present study did not show favorable influence of agomelatine on the COWAT performances; however, it should be noticed that our agomelatine sample size (n = 14) was not large enough to ensure adequate power to detect statistically significant changes in the COWAT scores.

There are some limitations in this study. The low sample size is the main one, while an additional issue is that most of the patients we recruited were female. Besides this, our study lacked a control group, and we therefore do not know whether patients' cognitive performance reached a healthy subject's level with the help of these antidepressant treatments. The follow-up time of the

present study also could have been longer, which would help to better understand the effects of agomelatine and fluoxetine on neurocognitive functions. This study mainly focused on cognitive functioning and did not measure motivation, which is a potential confounder that has been measured in similar studies.[52] Nevertheless, to our knowledge, this is the first study comparing agomelatine's neuropsychological effects with a commonly used SSRI, fluoxetine, in MDD outpatients.

To sum up briefly, the outcomes of the present study mention that administering either fluoxetine or agomelatine improves sleep parameters. Only in terms of the subjective sleep quality subtest of the PSQI was there a significant difference in favor of agomelatine. Both agents improved attention, verbal memory, psychomotor speed, working memory, and executive functions. In verbal fluency, only fluoxetine had a significant effect, and there was a significant difference between the agents only on the TMT-B test, with agomelatine having a superior effect. The small sample size of the present study may pose a problem regarding the transferability of our results. In the future, our study should be replicated with larger samples.

Ethics Committee Approval: This study was approved by Ethics Committee of Medical Faculty of Atatürk University (Approval No: 3, Date: April 26,2012).

Informed Consent: Informed consent was obtained from all the patients who participated in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.F.A., M.G.; Design – E.F.A., M.G.; Supervision – E.O.; Resources – E.F.A., M.G.; Materials – E.F.A., M.G.; Data Collection and/or Processing – E.F.A., A.G.D.; Analysis and/or Interpretation – E.F.A., A.G.D., M.G.; Literature Search – E.F.A., M.G.; Writing E.F.A., M.G.; Critical Review – A.G.D., M.G., E.O.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

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