Brief Report

Effect of early morning awakening in major depressive disorder

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Abstract

Patients with the major depressive disorder usually manifest with sleep disturbance. Early morning awakening is more closely related to major depressive disorder than other sleep disturbances. This study aimed to assess the effect of early morning awakening in treating patients with major depressive disorder. The eligible patients were divided into two groups according to whether they woke up at 2-4 a.m: early morning awakening and non-early morning awakening group. All patients were assessed using the Hamilton Depression Scale, Hamilton Anxiety Scale, and Repeatable Battery for the Assessment of Neuropsychological Status scores at baseline and the fourth week. Twenty-one men and 31 women (mean age 25.13 ±10.67 years) were enrolled. There was a significant main effect of early morning awakening in the Hamilton Depression Scale ($P = 0.04$) and Hamilton Anxiety Scale ($P = 0.01$) at the fourth week after treatment. But there was no significant difference in cognitive changes between the two groups. In conclusion, a major depressive disorder with early morning awakening may result in statistically and clinically significant delay in recovery.

Keywords: Sleep disturbance; early morning awakening; major depressive depression; cognition; psychiatry.

1. Introduction

Major depressive disorder (MDD) is a complex disease affecting individual health with an enormous toll [1]. There is a wide variation of clinical symptoms in affected individuals. It is a chronic psychiatric condition characterized by changes in emotional states, such as reduced positive emotions, cognitive impairments, and memory difficulties [2]. Currently, 30-50% of patients with MDD are resistant to the current treatment[3]. In addition, it has a considerable economic impact.

Sleep disturbance afflicts nearly a quarter of the population in the world [4]. People with perennial sleep problems are more likely to suffer from mental disorders, especially MDD [4]. In many cases, sleep disturbance is the main symptom of MDD. Sleep neurophysiological changes in patients with MDD are often observed [5]. In the past, sleep disturbance was regarded as a concomitant symptom of MDD. It is generally believed that sleep disturbance can be alleviated as symptoms related to the treatment of MDD. It has been found that depressed patients with sleep disturbance may have more serious symptoms and treatment difficulties [6]. In addition, insomnia is a common residual symptom in patients with MDD. It is an important predictor of MDD recurrence and may lead to unpleasant clinical outcomes [7]. It has been known that insomnia is an independent diagnostic entity that may lead to the onset of MDD. However, in clinical practice, only about half of patients with MDD will seek treatment [8].

Insomnia in young people may lead to a risk of MDD for at least 30 years. Studies have confirmed the importance of insomnia as a risk factor for MDD and the necessity of early treatment of insomnia [9]. The diagnosis of insomnia is based on four different symptoms: early morning awakening, difficulty falling asleep, and difficulty maintaining sleep. In addition, patients with MDD usually manifest sleep disturbance and early morning awakening [10]. It has been reported that about half of depressed patients have early morning awakening [11].

Furthermore, early morning awakening is more closely related to MDD than other sleep disturbances [12]. Hence, studying early morning awakening in depressed patients remains critically important. Moreover, examining early morning awakening plays an important role in evaluating the treatment of MDD in the current study.

Therefore, we studied MDD patients with or without early awakening to clarify the impact of early awakening on the prognosis of MDD.

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2. Method

2.1. Participants

Patients were recruited from psychiatric inpatients at the department of psychiatry, the Nanhai Public Health Hospital of Foshan, China. Patients aged between 17–60 years old had a current diagnosis of MDD based on the Diagnostic and Statistical Manual-5 (DSM-5) and were not treated with any psychiatric medications.

Standard clinical assessment of patients was undertaken, which included psychiatric assessment, structured diagnostic interview, and medical history. Subjects were grouped according to whether patients woke up at 2-4 a.m for more than 3 months and at least 3 times a week before admission, and the night before admission, they were monitored from the SOMNOscreen plus (https://somnomedics.de/) to make sure they indeed woke up at 2-4 a.m. They were assigned into two groups: early morning awakening and non-early morning awakening group.

2.2 Assessment

All patients were assessed using Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores at baseline and at the fourth week. Two senior psychiatrists rated the patients, and the internal reliability of HAMD and HAMA was > 90%. We used HAMD and HAMA (the fourth week) scores to assess remission and remission rates. We assessed neuropsychological states using RBANS scores.

All patients were treated with escitalopram (H. Lundbeck A / s, Denmark) with or without oxazepam (Beijing Yimin Pharmaceutical Co., Ltd.) according to their condition, which is conventional therapy according to depression treatment guidelines [13].

