Evaluating the Effects of Melatonin on Sleep Quality in Patients With Generalized Anxiety Disorder or Major Depressive Disorders

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Abstract

Background: Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are among the most common mental disorders contributing to sleep disturbance. Given the decline in sleep quality of these patients, improving sleep may be addressed alongside other treatment strategies. This study evaluated the effect of melatonin on improving sleep quality in patients who were diagnosed with MDD or GAD.

Methods: Seventy-eight patients diagnosed with MDD or GAD were randomly assigned to two groups, including the intervention group, which received oral melatonin 3 mg daily for four weeks and the control group, which received only placebo. Assessments were made by the Groningen Sleep Quality Scale (GSQS) and Pittsburgh Sleep Quality Index (PSQI) questionnaire at the beginning and after four weeks using SPSS software.

Results: The mean age of patients was 38.78±14.12 years. There was no significant difference between the two groups in terms of demographic data. According to the analysis, although the change in GSQS scores between the placebo and melatonin groups was not significantly different from baseline scores, the difference in PSQI scores before and after the use of melatonin was significant (P=0.01). There was also a significant difference regarding the GSQS score between the two groups before and after the intervention (P=0.04).

Conclusion: The present study illustrated that melatonin use for one month could improve the quality of sleep among MDD and patients with GAD to some degree; however, according to the PSQI and GSQS scoring, there is no credible evidence that shows a significant improvement in the sleep quality of our study population.

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Introduction

Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) are identified as common psychiatric disorders. The MDD is characterized by five or more of the nine symptoms according to the DSM-5 definition, which has lasted for at least two weeks, resulting in significant impairment in social and occupational functions (1). Weight gain or weight loss, insomnia or hypersomnia, fatigue, and impaired concentration are important physical symptoms of MDD patients. GAD is defined as excessive anxiety or worry that is associated with three or more of the DSM-5 symptoms which have been persistent for more days than not, in the

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past 6 months (1). Physical symptoms in patients with GAD consist of being easily fatigued, muscle tension, irritability, and disturbance in concentration and sleep. These symptoms affect the patient's performance and impair social and occupational areas.

Sleep disturbance is one of the common symptoms among patients with MDD and GAD. There is a strong correlation between sleep and depression in such a way that about three-quarters of patients with depression experience insomnia, with a higher prevalence among females (2). Sleep disturbance along with other symptoms contributes to diminished quality of life in MDD patients. Studies showed that insomnia in individuals without depression could be considered a risk factor for depression. Clinical research also demonstrated that difficulty in initiating or maintaining sleep or both, was reported in 75% of patients with MDD (1). In addition, insomnia symptoms are worsened by increasing age in patients with MDD (1). Sleep disorders include difficulty falling asleep, difficulty staying asleep, or sleep disturbance with decreased daily performance. Although the common sleep disorder was difficulty in maintaining sleep, difficulty in falling asleep has a prevalence of 23% among patients with MDD (3). Sleep disturbance may be present in 60 to 80% of patients with MDD along with other symptoms and is considered a comorbidity (3).

Few questionnaires are available to evaluate sleep quality in clinical populations; one of them is the Pittsburgh Sleep Quality Index (PSQI). PSQI is a self-related questionnaire that includes 19 individual items with seven domains, and it evaluates sleep quality over one month (4). These seven components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep distribution, use of sleeping medication, and daytime dysfunction. Each item is scored from 0 to 3 and the total score is defined as the global PSQI score, which ranges from 0 to 21. The total score over 5 reveals poor sleep, which is related to clinical and laboratory measures and higher scores show poorer sleep quality. Another questionnaire, the Groningen Sleep Quality Scale (GSQS), was designed to evaluate the sleep quality of depressive patients (5). This scale contains 14 items in six categories, which include general sleep quality, insufficient sleep, tossing and turning, trouble with sleeping and waking up unrested. Total Score ranges from 0 to 14, with scores between 0 and 2 indicating normal sleep, and scores ≥6 indicating disturbed sleep.

