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Comparing Effects of Melatonin versus Trazodone on Sleep Quality in Major Depressed Patients Receiving Sertraline

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ABSTRACT

Background: Sleep disturbance is a common complaint in major depressive disorder (MDD) including impairment of both subjective and objective parameters, additionally selective serotonin reuptake inhibitors (SSRIs) that are among highly consumed antidepressant, affect sleep architecture (SA) as well. This randomized trial was designed to compare the effects of trazodone with melatonin on sleep quality (SQ) of patients with MDD who were started on sertraline per their psychiatrists' orders. The diagnosis of MDD based on Diagnostic and Statistical Manual for Mental Disorders –5th edition (DSM-5) criteria.
Methods: Patients with MDD who complied with the study criteria entered this trial. Subjects were randomized into two groups receiving and started on either trazodone or melatonin concurrent with sertraline. They were evaluated for sleep quality and depression severity by using Pittsburgh Sleep Quality Index (PSQI) and Hamilton Depression Rating Scale (HAM-D) respectively, at baseline and after weeks 4 and 8.
Results: 246 patients were screened out of whom sixty met the criteria of the trial. 32 patients completed the study. Fourteen patients received melatonin and eighteen patients received trazodone before sleep time. After 4 and after 8 weeks treatment with melatonin or trazodone, significant improvements in SQ were shown in both groups ($p<0.001$). Additionally, a significant reduction in sleep latency (SL) was shown after 4 weeks of treatment with melatonin but not with trazodone.
Conclusions: This study demonstrated that both melatonin and trazodone would improve SQ in outpatients with MDD after 8 weeks of treatment with sertraline. However, melatonin created greater reduction in SL than trazodone did after the first 4 weeks of use.

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Introduction

Insomnia is a common symptom in patient with major depressive disorder (MDD). Sleep disturbances may also occur as side effect of antidepressants (1, 2). For instance,

selective serotonin reuptake inhibitors (SSRIs) may induce difficulty falling and/or continuing asleep or in early morning awakenings. These agents can exacerbate preexisting insomnia or cause new insomnia while improving other symptoms of depression (3, 4).

Melatonin and its analogues are considered to be safe when taken after sunset and affect circadian rhythm, decrease time to falling asleep, increase sleep duration and improve sleep quality (SQ) (5). Lemoine et al., noted that melatonin does not induce significant daytime sedation, withdrawal symptoms and rebound insomnia (6).

Trazodone have been reported to help primary and secondary insomnia by decreasing stage 1 and REM duration, increasing stage 3 and 4 (SWS), as well as improving early morning awakening (EMA), sleep continuity, sleep efficiency and SQ (7). Kaynak et al., noted similar effects of trazodone on subjective measures of sleep in depressed patients suffering SSRIs induced insomnia (4).

To our knowledge, there have not been any published data on the comparison between melatonin and trazodone for their effects on SQ in patients with depression. Therefore, this 8-week trial was designed to compare the effects of melatonin and trazodone on SQ and depression of patients with a diagnosis of MDD based on Diagnostic and Statistical Manual for Mental Disorders-5th edition (DSM-5) criteria.

Patients and Methods

Among of 246 patients who were screened, sixty outpatients visited at Roozbeh hospital clinic, who were diagnosed with MDD (based on DSM-5 criteria) met the criteria of the study and 32 patients completed the study. The inclusion criteria included patients between 18 to 60 years of age with a diagnosis of MDD who were not receiving any antidepressants for at least one month prior to the initiation of the study and with the ability of reading and writing for filling the questionnaires. The exclusion criteria included pregnancy and lactation, history of substance abuse during the past six months and, severe and uncontrolled medical conditions (cancer, cardiovascular and cerebrovascular diseases, thyroid disorders), other DSM-5 Axis I disorders and intellectual disability. Subjects who were working at night shifts for at least one month and patients who were taking other drugs that affect sleep, were also excluded prior to the study. All patients gave their signed informed consent. The study was approved by the Ethics Committee of the Faculty of Pharmacy at Tehran University of Medical Sciences (TUMS) and was conducted in accordance with the Declaration of Helsinki 1975 as revised in 2013.

This study was a randomized open label trial. Each patient involved in this research was assessed for depression severity, utilizing Hamilton Depression Rating Scale (HAM-D) and for SQ using Pittsburgh Sleep Quality Index (PSQI) at the baseline. The patients received 150 mg sertraline that started at the dose of 25 mg daily that was increased to 150 mg per day in 3 weeks and continued throughout the trial. Subjects were allocated to the trazodone group or the melatonin group by simple randomization method, and then assigned to receive either 3mg melatonin or 50 mg trazodone (which was started at the dose of 12.5 mg per night that was increased to 50 mg per night in 2 weeks and continued throughout the trial. and was increased up to 50 mg within 3 weeks). Changes in SQ and severity of depression were obtained at weeks 4 and 8 of the treatment using PSQI and HAM-D.

The Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index is an effective tool for subjective assessment of SQ in adults over the past month. It is a self-report questionnaire that measures seven components of sleep.

These components include: subjective Sleep Quality (component 1), Sleep Latency (component 2), Sleep Duration (component 3), Sleep Efficiency (component 4), Sleep Disturbances

(Component 5), using Sleep Medications (component 6), and Daytime Dysfunction (component 7). For each component, scores can be assigned from 0 to 3 which score three reflecting the greatest and score zero means the least problem. The PSQI has the reliability coefficient (Cronbach's alpha) of 0.83 for its seven components(8). Original scale is in English; however, in this study the Persian translation of the scale was used. The Persian version of PSQI has shown good psychometric properties (Cronbach's alpha of 0.82; test-retest reliability, r=0.88)[1].

The Hamilton Depression Rating Scale

The Hamilton Rating Scale for Depression (HRSD), also called the Hamilton Depression Rating Scale (HDRS), abbreviated HAM-D is a questionnaire that designed for adults and is used to rate their severity of depression. This scale is among the most frequently used psychometric instruments in the study of depression. The patients were rated among 17 to 29 items (depending on version) by a clinician, which each of them consists of four statements describing symptom severity. In this study, the patients were evaluated by HAM-D24. A score of 1720 is associated with mild depression, a score of 2125 with moderate depression and a score of 26-29 with severe depression.

The Hamilton scale was completed during the screening visit and at the time the participant was allocated to treatment. The Persian translation of the HAM-D24 scale was used in the present study. The HAM-D24 has good psychometric properties (Cronbach's alpha of 0.88; test-retest reliability, r=0.81) in previous works (9).

1. Quote from the authors

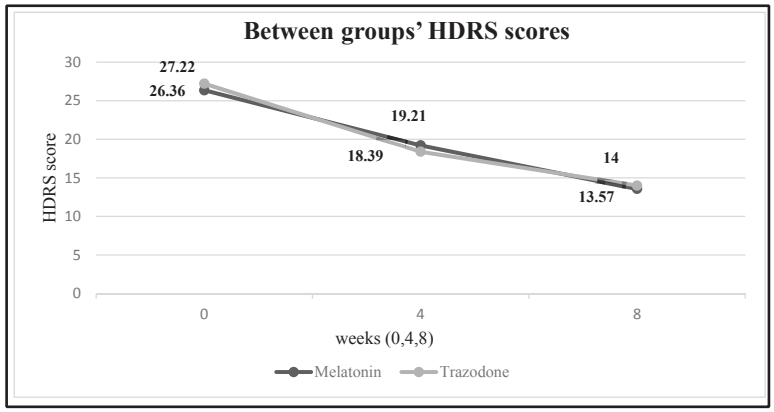

Figure 1. Effects of melatonin vs trazodone on depression severity (Hamilton Depression Rating Scale (HAM-D)) scores at weeks 0, 4 and 8.

Statistical Analysis

Data analysis was performed utilizing SPSS 22 software. General Linear Model (GLM), mixed repeated measures was used to survey the changes in HAM-D and PSQI scores at weeks 0, 4 and 8 between the two groups. The test was also used to assess the differences within the two groups. Changes in the scores of the PSQI components were detected using Friedman test with Wilcoxon as post hoc test. Between groups differences were determined using Mann-Whitney test. A value of $p < 0.05$ was established as minimal level of statistical significance.

Results

Sixty patients met the inclusion criteria for the study. 28 patients (19 in the melatonin group and 9 in the trazodone group) did not complete the study. The drop-outs were due to sexual adverse effects and somnolence, refusing the treatment by the patients or patients could not be located after their first visit due to relocation and change of address. Demographic characteristics of the 32 patients who completed this trial are shown in Table I. Fourteen patients were prescribed melatonin (6 females and 8 males); the mean ages in year ± standard deviation (SD) of these patients were 37.85 ± 12.24. Eighteen patients were prescribed trazodone (8 females and 10 males); the mean ages in year ± standard deviation (SD) of these patients in this group were 36 ± 10.51. (Table 1). Results of analyses showed no significant differences between the two groups with respect to age (p=0.47) and gender (p=0.93). These findings show the success of random assignment in producing equivalent groups on these variables at the baseline.