2.3 Statistical Analysis

The data we studied passed the Lilliefors test, suggesting that the data conforms to the normal distribution. For comparisons between the baseline of early morning awakening and non-early morning awakening group, one sample t-test was used. The student's t-tests of paired samples were used to compare pre-and post-intervention values. Regarding the predictive effect of early morning awakening on MDD recovery, we performed ANOVA using the difference between baseline and the fourth-week scores as HAMD, HAMA, and RBANS scores. $P < 0.05$ was considered statistically significant, and the data are presented as mean ± standard deviation (SD). All data were analyzed with SPSS Statistics, version 21.0 for Windows (IBM Corporation, Armonk, USA).

3. Result

3.1 Participant characteristics

Twenty-one men and 31 women (mean age 25.13 ± 10.67 years) were enrolled. There were no significant differences between the two groups in regards with age ($P = 0.75$), HAMD ($P = 0.65$), or HAMA ($P = 0.93$). The education level of both groups was higher than 9 years. Patient's baseline RBANS scores (Immediate memory (Learning), Immediate memory (Story Memory), Visuospatial Construction, Language, Attention (Digit span), Attention (Coding), Delayed memory (List Recall), Delayed memory (List Recognition), Delayed memory (Story Recall), Delayed memory (Figure Recall) is shown in **Table 1**.

3.2 Outcomes

There was a significant main effect of early morning awakening in HAMD ($P =0.04$) at the fourth week after conventional therapy. Similarly, we observed a significant main effect in HAMA ($P =0.01$). The results suggested that early morning awakening leads to a delay in rehabilitation during the observation period. (**Figure 1**)

Regarding neuropsychological status in the patients, the RBANS scores separately, considering details and integrity, were achieved by immediate memory, visuospatial construction, language, attention, and delayed memory. In addition, the characteristics of the participants from baseline to the fourth week were not significantly different between the early morning awakening and non-early morning awakening groups. (**Figure 2**).

Table 1. Baseline characteristics of the participants.

	Non-early morning awakening	Early morning awakening	*P*-value
Participants	14	27	
Age (years)	25.64 ± 10.81	24.67 ± 10.72	*P* = 0.75
Gender (M / F)	11 / 14	10 / 17	
Baseline HAMD score	24.48 ± 6.54	25.30 ± 6.32	*P* = 0.65
Baseline HAMA score	15.8 ± 5.48	15.93 ± 5.36	*P* = 0.93
RBANS			
Immediate memory (Learning)	28.48 ± 7.10	28.37 ± 5.61	*P = 0.95*
Immediate memory (Story Memory)	14.24 ± 5.70	15.26 ± 5.34	*P = 0.51*
Visuospatial Construction	18.24 ± 2.44	19.15 ± 1.51	*P = 0.11*
Language	17.10 ± 3.44	17.85 ± 4.62	*P = 0.69*
Attention (Digit span)	14.16 ± 2.61	14.22 ± 2.41	*P = 0.93*
Attention (Coding)	47.64 ± 11.59	50.22 ± 13.54	*P = 0.47*
Delayed memory (List Recall)	5.68 ± 2.87	6.48 ± 3.02	*P = 0.33*
Delayed memory (List Recognition)	19.28 ± 1.46	19.52 ± 1.01	*P = 0.49*
Delayed memory (Story Recall)	7.72 ± 3.22	8.04 ± 3.86	*P = 0.61*
Delayed memory (Figure Recall)	13.48 ± 4.06	14.48 ± 3.68	*P = 0.27*

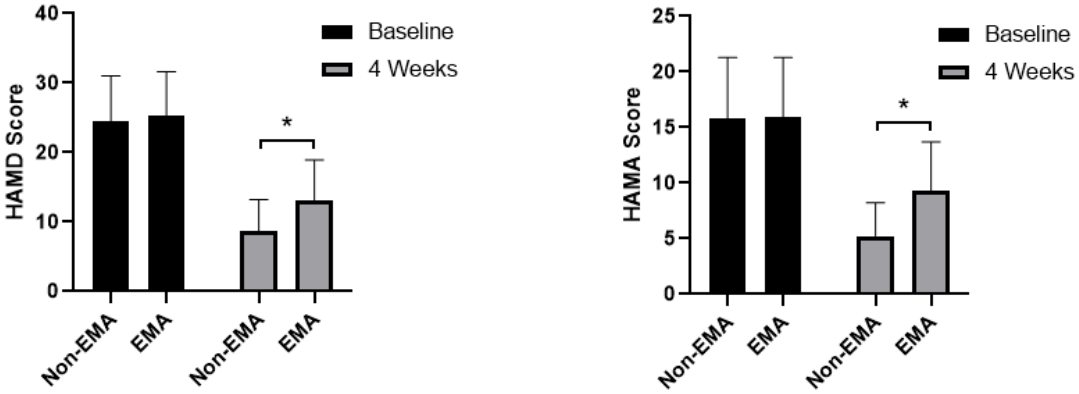

Figure 1. *Scores on the HAMD and HAMA at the time of baseline and the fourth week. Scores on HAMD and HAMA of non-EMA in the fourth week are 8.68±4.53 and 5.24±2.97; EMA is 13.07±5.85 and 9.33±4.36.*