Some medications that are used to treat depression may aggravate insomnia and lead to disruption of the patient's treatment plans (6). Medications that affect the serotonin system are the first-line treatment of depression due to the correlation between 5-hydroxytryptamine (5-HT), depression, and sleep disturbance pathogenesis (7,8). Although Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) medications are effective in these patients and are used widely, they may worsen sleep disturbance at the beginning of therapy and decrease the quality of sleep after improvement of depression symptoms (9-11). Benzodiazepines, zolpidem, zopiclone, and zaleplon are often used to counteract these undesirable effects which result in dependence and withdrawal syndromes. Some antidepressants have positive effects on sleep, including trazodone, nefazodone, mirtazapine, and Tricyclic Antidepressants (TCAs); however, they are not commonly used for sleep disturbance due to the various side effects and their potential for dependency (9-11). In patients with recurrent insomnia, a combination of antidepressants and hypnotic medications, along with cognitive behavioral therapy, may improve symptoms. Nevertheless, medication therapy for patients with MDD may decrease the quality of sleep or cause obstructive sleep apnea or its exacerbation. Thus, these medications should be used cautiously (12).

GAD is a relatively common disorder that typically presents in adulthood, and most of the patients reported dissatisfaction regarding the quality of sleep and moderate to severe insomnia (13). About 75% of patients with GAD experience sleep disturbance (14). The types of sleep disturbance include difficulty falling asleep, difficulty staying asleep, and restless sleeping among patients with GAD (1). Research among young individuals has identified insomnia as a risk factor for anxiety disorders (15,16). The prevalence and severity of insomnia in patients with GAD are evaluated in a limited number of investigations. They also reported that the prevalence of decreased quality of sleep, as well as anxiety disorder, is 39%, and insomnia in patients suffering from anxiety was reported at 40%, while only 18% of patients with GAD reported symptoms of insomnia before the first episode of anxiety (17). An epidemiological study showed that patients with insomnia are six times more likely to have anxiety disorders than those without insomnia (18).

Melatonin is a hormone that is naturally produced by the pineal gland in the human body through the tryptophan pathway and the conversion of serotonin to melatonin (19). In addition to its beneficial effects on falling asleep and synchronizing the circadian rhythm, melatonin can also improve depression and anxiety symptoms (20-23). Studies revealed that melatonin has demonstrated greater benefits than benzodiazepines on pre- and post-operative

anxiety disorders and sleep disturbance due to an operation (24,25). Agomelatine is an analog of melatonin which is approved by the European medical agency for treating MDD and it seems to be effective in patients with GAD (26). An investigation evaluated the sleep-inducing effect of melatonin in patients with MDD, and the results showed that the combination of extended-release melatonin with the standard treatments of depression could be effective in improving sleep disturbance of patients with MDD; however, it was not effective in improving depression symptoms (27). Interestingly, melatonin improves sleep maintenance in patients with MDD, and its use alongside SSRIs may reduce the need for additional sleep medications.

Sleep is one of the important factors in human life that directly affects the quality of life. Studies demonstrated that sleep deprivation and low-quality sleep could be associated with low quality of life, especially in individuals with anxiety or depression symptoms (28,29). Sleep disturbance is a common complaint of MDD and patients with GAD and using psychiatric medications for improving sleep disturbance has not been able to satisfy patients and physicians. As mentioned above, although melatonin has not been able to prove significant effects on psychiatric disorders, it has had a significant impact on reducing sleep onset time and increasing total sleep time. This study aimed to evaluate the effects of melatonin on sleep quality in patients diagnosed with MDD or GAD.

Methods

This study was a double-blind, placebo-controlled, randomized clinical trial that was conducted in a psychiatric clinic of Tabriz University of Medical Sciences. The study was conducted from October 2021 to July 2022. The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences before the study (Ethics code IR.TBZMED.REC.1400.401). The study protocol was also registered in the Iranian Registry of Clinical Trials, and it is available under the registry number IRCT20210921052540N1. All patients signed written informed consent before enrollment.

Study Population and Procedure

The study population was selected from the outpatients with a baseline diagnosis of GAD or MDD. At the time of enrollment, the patients' quality of sleep was assessed by the GSQS and PSQI questionnaires, which were evaluated before intervention and after four weeks. The scores were chosen based on clinical experience in Iranian patients and availability of their validated Persian formats. Patients older than 18 years, with PSQI scores of more than 5 and GSQS scores of more than 6, were included in the study. The exclusion criteria were a positive history of hypersensitivity reactions with melatonin, using benzodiazepines for sleep disturbance, non-adherence to the drug, or anxiety. The patients in both groups received 3 mg melatonin or placebo every night, at 9 pm, for four weeks (30). The patients' compliance was evaluated through pill counts and asking from the patients.