The results of General Linear Model (GLM) test on HAM-D and PSQI scores for both treatments are shown in Table II Analysis of the HAM-D scores using GLM showed no significant difference between the two

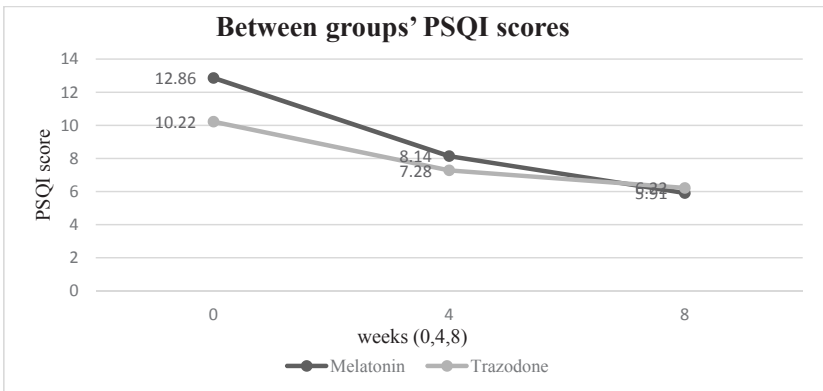

Figure 2. Effects of melatonin vs trazodone on sleep quality (Pittsburgh Sleep Quality Index (PSQI)) at weeks 0, 4 and 8.

Table 1. Baseline demographic and clinical characteristics of the patients.

Variable	Melatonin (n=14)	Trazodone (n=18)	P (2-Tailed)
Age (Mean±SD) Age range	37.8 ± 12.2 20-52	36 ± 10.5 23-56	0.5*
Gender Female (n)%	6, 42.9%	8, 44.4%	0.9**
Marital status (n)% Single Married	10, 71.4% 4, 28.6%	4, 22.2% 14, 77.8%	0.006
Depression severity HDRS score (Mean±SD)	6.5± 26.4	27.2 ± 5.6	0.7*
Sleep Quality PSQI score (Mean±SD)	12.9 ± 5.6	10.2 ± 4.7	0.2*

SD: Standard deviation. HDRS: Hamilton Depression Rating Scale, PSQI: Pittsburgh Sleep Quality Index

*Two-independent Sample T test;**$\chi 2$ Square test.

treatments (p=0.862). However, within group differences were significant for both drugs (p< 0.001) (Figure 1).

At the end of week 8, melatonin and trazodone were equally effective on improving PSQI scores and again no significant difference was seen between the two groups (p=0.61) (Table 2,3 and 4). However, within group differences were significant (p<0.001) (Figure 2).

The results of Friedman test on scores of PSQI components were shown a significant difference in component 1 (SQ) ($P_{melatonin}$ =0.001, $P_{trazodone}$ =0.002), component 4 (sleep efficiency) (P_m=0.021, P_t=0.011) and also in component 2 (Sleep Latency) (p<0.001), component 7 (daytime dysfunction) (p=0.001) only in melatonin group. However, Mann-Whitney test results showed a significant difference only for component 2 between the two treatments at weeks 0 and 4 (two sided P_{value}=0.049). The details of differences in which period of time were shown is in Table 5.

Discussions

Antidepressant drugs can affect sleep architecture (SA) by different mechanisms. For Example, activation of 5-HT_{1A} receptors may cause REM suppression; stimulation of 5-HT_2 receptors may cause sleep fragmentation and, therefore, results in sleep disturbances. In this trial the effects of melatonin and trazodone on SQ of patients with major depression were evaluated. The effectiveness of both drugs on improving SQ was similar after 4 and 8 weeks of treatment based on PSQI scores and had no significant difference. Also, melatonin compared to trazodone after 4 weeks of treatment, showed a significant decrease in time of falling in asleep in patients. SL reduction in Hughes et al., on 26 old patients with primary insomnia at a dose of 0.5 mg of melatonin was observed (p<0.05)(10). Brzezinski et al., in a meta-analysis of 17 studies reported that melatonin can improve SQ and decrease sleep latency (p=0.05) (SL)(11), as well as Cardinali et al., which reported the same effects in his review article (5). Leppamaki et al., have reported improvement in SQ in their study with 37 patients with seasonal mood disorder who received 2 mg sustained-release melatonin compared to 21 patients who received placebo (p=0.03) (12). Lemoine et al., showed the same effect, however on their trial was on patients over 55 years old (p=0.047) (6). The meta-analysis by Mayers et al., with the approach to the effects of antidepressants on sleep was demonstrated an improvement of SQ by 50-100 mg trazodone assessing by Pittsburgh and HAM-D scale (13). The findings from the study of Saletu-Zyhlarz et al., on 100 mg trazodone in 11 healthy volunteers and depressed patients by using polysomnography and Sleep and Awakening Quality Scale (SSA) were showed the effect of trazodone 100 mg such as, increasing in SQ (p<0.01), total sleep time (TST) (p<0.01), slow wave sleep (SWS) and decreased waking up during the night and in the early hours of the morning (7). Reports from study Kaynak et al., on 100 mg trazodone in 12 depressed women who were is treated with a low dose of SSRIs and venlafaxine showed an increase in SE, TST and stages 3 and 4 of sleep, compared to placebo during the 3-week

Table 2. Effects of melatonin and trazodone on sleep quality and depression severity.

