Effect of early morning awakening in major depressive disorder

Guohong Xu

The Third People's Hospital of Foshan

Yang Yu

The Third People's Hospital of Foshan

Chaohua Tang

The Third People's Hospital of Foshan

Zishan Liu

The Third People's Hospital of Foshan

Xiaoling Li

The Third People's Hospital of Foshan

Yukang Tan

The Third People's Hospital of Foshan

Xiancong Mai

The Third People's Hospital of Foshan

Runyi Li

The Third People's Hospital of Foshan

Caixia Xu

The Third People's Hospital of Foshan

Guojun Xie

The Third People's Hospital of Foshan

Jiaquan Liang (✉ 417891714@qq.com)

The Third People's Hospital of Foshan

Research Article

Keywords: Sleep disturbance, Early morning awakening, Major depressive depression, Cognitive impairment

Posted Date: January 27th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1281742/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Patients with major depressive disorder (MDD) usually manifest sleep disturbance. Early morning awakening is more closely related to MDD than other sleep disturbances.

Aim The aim of this study was to assess the effect of early morning awakening in the treatment of patients with MDD.

Methods Eligible patients were randomly assigned into two groups: early morning awakening and non-early morning awakening group. 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 the fourth week.

Results Twenty-one men and 31 women (mean age 25.13 ± 10.67 years) were enrolled. There is a significant main effect of early morning awakening in HAMD ($P = 0.04$) and HAMA ($P = 0.01$) at fourth week after escitalopram treatment.

Discussion This trial suggests that early morning awakening may result in statistically and clinically significant delay in the recovery of the MDD but cognitive impairment.

Introduction

Major depressive disorder (MDD) is a complex disease, which affects individual health with an enormous toll [1]. The clinical symptoms display a wide variation as affected individuals. It is a chronic psychiatric condition characterized by changes in the emotional states, such as reduction of 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. People with perennial sleep problems are more likely to suffer from mental disorders, especially for 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. Now 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 considered to be 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 in

falling asleep, difficulty in maintaining sleep, and non-restorative 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 clinical trial.

The aim of this study was to assess the effect of early morning awakening in the treatment of patients with MDD. First, we evaluated the Hamilton depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) as a predictor of the effect of early morning awakening on MDD. Second, we compared the results of HAMD, HAMA, RBANS scores and evaluated the effect of early morning awakening at the fourth week post-treatment follow-up.

Method

Study design and participants

Patients were recruited from psychiatric inpatients at the department of psychiatry, the third people's hospital of Foshan, China. Patients between 17–60 years of age, with a diagnosis of MDD based on the Diagnostic and Statistical Manual-5 (DSM-5).

Standard clinical assessment of patients, including psychiatric assessment, structured diagnostic interview, and medical history. According to the sleep monitoring of the polysomnography (SOMNOscreen plus, somnomedics, ed), group according to whether patients wake up at 2-4 a.m. Eligible patients were randomly assigned into two groups: early morning awakening and non-early morning awakening group.

Intervention

All patients received daily escitalopram (H.Lundbeck A/S, Denmark) treatment for 4 weeks, which start with 5mg/d, 5mg weekly increase, and up to 15mg/d. Patients with trouble falling asleep were treated with oxazepam (Beijing Yimin Pharmaceutical Co., Ltd.) 15-30mg/night. Escitalopram has little effect on sleep and is taken during the day. Oxazepam is a sleep adjuvant medication with short action time. It is a medication to promote sleep and has relatively little effect on sleep structure.

Outcome

All patients were assessed using HAMD, HAMA, and RBANS scores at baseline and at the fourth week. The patients were rated by two senior psychiatrists, 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.

Statistical Analysis

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 the values of pre- and post-intervention values. Regarding the predictive effect of early morning awakening on MDD recovery, we performed 2way ANOVA using the difference between baseline and the fourth week scores as HAMD, HAMA, and RBANS scores. $P < 0.05$ was considered as statistically significant, and the data are presented as mean $\pm$ standard deviation (SD). All data were analyzed with the SPSS Statistics, version 21.0 for Windows (IBM Corporation, Armonk, USA).