Sample Size Estimation

The sample size was estimated with Stata version 14 software. Two-sample means test and Satterthwaite's t-test were used for this estimation (Significance level (α) = 0.05, Power ($1-\beta$) = 0.90, Difference in means ($\Delta = \mu1 - \mu2$) = 3.0, Standard deviations: 4.0. $\mu1$ and $\mu2$ were taken from Oran. et al's study and standard deviation (SD) was taken from Chi Zhang's study (27,31). A sample size of 76 patients was calculated to conduct the study; each group included 38 patients. The blocked randomization method was used, and blocks 4 and 6 were considered for allocating patients to the group of drug or placebo group.

Placebo Preparation

The Pharmaceutics Department of Tabriz University of Medical Sciences prepared the placebo. The placebo ingredients were starch, lactose, magnesium stearate, and talc. Both melatonin and placebo tablets were delivered to the patients in the same containers which were labeled by a code according to the random number table. Patients, doctors, and investigators who collected the data were blinded. Only the person who prepared and labeled the placebo knew the contents of each container.

Study Outcomes and Data Collection

Demographic data and concomitant drugs of all patients were collected and compared between the melatonin and placebo groups. The PSQI and GSQS of the patients were collected at baseline and after four weeks according to the valid questionnaires.

Statistical Analysis

The statistical analysis was performed by SPSS software version 16. Normality was assessed using the Shapiro-Wilk test for all factors. Quantitative data with normal

distribution were analyzed by a two-sample independent t-test. The quantitative data that did not have a normal distribution, were analyzed using the Mann-Whitney U test. The qualitative data were compared using Pearson's Chi-square between the two groups. The paired sample t-test was also used to compare before and after GSQS and PSQI scores in each group. P-values of less than 0.05 were considered statistically significant.

Results

A total of 76 patients were divided into two equal groups of melatonin or placebo. Two patients in the melatonin group withdrew from the study due to inadequate compliance, considering the pill counts. The Consort flow diagram of the study is shown in Figure 1. Moreover, no adverse effects were reported by patients during the study.