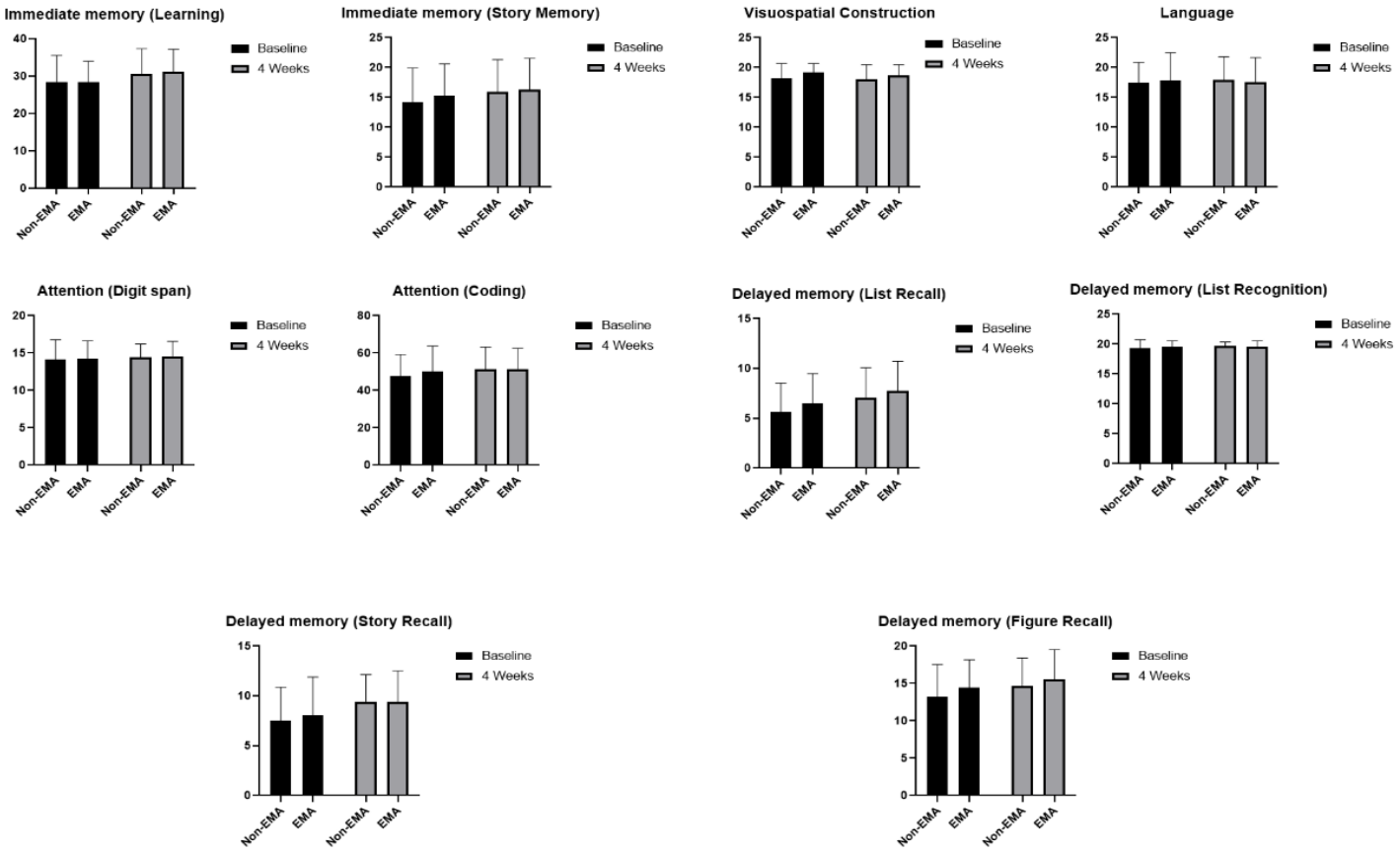

Figure 2. *Scores on the RBANS in time of baseline and the fourth week. Scores on Immediate memory (Learning), Immediate memory (Story Memory), Visuospatial Construction, Language, Attention (Digit span), Attention (Coding), Delayed memory (List Recall), Delayed memory (List Recognition), Delayed memory (Story Recall), Delayed memory (Figure Recall) of non-EMA at fourth week are 30.60±6.71, 15.96±5.37, 18.00±2.47, 17.96±3.81, 14.48±3.81, 51.20±12.02, 7.12±12.02, 19.64±0.70, 9.44±2.71 and 14.60±3.81; EMA is 31.19±5.96, 16.30±5.25, 18.70±1.77, 17.59±4.06, 14.59±1.97, 51.56±10.90, 7.78±2.95, 19.56±0.97, 9.41±3.10 and 15.56±3.97.*

4. Discussion

This study demonstrates early morning awakening in patients with MDD may lead to delays in recovery. According to HAMD and HAMA scores, depressed patients with early morning awakening had poor recovery in depressive and anxious symptoms after the treatment in the fourth week. In addition, there is no significant change in neuropsychological states (as the RBANS score).

Insomnia is a syndrome: Its diagnosis relies on the patient's subjective report, which is defined as difficulty in falling asleep, maintaining sleep, non-restorative sleep, or early morning awakening [14]. It has been reported that approximately 30% of the population have some insomnia symptoms, and 10% experience chronic and persistent insomnia symptoms [15]. The consequences associated with insomnia include fatigue, drowsiness, memory deficits, mood disorders, and impaired attention [16]. Insomnia is a condition caused by other diseases, completely independent of these diseases, and can also cause coexisting diseases. Mental disorders (depression and anxiety), circadian rhythm disorders (phase delay syndrome), or other sleep disorders (sleep-related respiratory disorders) may be the disorders [14]. As many as 51.9% of patients have early morning awakening complaints. It has been reported that as many as 24% to 58% of patients with sleep disturbance meet the criteria of MDD [17]. As a subtype of sleep disturbance, early morning awakening is frequent in patients with MDD. In treating MDD and anxiety, this may be of great significance in preventing the onset or recurrence of the disorder.

Insomnia can lead to sleep disturbance symptoms and excessive performance in patients with MDD, and vice versa [17]. Our results showed that after 4 weeks of regular medication, the early morning awakening patients' treatment effect was not obvious. The symptoms of insomnia and MDD reflect a bidirectional relationship. Previous studies have shown a close relationship between depressive and insomnia symptoms, and insomnia is correlated with poor treatment results [17, 18]. Sleep disturbance strongly affects the development of MDD. Sleep disturbance-related symptoms may be important and modifiable risk factors for preventing MDD and/or achieving and maintaining MDD remission [19, 20].