Result

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 regard to age ($P = 0.76$) or duration of illness on HAMD ($P = 0.86$), HAMA ($P = 0.89$). The education level of both groups was higher than 9 years. In addition, the baseline of 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 showed in Table 1.

Outcomes

The rehabilitative effects of early morning awakening on MDD patients observed during the trial are showed in Figure 1. There is a significant main effect of early morning awakening in HAMD ($P = 0.04$) at the fourth week after escitalopram treatment. Similarly, regarding HAMA scores, we observed a significant main effect in HAMA ($P = 0.01$). The results suggest that early morning awakening leads to delay of rehabilitation during the trial.

In terms of neuropsychological status in the patients, the RBANS scores separately considering details and integrity are 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).

Discussion

This study demonstrates the inhibitory effect of early morning awakening on treatment in patients with MDD. According to HAMD and HAMA scores, depressed patients with early morning awakening had poor recovery in depressive and anxious symptoms after the treatment on the fourth week. In addition, there is no significant change in neuropsychological states (as the RBANS score). To our knowledge, this is the first study to demonstrate that early morning awakening is a determinant tolerant for treatment in patients with MDD.

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 [13]. It has been reported that approximately 30% of the population have some insomnia symptoms, and 10% experience chronic and persistent insomnia symptoms [14]. The consequences associated with insomnia include fatigue, drowsiness, memory deficits, mood disorders, and impaired attention [15]. 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 [13]. In this study, 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 [16]. As a subtype of sleep disturbance, early morning awakening is frequent in patients with MDD. In the treatment of MDD and anxiety, this may be of great significance to prevent the onset or recurrence of the disorder.

Insomnia can affect the trajectory of MDD and increase the severity and duration of this disorder. Poor subjective sleep quality before the treatment may indicate a reduced treatment response. A previous study reported that women with interpersonal therapy have higher pre-treatment sleep quality scores than women with no remission of MDD, significantly improved mood [17]. Furthermore, poor sleep quality is associated with poor response to depressed pharmacotherapy and psychotherapy [18]. Depressed patients with suicidal tendencies have poor sleep quality and a higher incidence of insomnia and hypersomnia [19]. As many as 42% of the elderly report sleep-related troubles [20]. A review reported that the prevalence of MDD is approximately 9% and insomnia is about 17% [21]. Studies assessing sleep quality in the elderly have found that insomnia increases the risk of MDD [22]. In addition, it has been reported that the severity of insomnia is one of the clinical features predicting suicide within 1 year, and this connection has been reported in adolescence [23]. Adolescents with insomnia have the most severe MDD, and those with insomnia have more severe MDD than those without sleep disturbance [24]. Sleep disturbances is also associated with an increased risk of suicide in adolescents [25]. The patients have a mean age of 24.67 years and ranged in age from 17 to 60 years in this study. It may indicate that the risk factor of early morning awakening is not particularly for the elderly, but for depressed patients of all ages.

Insomnia can lead to sleep disturbance symptoms and excessive performance in patients with MDD, and vice versa [16]. Our results showed that after 4 weeks of antidepressant treatment, although anti-insomnia treatment is carried out for early morning awakening patients, the treatment effect is not obvious. The symptoms of insomnia and MDD reflect a bidirectional relationship. Previous studies have shown that there is a close relationship between depressive and insomnia symptoms, and insomnia is correlated with poor treatment results. 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. For patients with insomnia, early morning awakening, combined with other medical or mental disorders and pharmacotherapy side effects should be considered. Furthermore, sleep disruption is associated with behavioral, emotional, and cognitive disorders [26]. Our results suggested that early morning awakening did not cause significant cognitive changes, which may be related to the limitations related to the measurement time.

Based on the above findings, clinicians must carefully evaluate the sleep symptoms of patients with MDD. The emerging view is that insomnia commonly coexists with MDD, rather than secondary to MDD. It suggests that insomnia and MDD need require specific treatment. Although there are few trials for insomnia complicated with MDD, the existing evidence indicates that attention should be paid to insomnia, especially early morning awakening, while treating MDD.