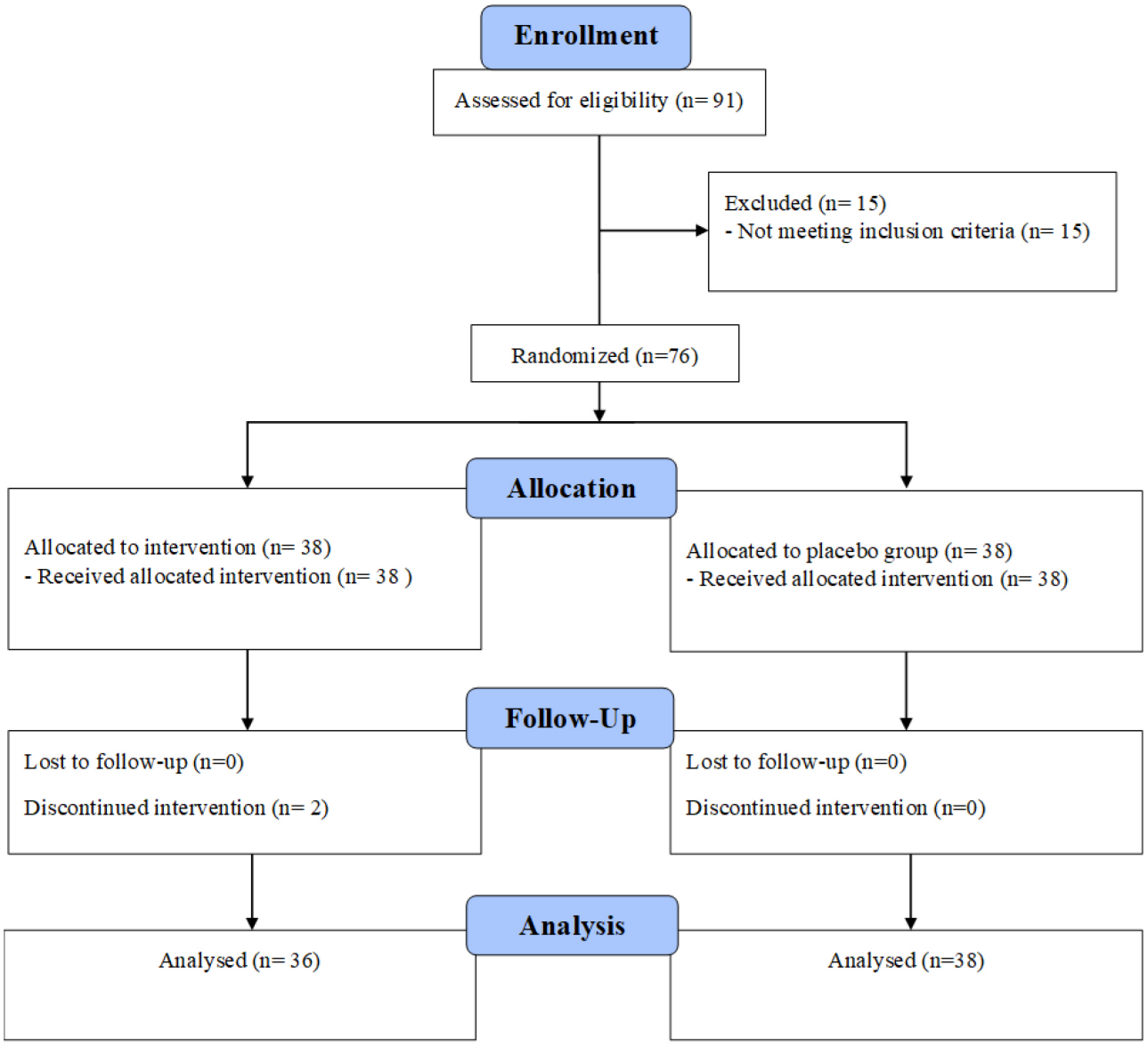


Figure 1. CONSORT Flow Diagram of the study

Demographic and Baseline Characteristics

In general, 76 patients were enrolled in the study, of which 38 patients received melatonin, and 38 patients received placebo, and the adherence rate was also 97.4%. Demographic data collected from patients are shown in Table 1. The mean (SD) age of the study population was 36.92 (13.11) and 40.82 (15.13) in the intervention and placebo groups, respectively. The demographic data had a normal distribution, and there was no significant difference between the two groups regarding age, body mass index (BMI), and gender. Data related to smoking and alcohol addiction of patients were also collected. The analysis showed a significant difference between the two groups in terms of smoking status.

Table 1. Demographic information of patients

Characteristics		Intervention group	Placebo group	P-value
Number of patients		36	38	-
Age, Years, Mean ± SD		36.92± 13.11	40.82± 15.13	0.23
sex, N (%)	**Male**	15(39.5%)	21(52.5%)	0.25
	Female	23(60.5%)	19(47.5%)	
BMI, Kg/M2, Mean ± SD		26.79± 4.76	25.73± 4.93	0.35
Smoking, N (%)		0(0%)	7(17.5%)	**0.007**
Alcoholism, N (%)		3(7.9%)	0(0%)	0.07
Baseline diagnosis, N (%)	**MDD**	21(55.3%)	24(60%)	0.67
	GAD	21(55.3)	21(52.5%)	0.81
Concomitant drugs, N (%)	**SSRI**	19(50%)	17(42.5%)	0.51
	SNRI	3(7.9%)	4(10%)	0.74
	TCA	1(2.6%)	0(0%)	0.30
	Beta blockers	13(34.2%)	14(35%)	0.94
	Atypical antidepressant	5(13.2%)	6(15%)	0.81
	Miscellaneous	9(23.7%)	14(35%)	0.27

SD: Standard Deviation, IQR: Interquartile Range, BMI: Body Mass Index, MDD: Major Depressive Disorder, GAD: Generalized Anxiety Disorder, SSRI: Selective Serotonin Reuptake Inhibitor, SNRI: Serotonin Norepinephrine Reuptake Inhibitor, TCA: Tricyclic Antidepressants.

The data related to the use of psychiatric drugs for MDD and GAD are shown in Table 1. There was no significant difference between the placebo and intervention groups regarding psychiatric drug use.