Interestingly, the paradoxical therapeutic effect of sleep deprivation therapy, often performed during the latter portion of the night, can improve sleep and mood. However, the effect of this treatment is short-term [21]. However, long-term sleep deprivation can affect cognition and emotion [20]. Our study showed a trend of mood improvement, indicating that routine clinical treatment still has a certain effect.

Furthermore, sleep disruption is associated with behavioral, emotional, and cognitive disorders [22, 23]. However, our results indicated that after 4 weeks of routine treatment, MDD with early morning awakening did not cause significant cognitive changes, which meant after timely and regular drug treatment, the cognitive impact of early awakening on MDD seemed to be saved.

In addition, there is a lack of independence between sleep and mood in the HAMD and HAMA since the HAMD has three insomnia questions and the HAMA has one insomnia question. Furthermore, there is no additional grouping for those with difficulty falling asleep who may be included in the non-early wake-up group. Meanwhile, the influence of conventional drug treatment has caused an inevitable deviation from the conclusion. Therefore, further prospective studies are necessary to strengthen these conclusions.

5. Conclusion

The study aimed to assess early morning awakening as a comorbid disorder for patients with MDD, which may bring uncertain treatment consequences to these patients. Our findings suggest that MDD with early morning awakening may result in statistically and clinically significant delays in recovery.

Abbreviations:

HAMD, Hamilton Depression Scale;
HAMA, Hamilton Anxiety Scale;
EMA, Early morning awakening.
RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

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Authors' contributions

XX. W and LJ. G conceived and designed the experiments; XX. W and N. C performed the experiments; XX. W and L. D analyzed the data; XX. W and LJ. G wrote the paper.

Ethics approval and consent to participate

We obtained written informed consent from all patients. The ethics committee approved this study of the Nanhai Public Health Hospital of Foshan, China and the experiments were conducted following the declaration of Helsinki.

Conflict of Interest:

The authors declare no conflicts of interest.

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