Conclusions

The project was inspired to assess early morning awakening as a comorbid disorder for patients with MDD, which may bring uncertain treatment consequences to these patients. This trial suggests that early morning awakening may result in statistically and clinically significant delays in the recovery of the MDD. Whether the effect of early morning awakening on MDD needs to be in large clinical trials, which will be of great correlation with public health.

Declarations

Funding

This research was supported by the project of Foshan Science and Technology Bureau (1920001001018) and the High-level Hospital Development Program for Foshan “Climbing” Project (DF-04-02-002).

Authors' contributions

Guohong Xu and Jiaquan Liang made substantial contributions to the conception or design of the work as well as the acquisition, analysis, or interpretation of data; they aided in drafting the work, gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations

Ethics approval and consent to participate

We obtained written informed consent from all patients. This study was approved by the ethics committee of the Third People's Hospital of Foshan, China and the experiments were conducted following the declaration of Helsinki.

Consent for publication

Not applicable.

Competing Interest

The authors have no potential or actual conflicts of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Acknowledgments

Not applicable.

References

1. Fox ME, Lobo MK: **The molecular and cellular mechanisms of depression: a focus on reward circuitry.** *Molecular psychiatry* 2019, **24**(12):1798-1815.
2. Dehn LB, Beblo T: **[Depressed, biased, forgetful: The interaction of emotional and cognitive dysfunctions in depression].** *Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Österreichischer Nervenärzte und Psychiater* 2019, **33**(3):123-130.
3. Dudek KA, Dion-Albert L, Kaufmann FN, Tuck E, Lebel M, Menard C: **Neurobiology of resilience in depression: immune and vascular insights from human and animal studies.** *The European journal of neuroscience* 2021, **53**(1):183-221.
4. Fang H, Tu S, Sheng J, Shao A: **Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment.** *Journal of cellular and molecular medicine* 2019, **23**(4):2324-2332.
5. Armitage R: **Sleep and circadian rhythms in mood disorders.** *Acta psychiatrica Scandinavica Supplementum* 2007(433):104-115.
6. Jaussent I, Bouyer J, Ancelin ML, Akbaraly T, Pérès K, Ritchie K, Besset A, Dauvilliers Y: **Insomnia and daytime sleepiness are risk factors for depressive symptoms in the elderly.** *Sleep* 2011, **34**(8):1103-1110.
7. Hinkelmann K, Moritz S, Botzenhardt J, Muhtz C, Wiedemann K, Kellner M, Otte C: **Changes in cortisol secretion during antidepressive treatment and cognitive improvement in patients with major depression: a longitudinal study.** *Psychoneuroendocrinology* 2012, **37**(5):685-692.
8. Smith MT, Huang MI, Manber R: **Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders.** *Clinical psychology review* 2005, **25**(5):559-592.
9. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ: **Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study.** *American journal of epidemiology* 1997, **146**(2):105-

114.