Main outcomes of the study

Intragroup changes in PSQI and GSQS scores are summarized in Table 2. Although GSQS changes in the placebo and medication groups were not significantly different compared to the baseline score, the change in PSQI score before and after melatonin use was significant (P=0.01).

Table 2. Comparing GSQS and PSQI before and after intervention in each group

	Placebo group (N=38)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	9 (7,11)	10 (8.25, 12)	0.12
PSQI	13 (10, 17.75)	12.5 (9.25, 18.75)	0.77
	Intervention group (N=36)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	8 (6,10)	9 (5, 10.25)	0.74
PSQI	15 (10.75, 19.25)	12 (6,19)	0.01

GSQS: Groningen Sleep Quality Score, PSQI: Pittsburgh Sleep Quality Index.

Data of the comparison between PSQI and GSQS scores before and after the intervention in groups of the patients who received and did not receive SSRIs, SNRIs, and TCAs are provided in Tables 3 and 4, respectively. Among patients receiving melatonin without concurrent use of neuropsychiatric medications, the PSQI score was significantly reduced compared to the baseline (P=0.01).

Table 3. Comparing GSQS and PSQI before and after intervention in patients who received TCA, SSRI, and SNRI in each group

	Placebo group (N=21)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	9.5 (8.5, 12.5)	12.5 (10.5,14.5)	0.65
PSQI	12 (10.5,16.75)	10.5 (8,17)	0.05
	Intervention group (N=23)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	11.5 (9.5, 13.75)	9 (7,12.5)	0.08
PSQI	16 (13.75, 22.25)	14.5 (9, 16.25)	0.45

GSQS: Groningen Sleep Quality Score, PSQI: Pittsburgh Sleep Quality Index, TCA: Tricyclic Antidepressants, SSRI: Selective Serotonin Reuptake Inhibitors, SNRI: Serotonin Norepinephrine Reuptake Inhibitors.

Table 4. Comparing GSQS and PSQI before and after intervention in patients who didn't receive TCA, SSRI, and SNRI in each group

	Placebo group (N=17)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	11.5 (8.5, 12.5)	12.5 (8.5, 11.5)	0.16
PSQI	12 (11.25, 18.25)	13 (11.5, 17)	0.52
	Intervention group (N=13)		
	Before intervention	**After intervention**	**P-value**
	Median (Q1, Q3)	Median (Q1, Q3)	
GSQS	9.5 (8.75, 11.75)	10 (7.5, 11.5)	0.59
PSQI	15.5 (11.5, 21.5)	12.5 (6.25, 19.25)	0.01

GSQS: Groningen Sleep Quality Score, PSQI: Pittsburgh Sleep Quality Index, TCA: Tricyclic Antidepressants, SSRI: Selective Serotonin Reuptake Inhibitors, SNRI: Serotonin Norepinephrine Reuptake Inhibitors.

Discussion

Most patients with psychiatric disorders experience symptoms of insomnia. Although it is difficult to prove the absence of a connection between psychiatric and sleep disorders is very hard, they may occur independently of each other (32). Moreover, abnormal changes in the concentration of melatonin could lead to depression; however, the exact mechanisms of this disorder are not clear (33,34). Thus, melatonin agonists such as agomelatine, ramelteon, piromelatine, and tasimelteon are commonly used by physicians for the treatment of patients with depression and associated disorders (35). Measuring melatonin levels in saliva, plasma, or 6-sulfametoxymelatonin in urine indicates significant changes in melatonin secretion level and the time of secretion in the acute phase of depression.

Although the biochemical mechanisms of psychiatric disorders are not clear, the measurement of melatonin in saliva, plasma, or its metabolite 6-sulfatoxymelatonin in urine has revealed significant alterations in melatonin secretion during the acute phase of depression. These changes are not only evident in melatonin levels but also in the timing of its secretion, which is notably disrupted in psychiatric disorders (36). In a study that included 80 patients diagnosed with GAD, the effects of melatonin

were evaluated. Primary outcomes demonstrated that melatonin agonists showed no significant improvement in short-term symptoms in comparison to the SSRIs and SNRIs; however, the risk of melatonin dependence was much lower than other medications (26).