Measures	Between groups (P)	Within groups (P)
Sleep Quality (Mixed Repeated Measures)	P=0.61	P<0.001
Depression Severity (Mixed Repeated Measures)	P=0.86	P<0.001

Table 3. The mean of Pittsburgh Sleep Quality Index (PSQI) scores of patients in weeks 0, 4, 8

Group week	Melatonin (Mean±SD)	Trazodone (Mean±SD)
0	12.9 ± 5.65	10.2 ± 4.8
4	8.14 ± 4.4	7.3 ± 3.4
8	5.9 ± 3.8	6.2 ± 3.75

Table 4. The mean of Hamilton Depression Rating Scale (HAM-D) scores of patients in weeks 0, 4, 8.

Group week	Melatonin (Mean±SD)	Trazodone (Mean±SD)
0	26.4 ± 6.5	27.2 ± 5.6
4	19.2 ± 7.5	18.4 ± 6.95
8	13.6 ± 6.9	14 ± 6.10

Table 5. Effect of melatonin and trazodone on Pittsburgh Sleep Quality Index (PSQI) components.

Variable	Friedman P	Mann-Whitney P	Wilcoxon P
Component 1 Subjective Sleep Quality	Melatonin: p=0.001 Trazodone: p=0.002	p=0.7 :0 p=0.6 :4 p=0.8 :8	M: (0-4): p=0.008 (4-8): p=0.41, (0-8): p=0.01 T: (0-4): p=0.01 (4-8): p=0.03, (0-8): p=0.05
Component 2 Sleep Latency	Melatonin: p<0.001 Trazodone: p=0.2	p=0.001 :0 p=0.05 :4 p=0.7 :8	M: (0-4) :p=0.01 (4-8): p=0.01, (0-8): p=0.03
Component 3 Sleep Duration	Melatonin: p=0.1 Trazodone: p=0.5	p=0.4 :0 p=0.8 :4 p=0.9 :8	
Component 4 Sleep Efficiency	Melatonin: p=0.02 Trazodone: p=0.01	p=0.6 :0 p=0.2 :4 p=0.9 :8	M: (0-4): p=0.26 (4-8): p=0.03, (0-8): p=0.03 T: (0-4): p=0.02 (4-8): p=1, (0-8): p=0.03
Component 5 Sleep Disturbance	Melatonin: p=0.3 Trazodone: p=0.1	p=0.9 :0 p=0.1 :4 p=0.4 :8	
Component 6 Using Sleep Medicine	Melatonin: p=0.05 Trazodone: p=0.05	p=0.8 :0 p=1 :4 p=1 :8	
Component 7 Daytime Dysfunction	Melatonin: p=0.001 Trazodone: p=0.1	p=0.1 :0 p=0.1 :4 p=0.2 :8	M: (0-4): p=0.008 (4-8): p=1, (0-8): p=0.004

M: melatonin; T: trazodone

study with using HAM-D and PSQI scales (p<0.05) (4). The research results of Zavesicka et al., which was on the treatment of 100 mg trazodone with CBT in 20 patients who were suffering from primary insomnia reflected the positive effects of trazodone on all components of sleep such as reducing SL (p=0.03), increasing SE (p=0.004), TST and SWS(14). Not only in these studies were used the higher doses of trazodone rather than our study and also polysomnography for evaluation was utilized as a more accurate method than using a questionnaire.

One limitation of this study was the use of Benzodiazepines (BZDs) that may cause sedation in

certain situations. However, to lessen the effect of these medications on the result of this study, BZDs were allowed in this study only as needed for anxiety and agitation at doses less than 1 mg/day of lorazepam or its equivalent. Unlike many studies that have noted melatonin could induce depressed mood, the interesting finding in this study was a lack of negative effect of melatonin on depression in patients receiving this medication.

Conclusions

This study showed that both melatonin and trazodone could result in significant improvement in SQ of MDD patients who received sertraline after 4 and 8 weeks of treatment. However, due to the significant effect of melatonin on some components of sleep and improving the SL, SE and Daytime Dysfunction without causing side effects such as drowsiness and lack of serotonin syndrome in combination with SSRIs, this would be a better choice of treatment in comparison to trazodone. More randomized controlled trials with larger sample sizes and/or more accurate ways of assessing SQ may are suggested to confirm these findings.

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