10. Xiang YT, Ma X, Cai ZJ, Li SR, Xiang YQ, Guo HL, Hou YZ, Li ZB, Li ZJ, Tao YF *et al*: **The prevalence of insomnia, its sociodemographic and clinical correlates, and treatment in rural and urban regions of Beijing, China: a general population-based survey.** *Sleep* 2008, **31**(12):1655-1662.
11. Grunhaus L, Flegel P, Carroll BJ, Greden JF: **Self-reported diurnal mood changes, early morning awakening and the dexamethasone suppression test in endogenous depression.** *Journal of affective disorders* 1985, **8**(1):1-7.
12. Yokoyama E, Kaneita Y, Saito Y, Uchiyama M, Matsuzaki Y, Tamaki T, Munezawa T, Ohida T: **Association between depression and insomnia subtypes: a longitudinal study on the elderly in Japan.** *Sleep* 2010, **33**(12):1693-1702.
13. Bastien CH: **Insomnia: Neurophysiological and neuropsychological approaches.** *Neuropsychology review* 2011, **21**(1):22-40.
14. Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C: **Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors.** *Sleep medicine* 2006, **7**(2):123-130.
15. Olaithe M, Bucks RS, Hillman DR, Eastwood PR: **Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation.** *Sleep medicine reviews* 2018, **38**:39-49.
16. Franzen PL, Buysse DJ: **Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications.** *Dialogues in clinical neuroscience* 2008, **10**(4):473-481.
17. Buysse DJ, Tu XM, Cherry CR, Begley AE, Kowalski J, Kupfer DJ, Frank E: **Pretreatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters.** *Biological psychiatry* 1999, **45**(2):205-213.
18. Dew MA, Reynolds CF, 3rd, Houck PR, Hall M, Buysse DJ, Frank E, Kupfer DJ: **Temporal profiles of the course of depression during treatment. Predictors of pathways toward recovery in the elderly.** *Archives of general psychiatry* 1997, **54**(11):1016-1024.
19. Singareddy RK, Balon R: **Sleep and suicide in psychiatric patients.** *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists* 2001, **13**(2):93-101.
20. Lyness JM, Caine ED, King DA, Conwell Y, Duberstein PR, Cox C: **Depressive disorders and symptoms in older primary care patients: one-year outcomes.** *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2002, **10**(3):275-282.

21. Pigeon WR, Hegel M, Unützer J, Fan MY, Sateia MJ, Lyness JM, Phillips C, Perlis ML: **Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort?** *Sleep* 2008, **31**(4):481-488.

22. Mallon L, Broman JE, Hetta J: **Relationship between insomnia, depression, and mortality: a 12-year follow-up of older adults in the community.** *International psychogeriatrics* 2000, **12**(3):295-306.

23. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R: **Time-related predictors of suicide in major affective disorder.** *The American journal of psychiatry* 1990, **147**(9):1189-1194.

24. Clarke G, Harvey AG: **The complex role of sleep in adolescent depression.** *Child and adolescent psychiatric clinics of North America* 2012, **21**(2):385-400.

25. Liu X, Buysse DJ: **Sleep and youth suicidal behavior: a neglected field.** *Current opinion in psychiatry* 2006, **19**(3):288-293.

26. O'Brien LM: **The neurocognitive effects of sleep disruption in children and adolescents.** *Child and adolescent psychiatric clinics of North America* 2009, **18**(4):813-823.

Tables

Table 1. Baseline characteristics of the participants.

	Non- early morning awakening	Early morning awakening
Participants	25	27
Age (years)	25.64±10.81	24.67±10.72
Gender (M/F)	11/14	10/17
Education		
Up to 9 years, n (%)	3 (12.0)	4 (14.8)
10–12 years, n (%)	8 (32.0)	7 (25.9)
13–17 years, n (%)	14 (54.0)	16 (59.3)
Drinking, n (%)	0 (0)	0 (0)
Smoking, n (%)	2 (8.0)	1 (3.7)
Baseline HAMD score	24.48±6.54	25.30±6.32
Baseline HAMA score	15.8±5.48	15.93±5.36
RBANS		
Immediate memory (Learning)	28.48±7.10	28.37±5.61
Immediate memory (Story Memory)	14.24±5.70	15.26±5.34
Visuospatial Construction	18.24±2.44	19.15±1.51
Language	17.10±3.44	17.85±4.62
Attention (Digit span)	14.16±2.61	14.22±2.41
Attention (Coding)	47.64±11.59	50.22±13.54
Delayed memory (List Recall)	5.68±2.87	6.48±3.02
Delayed memory (List Recognition)	19.28±1.46	19.52±1.01
Delayed memory (Story Recall)	7.72±3.22	8.04±3.86
Delayed memory (Figure Recall)	13.48±4.06	14.48±3.68

HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status

Figures

Figure 1

Scores on the HAMD and HAMA in time of baseline and the fourth week.

HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; EMA, Early morning awakening.

Figure 2

Scores on the RBANS in time of baseline and the fourth week.

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; EMA, Early morning awakening.