There is insufficient research evaluating the adverse effects of melatonin in MDD and GAD disorders. Nevertheless, when minimizing adverse effects and risks is a priority, melatonin is often the preferred option due to its comparatively fewer documented side effects than medications like benzodiazepines (37,38). A meta-analysis of four clinical trials involving patients diagnosed with depression revealed that melatonin was not effective in improving the mood symptoms of patients (39).

An investigation that was performed in 1998 with a sample size of 19 patients demonstrated that extended-release melatonin is effective for improving the sleep of patients with depressive disorders; nevertheless, it could not improve the symptoms of depression in MDD patients. The mean PSQI scores were 14 and 11 in the intervention and control groups, respectively, at the beginning of the study and they decreased and reached 6 and 10 in the same order over four weeks (P=0.01) (27). Their findings are in line with our findings in the present study; the average PSQI score declined by 0.56 from baseline. Although the amount of reduction was less than one, the P-value was less than 0.05, indicating a statistically significant effect of melatonin.

The positive effects of melatonin on insomnia and other symptoms of depression were evaluated by Serfaty et al. (40). This evaluation was performed for four weeks in 33 patients and it showed that melatonin may be helpful in treating insomnia in patients with MDD. The average score of Hamilton Rating Scale for Depression (HDRS) in the intervention and control groups was 16.8 and 18.8 before the investigation and decreased to 13.3 and 14.7, respectively ($P < 0.05$). It seems that melatonin is safe and well tolerated; however, its potential role in treating depression in patients unwilling to take antidepressant medications needs more evaluation. In the present study, statistical analysis showed no significant within-group differences in GSQS scores before and after the intervention. However, a significant difference was observed between the two groups ($P < 0.05$).

In a study in 2012, the effects of the combination of melatonin and buspirone were evaluated in 134 patients (41). This combination was well tolerated, and analysis of the 16-item quick inventory of depressive symptomatology (QIDS-SR16) scores showed no significant difference between the patients who received melatonin and buspirone and those who received placebo ($P > 0.05$). Owing to the use of melatonin in combination with buspirone in this study, evaluating the effects of melatonin alone is challenging.

A recent study was conducted by Ghaeli et al. to compare the effects of melatonin and oxazepam for the management of anxiety and insomnia (42). The anxiety was evaluated by the Hamilton score (HAM-A) and the quality of sleep was evaluated by the Groningen score. This study revealed that melatonin could not improve the quality of sleep significantly in comparison to oxazepam (P=0.04); however, melatonin was effective in reducing anxiety according to the HAM-A ($P < 0.01$).

Studies demonstrate that patients with mood disorders like MDD and GAD have unstable circadian rhythms in comparison with healthy individuals (30). Moreover, many signs of circadian rhythm sleep disorders are observed in mood disorders. Some studies also showed that patients suffering from neuropsychiatric disorders usually have abnormal amounts and timing of melatonin secretion (30). Therefore, melatonin, which plays a crucial role in controlling circadian rhythm, could be effective for sleep disturbance in patients with MDD and GAD. Positive results observed in this study in patients with MDD and GAD may support the aforementioned hypothesis.

Further studies are needed to provide clinicians with stronger evidence to support or refute the use of melatonin in patients with MDD or GAD. Although robust data on the use of melatonin in these populations of patients is mainly lacking, melatonin is being used by physicians or patients themselves to improve sleep quality off-label or over the counter (27,43).

Study limitations and suggestions for further investigations

The primary limitations of this study are its short evaluation period and small sample size. Additionally, using alternative measures of sleep quality could be considered, as they may provide more insightful outcomes. The dosage of melatonin may also play a crucial role in achieving better results. Therefore, further studies with larger sample sizes, longer evaluation periods, and various doses of melatonin are needed to validate its potential benefits in improving sleep quality in patients with MDD or GAD.

Conclusion

The present study demonstrated that melatonin consumption for one month may improve the quality of sleep among patients with MDD and GAD to some degree. Nevertheless, PSQI and GSQS scores do not provide strong evidence of a significant improvement in sleep quality in our study population. Given the absence of adverse effects on MDD and GAD symptoms in any of the patients, it can be concluded that melatonin has positive effects on improving the sleep quality of the patients. The effects of melatonin are mainly related to sleep initiation

and further research may evaluate its effects in patients with psychiatric disorders and problems falling asleep.

Conflicts of Interest

The authors have nothing to declare.

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